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AN INVESTIGATION INTO MORNING LIGHT THERAPY, CIRCADIAN RHYTHMS AND SLEEP-WAKE CYCLES IN POSTOPERATIVE CARDIAC PATIENTS

Anisoara C. N. Jardim

Abstract

Hospitalisation, surgery and anaesthesia have been shown to cause disruption of sleep-wake cycles and circadian rhythms in animal models and in humans. These disturbances may adversely affect the well-being and recovery of patients. In this thesis, I describe a stepwise investigation to determine the effects of the clinical lighting environment on the lengths of hospital stay of postoperative cardiac patients, and to establish whether morning light therapy improves the postoperative disruption of sleep and circadian rhythms in the patients.

First, the validity of the ambulatory measurement of light exposure in hospital using wrist-level light monitoring devices was assessed. Wrist-worn devices were found to estimate eye-level light exposure adequately for the purposes of research, when compared to eye-level light monitoring devices. There was agreement between the two devices, with differences of less than 10 lux at eye-level light intensities less than 5000 lux. This is the first study to evaluate the validity of wrist-level monitoring devices for the measurement of light levels in the clinical setting. The results support their continued use for research purposes.

I then investigated the relationship between the hospital lighting environment and lengths of stay of patients in a 12-month prospective audit in 654 postoperative cardiac patients. Median daytime light levels in the ward ranged from 8 lux to 406.7 lux. There was no relationship between these light levels and patients’ lengths of stay in the ward (p = .99).

Finally, I conducted the first randomised placebo controlled trial of the efficacy of morning light therapy for the amelioration of circadian and sleep disruption in postoperative cardiac patients. Sixty-one cardiac patients were randomised to receive either morning bright light therapy or placebo light therapy, administered between 7:30 a.m. and 9:30 a.m., for three days postoperatively. Sleep-wake cycles (monitored using actigraphy), circadian rhythms (monitored using 6-sulphatoxymelatonin sampling), mood (monitored using the Beck Depression Inventory) and patients’ lengths of hospital stay were assessed. There was no identifiable circadian rhythm in the mean 6-sulphatoxymelatonin excretion rates in the placebo group. In the light therapy group, there were identifiable rhythms in the mean postoperative 6-sulphatoxymelatonin excretion rates on postoperative days two and three (acrophases of 5:35 a.m. and 3:59 a.m., respectively). Postoperatively, placebo patients excreted significantly less 6-sulphatoxymelatonin overnight than they did preoperatively (mean difference 261.1 ng/h, 95 % CI = 18.4-503.9, p = .03). There was no significant
difference in preoperative and postoperative excretion rates in the light therapy group (mean difference = 111, CI = -95.1-417.1, p = .7). However, I was unable to detect a significant improvement in postoperative sleep quality or quantity in the light therapy group. There was also no detectable difference in postoperative length of hospital stay and in mood scores between the two groups.

These results indicate that in this poorly lit clinical setting, there is no relationship between length of hospital stay and ambient light levels. Morning light therapy may entrain the circadian rhythms of postoperative cardiac patients, but the results did not translate into obvious clinically important benefits. Further investigation of this therapy is warranted.
Acknowledgements

Completing this thesis has been a lovely and interesting, if somewhat stressful, experience. During the course of my doctoral program, I was fortunate to have two gentlemen guiding me. Firstly, I would like to express my special thanks to my primary supervisor, Dr Guy Warman for his ideas, his guidance and his eternal patience. I would like to thank Professor Alan Merry for assisting me in the final write-up. Unfortunately, my love of compound nouns remains unwavering.

I gratefully acknowledge the University of Auckland and the Velux Stiftung Foundation. The University of Auckland Doctoral Scholarship and the Velux Stiftung Doctoral Stipend made it possible for me to conduct this research.

I am extremely grateful to the members of the Department of Anaesthesiology. All of you have been incredibly supportive and I have enjoyed our time immensely. In particular, I would like to thank Debbie Beaumont for her patience and her smiles.

I would like to thank the following people for their help over the course of my program: Dr James Cheeseman for his help with study design and proofreading, Dr David Cumin for his assistance with the cosinor analysis, Jacqueline Hannam for her considerable support and assistance over the years and especially in completing the final product, Dr Daniel Devcich for his assistance with the write up and, of course, Dr Matthew Pawley for his statistical expertise. Mirjam Guesgen and Kerry-Lee de Villiers assisted with data collection.

I would also like to thank Dr Deborah Sloboda and Ms Rachna Patel of the Liggins Institute. They were kind enough to let me use their facilities, and to teach me everything I needed to know, and more, about ELISAs. Thanks to Dr Craig Millar for allowing me to use his lab.

The CVICU and ward staff on Level 4 played a key role in the successful completion of the research described here. Their good-natured patience and dedication made it possible for me to finish my Pee-hD. The participants in the trials described in this thesis were kind enough
to give something of themselves, literally and figuratively, during a difficult and painful time in their lives. I am incredibly grateful to them all!

In my years with this department, I have met some lovely people. Guy, Mat, James, Elaine, Deb, David, Kylie and Nic, long may the coffees and drinks continue. Jacqui - I’m afraid Jani will just have to take over the world from an alternative operational base.

My family and friends have been consistently patient and supportive. I especially thank my parents, António and Alceste Jardim for their steadfast confidence and support.

Lastly, I’d like to thank my partner, Glenn, for everything. This would not have been possible without you.
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# Glossary

**Acrophase**
The time at which a cycle peaks. In the context of this thesis, it specifically refers to the peak of the cosine wave fitted to 6-sulphatoxymelatonin excretion data.

**Amplitude**
The difference between the peak and the mean value of a wave.

**Circadian rhythm**
An endogenous biological rhythm with a 24 hour period.

**Coefficient of determination**
A “goodness of fit” indicator; a descriptor of how well the datapoints fit a curve.

**Cosinor analysis**
A least squares method of fitting a sine wave.

**Entrainment**
The synchronization of the period of the endogenous biological rhythm to the period of an exogenous environmental cue.

**Fragmentation index**
The ratio of time spent awake to time spent asleep.

**General anaesthesia**
A pharmacologically induced and reversible state of unconsciousness which is coupled with a decreased response to stimuli.

**Interdaily stability**
A non-parametric circadian rhythms analysis variable that quantifies the variability of the rest-activity rhythm between days.

**Intradaily variability**
A non-parametric circadian rhythms analysis variable that quantifies the frequency and extent of transitions between rest and activity.

**Mean activity score**
The mean value of the activity counts per minute for an actigraphically derived sleep interval.

**Peak-to-trough amplitude**
The difference between the peak and trough of the rhythm.

**Phase**
A specific time point within a period.

**Phase advance**
The lengthening of the period of a rhythm in response to a stimulus.

**Phase delay**
The shortening of the period of a rhythm in response to a stimulus.

**Phase response curve**
The differential change in circadian phase caused by a single zeitgeber pulse, plotted as a function of time.

**Relative amplitude**
A non-parametric circadian rhythms analysis variable used to quantify the amplitude of the rest-activity rhythm as the ratio of the difference between the most active ten-hour period and the least active five-hour period, and the sum thereof.
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Sleep</td>
<td>A periodical state of quiescence, in which there is minimal processing of sensory information and no interaction with conspecifics or the environment.</td>
</tr>
<tr>
<td>Sleep bouts</td>
<td>The number of episodes of uninterrupted sleep within a sleep interval.</td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>The ratio of the time spent asleep to the interval duration (expressed as a percentage).</td>
</tr>
<tr>
<td>Sleep homeostat</td>
<td>The innate regulation of sleep need.</td>
</tr>
<tr>
<td>Sleep onset latency</td>
<td>The time between the start of a rest interval (from a sleep diary) and the actigraphically derived sleep start time.</td>
</tr>
<tr>
<td>Total activity score</td>
<td>The total number of activity counts between start and end of an actigraphically derived sleep interval.</td>
</tr>
<tr>
<td>Total sleep time</td>
<td>The total amount of time (in minutes) in a rest period spent immobile, consequently scored as “sleep”.</td>
</tr>
<tr>
<td>Wake After Sleep Onset (WASO)</td>
<td>The total amount of time (in minutes) spent awake between the start and end of the actigraphically derived sleep interval.</td>
</tr>
<tr>
<td>Zeitgeber</td>
<td>The exogenous environmental cues which entrain the biological rhythm.</td>
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## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>µg</td>
<td>Microgram</td>
</tr>
<tr>
<td>a.m.</td>
<td>Ante meridiem</td>
</tr>
<tr>
<td>Ach</td>
<td>Acetylcholine</td>
</tr>
<tr>
<td>ASA</td>
<td>American Society of Anesthesiologists</td>
</tr>
<tr>
<td>BDI</td>
<td>Beck depression inventory</td>
</tr>
<tr>
<td>cm</td>
<td>Centimetre</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>Cry/ cry</td>
<td>Cryptochrome</td>
</tr>
<tr>
<td>CVICU</td>
<td>Cardiovascular intensive care unit</td>
</tr>
<tr>
<td>d</td>
<td>Day</td>
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<td>FI</td>
<td>Fragmentation index</td>
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<td>GABA</td>
<td>Gamma-aminobutyric acid</td>
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<td>Metre</td>
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<td>MAS</td>
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<td>nm</td>
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<td>NREM</td>
<td>Non-rapid eye movement</td>
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<td>NZDT</td>
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<td>Ventrolateral preoptic nuclei</td>
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<td>WASO</td>
<td>Wake after sleep onset</td>
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Co-Authorship Form

This form is to accompany the submission of any PhD that contains research reported in published or unpublished co-authored work. Please include one copy of this form for each co-authored work. Completed forms should be included in all copies of your thesis submitted for examination and library deposit (including digital deposit), following your thesis Abstract.

Please indicate the chapter/section/pages of this thesis that are extracted from a co-authored work and give the title and publication details or details of submission of the co-authored work.

The findings in chapter two were published in a peer-reviewed journal:


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<th>Nature of contribution by PhD candidate</th>
<th>Experimental design, study execution, data analysis, writing and revising of the final manuscript.</th>
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**CAUTHORS**

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<tr>
<td>Dr Matthew Pawley</td>
<td>Data analysis and revising of the final manuscript</td>
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<tr>
<td>Dr James Cheeseman</td>
<td>Writing and revising of the final manuscript</td>
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<tr>
<td>Miss Mirjam Guergan</td>
<td>Study execution.</td>
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<td>LOR Chris Steele</td>
<td>Providing encouragement and reviewing of the final manuscript.</td>
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<tr>
<td>Dr Guy Warman</td>
<td>Experimental design, analysis, writing and revising of the final manuscript.</td>
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**Certification by Co-Authors**

The undersigned hereby certify that:
- the above statement correctly reflects the nature and extent of the PhD candidate's contribution to this work, and the nature of the contribution of each of the co-authors; and
- in cases where the PhD candidate was the lead author of the work that the candidate wrote the text.

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Chapter 1. General introduction

The primary objective of the work described in this thesis was to determine whether light therapy can reduce circadian and sleep-wake cycle disruption in postoperative cardiac patients. To address this question, I conducted a stepwise investigation. I described the hospital ambient lighting environment, and subsequently determined the relationship between the light levels in different bedspaces and postoperative cardiac patients’ lengths of hospital stay. Finally, I conducted an interventional randomised placebo controlled trial of morning bright light therapy in postoperative cardiac patients.

This chapter serves as an introduction to the following topics: (a) sleep, (b) the control of sleep and (c) circadian rhythms. The potential consequences of disrupting circadian rhythms and sleep for overall health, and in particular for recovery from surgery, are discussed.
1.1. Sleep

This thesis deals with sleep, and so a basic understanding of sleep, its control and its functions is necessary. In particular, it is relevant to discuss sleep in the hospital environment and the consequences of poor sleep.

Sleep has been defined, by the sleep researcher Alexander A. Borbély (p 17, (Borbély, Sejnowski et al. 2000)), as:

“a periodical state of quiescence, in which there is minimal processing of sensory information and no interaction with conspecifics or the environment”.

While accurate, this definition provides little detail about what sleep is or what it really does. Sleep-like states have been identified in every living thing from simple eukaryotes such as nematodes (Caenorhabditis elegans) to humans (Raizen, Zimmerman et al. 2008). In humans, regular sleep of good quality has been shown to be essential. Chronic sleep deprivation adversely affects day-to-day functionality, subjective well-being and emotional stability. Chronic and acute sleep deprivation can both lead to dysfunction of metabolism and immunity (Altena, Van Der Werf et al. 2008; Meerlo, Mistlberger et al. 2009).

1.1.1. Sleep architecture

The 90 minute (min) sleep cycle is broadly structured into two parts: non-rapid eye movement sleep (NREM) and rapid eye movement sleep (REM) (Figure 1:1).
Figure 1:1
An example hypnogram showing the architecture of the sleep stages at the beginning and the end of the nightly consolidated sleep period.

Note: W indicates wake, 1 indicates NREM sleep Stage 1, 2 indicates NREM sleep Stage 2, 3 indicates NREM sleep Stage 3 (previously separated into Stages 3 and 4, as of 2007 it is all categorised as one combined stage) and R indicates REM sleep (Medicine 2007). The blue A line indicates that in the early portion of the night non-rapid eye movement (NREM) sleep stage three dominates the sleep cycle. The blue B line indicates that in the latter portion of the night the sleep cycle is dominated by rapid eye movement (REM) sleep.

NREM sleep is categorised into three separate stages (Medicine 2007). It is primarily characterised by a low frequency electroencephalogram (EEG) which indicates a reduction in brain activity (Medicine 2007). Stage one of NREM sleep is the first and lightest stage of sleep, lasting on average seven minutes (Evans and French 1995). Characteristics include EEG theta waves (frequency oscillation of 6 – 10 Hertz (Hz)) myoclonic jerks, drowsiness, reduced awareness of surroundings and the start of a decrease in core body temperature (Lukasiewicz-Ferland 1987; Evans and French 1995; Parker 1995; Lee 1997). Stage two is the stable transition phase where the eyes begin gradual rolling movements and metabolism slows (Grant and Kell 1974; Landis 1988; Lee 1997). People are still easy to awaken during this 15 – 20 min period (Grant and Kell 1974; Landis 1988; Lee 1997). The stage two EEG is characterised by K-complexes and sleep spindles. Stage three is the delta wave stage
(frequency oscillation of 0-4 Hz), known as slow wave sleep (SWS) (Grant and Klell 1974; Landis 1988; Parker 1995; Lee 1997). In stage three muscle tone decreases, vital signs continue to slow and sleep deepens. Fifteen to 20 min after falling asleep the parasympathetic nervous system is in control and oxygen consumption is reduced (Hayter 1980; Lukasiewicz-Ferland 1987; Edwards and Schuring 1993; Evans and French 1995; Krachman, D'Alonzo et al. 1995). After periods of sleep deprivation, stages one and two are shortened and the cycle switches rapidly to SWS.

REM sleep is characterised by low voltage, high frequency EEG, muscle atonia and rapid eye movements. In a standard 90 min sleep cycle, REM sleep follows NREM sleep. In a consolidated sleep period (for example, an overnight sleep period with several consecutive cycles) the ratio of the duration of REM sleep to NREM sleep within each cycle increases as the sleep period progresses (Figure 1:1).

1.1.2. The functions of sleep

The frequency and duration of sleep may vary, but sleep has been identified in multiple organisms. Yet, a satisfactory answer to the question “Why do we sleep?” still escapes us (Lyamin, Mukhametov et al. 2002; Raizen, Zimmerman et al. 2008). As we understand something of the neuroanatomy of sleep and the structure of the sleep cycle, it is possible to discuss potential functions of sleep. Memory consolidation, predatory avoidance, growth, development and restoration are some. Three of the primary functions are discussed below.

1.1.2.1. Growth and development

A meta-analysis of quantitative sleep variables has shown that across the human lifespan the need for sleep decreases linearly with age and children require more sleep than adults (Ohayon, Carskadon et al. 2004). These changes indicate a role for sleep in growth and development. It has been suggested that sleep architecture marks and directs the course of brain maturation. REM sleep deprivation in rats aged 16 days (d) has been shown to decrease long term potentiation stability while adolescent (44 d) rats remained unaffected (Lopez, Roffwarg et al. 2008). This led to the conclusion that deprivation of REM sleep in early life
negatively affected hippocampal development, possibly hindering expression of mature synaptic components and indicating a role for REM sleep in the maturation of neuronal circuits (Lopez, Roffwarg et al. 2008). In children, developmental domains have been shown to correlate with chronic sleep deprivation in children: behavioural/social adequacy, cognitive performance (measured by picture vocabulary and intelligence testing), and body mass. Short nocturnal sleep (< 10 hours (h)) in early childhood has been correlated with high hyperactivity-impulsivity scores (22.2 % versus 11.2 % of children sleeping 10 h ($p = .01$)). It has also been associated with low performance on cognitive tests (41 % of children who slept < 10 h performed poorly compared to 16.6 % of children who slept 10 h ($p = .01$) and compared to 13.5 % of children who slept 11 h ($p = .001$)), and with weight gain/obesity (with higher body mass indices (BMI) reported in 22.1 % of short sleepers versus 10 % of 11 h sleepers) at 6 years (y) of age (Touchette, Petit et al. 2007; Touchette, Petit et al. 2008). The evidence suggests a role for sleep in growth and development which is worthy of further investigation.

1.1.2.2. Restoration

Sleep has been shown to play a role in immunity and recovery from disease. Immune function has been shown to decline following acute sleep deprivation. A PubMed search using the search term: “‘sleep deprivation’ AND ‘immunity’” yielded 43 results, of which 11 were original studies showing a relationship between (both chronic and acute) sleep deprivation and depressed immune function in humans (Palmblad, Petrini et al. 1979; Moldofsky, Lue et al. 1989; Irwin, Mascovich et al. 1994; Irwin, McClintick et al. 1996; Shearer, Reuben et al. 2001; Dimitrov, Lange et al. 2007; Hui, Hua et al. 2007; Okun and Coussons-Read 2007; Faraut, Boudjeltia et al. 2011; Fondell, Axelsson et al. 2011; Patel, Malhotra et al. 2012). Three of these studies examined the effects of chronic sleep deprivation on the adult human immune system, finding an increase in inflammatory markers (macrophage complement component-reactive protein (C-reactive protein), tumour necrosis factor receptor subunit 2A, N-methyl-D-aspartate receptor subunit 2B, α-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid receptor subunit 1, Post-synaptic density protein 95 and calcium/calmodulin Kinase II were less than those in age-matched control groups.

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1 N-methyl-D-aspartate receptor subunit 2A, N-methyl-D-aspartate receptor subunit 2B, α-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid receptor subunit 1, Post-synaptic density protein 95 and calcium/calmodulin Kinase II were less than those in age-matched control groups.
factor-alpha (TNF-α)), a decrease in natural killer cell numbers and increased risk of pneumonia (Okun and Coussons-Read 2007; Fondell, Axelsson et al. 2011; Patel, Malhotra et al. 2012). Eight studies explored the effects of acute sleep deprivation on the adult human immune system, reporting decreased natural killer cell numbers and activity, increased inflammatory markers, decreased deoxyribonucleic acid (DNA) synthesis and changes in sleep architecture (Palmblad, Petrini et al. 1979; Moldofsky, Lue et al. 1989; Irwin, Mascovich et al. 1994; Irwin, McClintick et al. 1996; Shearer, Reuben et al. 2001; Dimitrov, Lange et al. 2007; Hui, Hua et al. 2007; Faraut, Boudjeltia et al. 2011). Although all eleven studies reported indicate a relationship between sleep disruption and decreased immune function, they were conducted in healthy, homogeneous populations, and that may limit their generalisability.

In two further studies, results also indicate that sleep deprivation may negatively affect immune function. Patients vaccinated against hepatitis A, and subsequently deprived of one night of sleep, generated half as many antibodies as control patients (Lange, Perras et al. 2003). A study of 1477 people showed that regular consolidated sleep cycles of fewer than six hours were associated with increased incidences of diabetes mellitus (a purported 32.8% of normal sleepers (≤ 5 h) versus 18.2% of mean sleepers (7-8 h) (p = .01)) (Gottlieb, Punjabi et al. 2005).

The results of this small collection of studies indicate that chronic and acute sleep deprivation may negatively affect the homeostasis of the immune system.

1.1.2.3. Memory consolidation

The ability to encode and store information and experiences in the brain is known as “memory”. The processing of memories involves encoding and consolidation (Bledowski, Kaiser et al. 2010). Specific events or experiences are stored (encoding) and these are then thought to be regularly processed and analysed (consolidation) (Walker 2008; Bledowski, Kaiser et al. 2010). The initial process of encoding memories may require morphological changes at a synaptic level. The consolidation of both declarative and procedural memory has been shown to require both a synaptic component and a time-dependent “whole systems”
process. The continuous encoding of new memories is also thought to rely on the regular recategorisation and reprocessing of current memory. This continuous subconscious event consolidation is thought to reduce the incidence of memory decay.

It has been proposed that both declarative (episodic, semantic) memories and procedural (implicit, skill) memories are integrated into the cortex through a sleep-dependent process (Born and Wagner 2004; Frankland and Bontempi 2005). Contemporary models of memory formation suggest that experiences are initially encoded in parallel in both cortical and hippocampal regions. The memories are then replayed during sleep to strengthen their position in the cortex, and consequently strengthen their permanence. The evidence for these theories is primarily correlative – where behavioural studies indicate a positive effect of sleep on memory. For example, in one trial 46 patients were tested for their ability to recall words after a nap (Saletin, Goldstein et al. 2011). It was found that those in the “sleep group” recalled more than twice the number of words than those in the “no sleep” group (Saletin, Goldstein et al. 2011). There is evidence that both procedural memory (tested with mirror tracing tasks) and declarative memory (tested with word-pairing tasks) are well preserved after short term sleep restriction. In 88 healthy adolescents, participants were tested after a four day sleep restriction protocol (twice, at two days and four weeks) and results indicated that the participants’ memory preservation remained (Voderholzer, Piosczyk et al. 2011). Stickgold et al. (2000) showed that visual discrimination learning appears to require post-training sleep for memory integration (Stickgold, James et al. 2000). One hundred and thirty-three subjects were taught, then tested between three hours and seven days post-learning (Stickgold, Whidbee et al. 2000). Of those subjects, 11 were sleep-deprived (Stickgold, Whidbee et al. 2000). Results indicated that testing on the same day showed no significant improvement in learning (assessed as an improvement in performance speed, in milliseconds (ms)), when re-tested (-0.49 ms, $p > .05$) (Stickgold, Whidbee et al. 2000). Testing after one night’s sleep showed improvement in learning (12.6 ms, $p < .0001$) (Stickgold, Whidbee et al. 2000). Those patients showed a significant improvement in learning for up to four days after training (18.9 ms, $p < .05$), while those deprived of one night’s post-training sleep (followed by two full nights of recovery sleep) showed no
significant improvement (3.9 ms, \( p > .3 \)) (Stickgold, Whidbee et al. 2000). Control subjects improved significantly (18.9 ms, \( p < .005 \)) (Stickgold, Whidbee et al. 2000).

There is also evidence to indicate that the dependence of memory on sleep may be directly related to the architecture of the sleep-wake cycle. It has been suggested that slow wave sleep (SWS) may stabilise declarative memory and rapid eye movement (REM) sleep may stabilise procedural memory (Plihal and Born 1997).

1.1.3. The control of sleep

Sleep has been shown to be controlled by two separate, but interactive, processes; the sleep homeostat and the circadian clock. Borbély et al.(1982) first proposed that the sleep homeostat and circadian clock processes contribute equally to the control of sleep-wake cycles (Borbély 1982). The study of sleep disruption must account for the interactions of these two functionally and anatomically distinct processes (Dijk and Czeisler 1994).
Chapter 1: General introduction

Figure 1.2
The control of sleep-wake cycles by the circadian clock and the sleep homeostat.

Note: In this diagram the black line indicates the circadian sleep drive, the red line indicates the sleep homeostat sleep drive and the blue line indicates their combined effects. The circadian sleep drive is based on time of day and is highest in the morning and lowest in the evening. The sleep homeostat sleep drive is based on the amount of time spent awake and steadily increases with prolonged wakefulness. The drive for sleep increases the longer you stay awake, as the pressure applied by the circadian clock, which keeps us awake and active, lessens.

1.1.3.1. The sleep homeostat

The sleep homeostat measures our propensity for sleep (Borbély 1982). The more time one spends awake, the greater the resultant drive for sleep applied by the sleep homeostat. Thus, the homeostatic drive for sleep is lowest straight after waking and increases with time spent awake, peaking with prolonged sleep deprivation (Borbély 1982). The sleep homeostat controls the depth of sleep, the length of the individual stages of the sleep cycle and the duration of the consolidated sleep period (Borbély 1982).

1.1.3.2. The neurochemistry of the sleep homeostat

The detailed neuroanatomy and neurochemistry of sleep (both NREM and REM) are somewhat beyond the scope of this thesis. However, as sleep and general anaesthesia may
share some mechanistic pathways, the following brief outline of the neurochemistry of sleep is relevant.

The modulation of arousal comes from multiple neuronal groups projecting to the thalamus and the brainstem. Projections extend from cholinergic, monoaminergic and lateral hypothalamic orexin cell groups. NREM sleep is generated and controlled primarily through the inhibition of basal forebrain wakefulness promoting neurons. In sleep promoting pathways the ventrolateral pre-optic nuclei (VLPO) of the anterior hypothalamus project gamma-aminobutyric acid (GABA) and small amounts of galanin to all the arousal promoting areas (Figure 1:3).
Figure 1:3  
A simplified diagram of the arousal promoting pathways.

Note: The perifornical area (PeF) produces orexin (OX), the TMN (tuberomamillary nucleus) produces histamine (His), the LC (locus coeruleus) produces noradrenaline (NA), the tegmentum produces acetylcholine (ACh) and the DR (dorsal raphe nuclei) produces serotonin (5HT). In the sleep promoting pathway, the ventrolateral pre-optic nuclei (VLPO) of the anterior hypothalamus projects gamma-aminobutyric acid (GABA) to all the arousal promoting areas. During wakefulness, the REM OFF neurons located in the LC are inhibited by ACh produced by the cholinergic REM ON neurons in the tegmentum. In NREM sleep, these same REM OFF neurons are activated; during REM sleep the process is reversed and REM ON neurons fire and REM OFF are once again inhibited. The figure is adapted from Nelson et al. (2002), Fuller et al. (2006) and Pal and Mallick (2007) (Nelson, Guo et al. 2002; Fuller, Gooley et al. 2006; Pal and Mallick 2007).
1.2. The circadian clock

Sleep-wake cycles are controlled by the sleep homeostat and the circadian clock. In this section, the molecular mechanisms of the circadian clock, its control and its functions are discussed. Methods of marking the activity of the circadian clock and the consequences of disrupting the circadian clock are also considered.

Circadian rhythms are ubiquitous in eukaryotes and have also been identified in prokaryotes, such as cyanobacteria (*Synechococcus elongatus*) (Bell-Pedersen, Cassone et al. 2005; Kim, Vinyard et al. 2012). The circadian clock controls coordination and timing of activities, daily and seasonally. It moderates biological function and behaviour, and enables time sense. For our purposes, an important function of the clock is its control of sleep timing.

The mammalian circadian clock lies in the suprachiasmatic nuclei (SCN) (Moore and Klein 1974; Klein and Moore 1979). The SCN are two structures located in the anterior hypothalamus, above the optic chiasm. The master pacemaker is composed of approximately 20,000 single-cell oscillators that are self-contained. These cells synchronise to each other, to various peripheral cellular oscillators and to external environmental cues (Welsh, Logothetis et al. 1995). Together, the oscillators contribute to the control of timing of a multitude of physiological processes (Welsh, Logothetis et al. 1995).

The endogenous clock produces a circadian rhythm with a period approximating, but not equal to, 24 h (Saunders 1977). It is evident in several clock outputs (Saunders 1977). The master clock is entrained to 24 h by exogenous cues or zeitgeber (Aschoff and Wever 1962; Colin, Timbal et al. 1968). In humans, the principal zeitgeber is light (Section 1.2.1) (Aschoff and Wever 1962; Colin, Timbal et al. 1968).

1.2.1. Mammalian molecular clock mechanisms

The mammalian molecular clock is made up of interactive positive and negative transcriptional and translational feedback loops (Figure 1:4) (Reppert and Weaver 2001). Molecular analysis of the mechanisms of the circadian clock of the common fruit fly (*Drosophila melanogaster*) has highlighted similarities between the metazoan and
mammalian systems (Hsu, Zhao et al. 1996; Todo, Ryo et al. 1996). Homologues of *Drosophila* clock genes have been identified in mice, with basic significant similarities in the overall mechanisms of the clock.

![Diagram of mammalian circadian clock](image)

**Figure 1:4**
The primary feedback loops governing the mammalian circadian clock.

**Note:** Per indicates period, Cry indicates cryptochrome, Ckes/δ indicates casein kinase epsilon/delta, BMAL1 indicates Aryl hydrocarbon receptor nuclear translocator-like (or ARNTL) and CLOCK indicates circadian locomotor output cycles kaput. The intrinsic period length is governed by the length of time required for the processes of transcription, translation and translocation to occur. The proteins (PER and CRY) are translated before moving into the cytoplasm. Upon forming a protein heterodimer, the pair translocates into the nucleus and interacts with the transcription factors BMAL1 and CLOCK. These transcription factors then drive the transcription and subsequent translation of the genes Per and Cry. The figure is adapted from Schulz *et al.* (2009) (Schulz and Steimer 2009).

The feedback loops dynamically regulate the relevant proteins and genes. The basic helix-loop-helix PER-ARNT-SIM (bHLH-PAS) heterodimers, CLOCK and BMAL1 transcription factors, drive the transcription of the three period (Per) genes and the two cryptochrome (Cry) genes (Antoch, Song *et al.* 1997; King, Zhao *et al.* 1997; Gekakis, Staknis *et al.* 1998; Kume, Zylka *et al.* 1999; Zheng, Albrecht *et al.* 2001). Once translated, PER proteins, such as PER2, accumulate in the cytoplasm and are phosphorylated by casein kinases (δ and ε) into an unstable form of the protein. These phosphorylated protein forms are degraded through ubiquitylation. Later in the subjective day CRY proteins accumulate in
the cytoplasm. The phosphorylated PER form stable heteromultimeric proteins in the cytoplasm with CRY. The protein complex then translocates into the nucleus where the CRY protein of the multimeric complex then negatively interacts with CLOCK and BMAL1 to inhibit transcription (negative feedback loop) (Antoch, Song et al. 1997; King, Zhao et al. 1997; Gekakis, Staknis et al. 1998; Kume, Zylka et al. 1999; Zheng, Albrecht et al. 2001). BMAL1 production is also thought to be the rate limiting step for the entire clock interaction. Thus, we have the negative and positive feedback loops, with the BMAL1 and PER/CRY expressed at different phases and regulation of the negative feedback loop by the positive feedback loop. It has been proposed that the loop begins at the start of the circadian day, with the transcription of Per and Cry (Reppert and Weaver 2001). The time required for the loop to complete is thought to determine the period of behaviour. In an individual entrained to the 24 h day, this loop would take 24 h to complete (Duffy and Wright 2005). In normal free-running individuals, it would take 24.3 h to complete (Aschoff and Wever 1962). Where biochemical loops take, for example, 23 h or 24 h to complete, under constant conditions, the resultant behavioural cycles would last 23 h and 24 h, respectively.

1.2.2. Entrainment of the clock

The endogenous period of the human circadian clock deviates from a strict 24 h period. It is adjusted to 24 h on a daily basis by exogenous stimuli (Table 1:1). Light is the most important zeitgeber of the human circadian clock (Elmore, Betrus et al. 1994). The transitions of the light-dark cycle from light to dark and dark to light are central to entrainment.
Table 1:1
Examples of zeitgeber that are known to synchronise the human circadian clock.

Note: Ambient light signals are the main synchronisers of the clock. Pharmacological interventions may include exogenous melatonin.

To entrain, the clock changes its active velocity, shifting its phase according to the exogenous signal received. It may advance its phase, shortening the clock cycle, or it may delay its phase and lengthen its cycle. A functional clock will, without external input, continue to produce a robust rhythm.

Light enters the retina and stimulates the non-visual circadian photoreceptor melanopsin (which is maximally sensitive to blue light of up to 476 nm) in the retinal ganglion cells. This lighting information is then conveyed to the SCN. The major input pathway is the retino-hypothalamic tract (RHT) (Moore, Speh et al. 1995). The main neurotransmitter modulating this pathway is glutamate, with two peptides (substance P and pituitary adenylate cyclase-activating peptide) mediating the entrainment process (Ebling 1996; Chen, Buchanan et al. 1999; Hamada, Yamanouchi et al. 1999). Different pathways may be primary modulators of different inputs. For example, the indirect intergeniculate leaflet of the lateral geniculate nucleus, and the raphe nuclei, are thought to play roles in mediating circadian phase shifts that are not driven by light stimuli (Antle and Mistlberger 2000; Byku and Gannon 2000).

1.2.2.1. Phase response curves

The effects of zeitgeber on the activity of the circadian clock have been shown to differ depending on circadian phase. One may predict the effect of timed exposure to a zeitgeber,
using circadian markers to monitor clock activity (Section 1.2.3). In 1961, Patricia DeCoursey plotted the phase-dependent sensitivity to light of the biological clock in the flying squirrel (*Glaucomys volans*) using a phase response curve (PRC) (DeCoursey 1961). The PRCs she pioneered map the phase of the clock when it encounters an input variable (usually a light pulse, but there are PRCs to a number of *zeitgeber* including melatonin) to the resultant phase shift (Figure 1:5).
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1.2.3. Biological markers indicating clock activity

The circadian clock has several recognized physiological and behavioural outputs. These include cyclical variations in the production of hormones such as melatonin and cortisol, and changes in core body temperature. The mechanisms by which these variations are mediated are not completely elucidated. The SCN projects to the paraventricular nucleus of the hypothalamus. The SCN uses three major neurotransmitters to mediate its control of the timing of physiological processes: glutamate, vasopressin and GABA. Vasopressin was the first to be identified, with a clear circadian rhythm measured in the cerebrospinal fluid (Vandesande, DeMey et al. 1974; Burlet and Marchetti 1975; Swaab, Pool et al. 1975).
Humoral mediators of clock activity (outputs) include TNF-α, melatonin and prokineticin-2 (Kramer, Yang et al. 2001; Arendt 2005; Cheng, Bittman et al. 2005). The precise nature of the relationships between the SCN and all its outputs is yet to be fully elucidated, but some outputs have been extensively studied. Because the circadian clock is not a directly measurable entity, these outputs are effective proxies for clock activity. They oscillate with a rhythm stimulated directly by the clock and their profiles can be used to determine variables such as clock phase or amplitude. Some well-described markers are reviewed below.

1.2.3.1. Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is a hormone synthesized in the pineal gland, in the absence of light (Figure 1:6) (Lerner, Case et al. 1960; Wurtman, Axelrod et al. 1963; Lynch, Jimerson et al. 1978).
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Figure 1:6
The synthesis of melatonin, the circadian marker.

Note: Melatonin is synthesised from tryptophan in the pineal gland, in the absence of light (Ma, Idle et al. 2005). The primary precursor of melatonin is tryptophan; the enzymes tryptophan-5 hydroxylase and 5-hydroxytryptophan decarboxylase synthesise it into serotonin, a secondary melatonin precursor. The enzymes arylalkylamine-N-acetyltransferase and hydroxyindole-O-methyltransferase complete the synthesis into the hormone melatonin.

Melatonin is a marker of the circadian clock and is the primary humoral method of signalling time of day, and year. Its primary role is thought to be as a sleep-inducing hormone in the regulation of timing of sleep-wake cycles (Arendt 2005). Other proposed functions of melatonin include the control of glucose homeostasis by timing insulin release from the pancreatic β-cells and the regulation of parasympathetic vagal suppression (Maestroni 1998; la Fleur, Kalsbeek et al. 2001; Mutoh, Shibata et al. 2003; Scheer, Van Montfrans et al. 2004).

In entrained individuals, melatonin levels are low during the day (< 10 picograms per millilitre (pg/ml)) and rise in the evening to peak between 1:00 a.m. and 3:00 a.m. (Arendt 2006). In the absence of a light-dark cycle, a rhythm in melatonin production still exists, maintained by the clock. It is influenced by endogenous and exogenous non-photic stimuli, such as postural changes (Lerner, Case et al. 1960; Wurtman, Axelrod et al. 1963; Lynch,
Jimerson et al. 1978; Deacon and Arendt 1994; Haimov and Lavie 1997; Barrenetxe, Delagrange et al. 2004). Melatonin is produced and secreted into the circulation when there is no light present (and thus is considered a “darkness” hormone); light stimuli to the SCN halt melatonin production (Lerner, Case et al. 1960; Wurtman, Axelrod et al. 1963; Lynch, Jimerson et al. 1978). One of the SCN’s sympathetic responses to light entrainment is a phase shift in the rhythm of melatonin production (Lerner, Case et al. 1960; Wurtman, Axelrod et al. 1963; Lynch, Jimerson et al. 1978).

A number of medications and foods may also influence the synthesis and release of melatonin. There are foods that have been shown to increase the substrate (tryptophan) concentration for the production of melatonin, such as banana, pineapple and orange (Johns, Johns et al. 2013). Dopamine increases the synthesis and release of melatonin from the pineal by binding to the D4 receptors (Gonzalez, Moreno-Delgado et al. 2012). Similarly, β-adrenergic drugs can also bind directly to the pineal and consequently increase plasma melatonin levels (Gonzalez, Moreno-Delgado et al. 2012). Aspirin has been shown to decrease the prostaglandins required for the synthesis of melatonin (Murphy, Myers et al. 1996). In the clinical environment, the influence of preoperative and postoperative medications on melatonin production should be considered.

Melatonin is metabolised mainly through hepatic cytochrome P450 enzymatic metabolism (Figure 1:7). It is excreted in the urine primarily as the metabolite 6-sulphatoxymelatonin. As a marker, the timing and amplitude of the rhythm of 6-sulphatoxymelatonin correlates well with that of serum melatonin (Arendt 2005). The metabolism of melatonin can also be influenced by the effects of food and medication on the activity of the liver enzymes (Braam, van Geijlswijk et al. 2010). There are a number of medications which can act as competing substrates, such as ondansetron (an anti-emetic regularly administered to postoperative cardiac patients) and paracetamol that are similarly metabolised by isozomes in the CYP450 family and that are consistently prescribed to postoperative cardiac patients (Papagiannidou, Skene et al. 2014). There are also medications that inhibit the CYP450s, which would reduce the metabolism and the subsequent excretion, such as amiodarone, an antiarrhythmic agent commonly used in postoperative cardiac patients (Ohyama, Nakajima et al. 2000).
Abnormal liver function can also result in changes in the levels of the cytochrome P450 enzymes that metabolise melatonin, and thus decrease the levels of 6-sulphatoxymelatonin excreted (Facciola, Hidestrand et al. 2001; Ma, Idle et al. 2005). The accurate measurement of melatonin and its metabolite 6-sulphatoxymelatonin is influenced by diet, lifestyle, medications and organ function.
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Figure 1:7
The metabolism of melatonin, the circadian marker.

Note: Melatonin is metabolised primarily through 6-hydroxylation, where it is excreted in the urine as 6-sulphatoxyrmelatonin. It is also O-demethylated and excreted as N-acetyl-5-hydroxytryptamine, and deacetylated into a range of minor metabolites including pinoline, bufotenine, 5-hydroxytryptamine and N,N-dimethyltryptamine (Adapted from Ma et al., (2005)).

1.2.3.2. Cortisol

The hormone cortisol is regularly produced by the adrenal cortex. Production levels and timing of release are influenced by the SCN (Scheer and Buijs 1999; Morton, Wood et al. 2005; Scheer, Van Paassen et al. 2002). Light stimulus of the SCN causes the adrenocorticotropic hormone to increase adrenal cortex production of cortisol (Morton, Wood et al. 2005). In contrast with the nighttime peak production of melatonin, cortisol peaks when melatonin is declining, around the time of awakening (Monk, Buysse et al. 1997; Scheer and Buijs 1999; Morton, Wood et al. 2005; Scheer, Van Paassen et al. 2002).

Cortisol plays significant roles in the immune system, in gluconeogenesis during the fasting state (the formation of glucose from a number of substrates), in anti-stress and anti-inflammatory pathways, among others (Fietta 2007; Bauer, Jeckel et al. 2009; Cutolo, Buttgereit et al. 2011). It prevents the release of inflammatory substances in the body, and spares glucose for the brain, releasing reserves and redirecting their use from less immediately important systems, such as the immune system. In the context of postoperative
healing, there is both an increase and a change in the pattern of production of cortisol following the stress of a major surgical intervention (Ebrecht, Hextall et al. 2004; Christian, Graham et al. 2006). The findings of Gogenur et al. (2007), for example, indicate an increase in plasma cortisol levels for at least 48 h after major abdominal surgery (Gogenur, Ocak et al. 2007). The daytime cortisol levels increased from median preoperative levels of 231nmol/L to 535 and 490nmol/L on postoperative days one and two, respectively (Gogenur, Ocak et al. 2007).

1.2.3.3. Core body temperature

Core body temperature also marks circadian clock activity. It increases during the day and decreases at night. The maximum temperature is reached in the subjective late afternoon/early evening and the minimum in the early subjective morning (approximately 3:00 a.m. in an entrained individual) (Van Someren 2006; Kräuchi 2007a).

The most important core body temperature regulators are changes in heat production and loss, which follow a circadian rhythm (Kräuchi, Cajochen et al. 2000; Van Someren 2006). Core body temperature is homeostatically regulated around 37 degrees Celsius (°C) (Kräuchi, Cajochen et al. 2000). Changes in heat production and loss are concomitantly regulated. The production of heat (at rest) depends on the metabolic activity of the inner organs (Van Someren 2006; Kräuchi 2007a). This heat producing core transfers heat, using the cardiovascular system, to the distal regions of the body, even at constant temperatures (Van Someren 2006; Kräuchi 2007a). As surface heat is lost to the environment at night, core body temperature drops because of the transportation of heat distally (Kräuchi, Cajochen et al. 2000; Van Someren 2006). Consequently, core body temperature rises during the day and drops at night in a periodic and predictable manner, reflective of the activity of circadian clock (Hanneman 2001). Changes in core body temperature are also influenced by behavioural activity, digestive processes and posture (Kräuchi, Cajochen et al. 2000; Van Someren 2006).
In addition to being a circadian marker, core body temperature is also thought to be directly involved in modulating sleep mechanisms. The control of sleep and wakefulness and the circadian control of core body temperature are thought to be interactive. SCN lesions have been shown to abolish any circadian rhythmicity, but body temperature and sleep interact even after lesioning of the SCN (Ralph, Foster et al. 1990; Baker, Angara et al. 2005). The exact mechanisms by which these interactions occur are yet to be elucidated. However, changes in skin temperature (warming through peripheral vasodilation) may hasten sleep onset, while changes in core temperature are actually less effective in reducing sleep onset latency (Kräuchi, Cajochen et al. 1999; Van Someren 2000). All these modifications occur within the normal skin temperature range (Van Someren 2000). Changes in skin temperature have been shown to modulate neuronal activation in temperature sensitive sleep modulating areas of the brain. At a cellular level, changes in the midbrain reticular formation, hypothalamus and cerebral cortex occur when the skin is warmed that are similar to those during sleep (van den Heuvel, Noone et al. 1998; Gilbert, van den Heuvel et al. 2004). These changes are under the autonomous control of the circadian system, but also vary in accordance with changes in behavioural activity (van den Heuvel, Noone et al. 1998; Gilbert, van den Heuvel et al. 2004). This may indicate a tertiary signalling pathway for the circadian control of sleep-wake timing, in addition to the neuronal and humoral pathways.

During physical activity more heat is produced (Kräuchi, Cajochen et al. 2000; Van Someren 2006). Thus, the usefulness of core body temperature as a marker of the clock is influenced by factors such as activity, posture and digestion potentially masking true circadian clock activity (Kräuchi, Cajochen et al. 2000; Hanneman 2001; Van Someren 2006). Purification models, constant routine and forced desynchrony are examples of methods to remove these masking factors and can provide satisfactory indicators of true circadian phase and amplitude (Van Someren, Swaab et al. 1999; Waterhouse, Weinert et al. 2000; Hanneman 2001; Van Someren 2006; Kräuchi 2007b).
1.2.3.4. The measurement of circadian clock markers

Several methods have been developed to accurately measure circadian clock markers.

Melatonin can be effectively measured in saliva, plasma and urine (as 6-sulphatoxymelatonin). The onset of melatonin production can be determined using the dim light melatonin onset (DLMO) technique (Wirz-Justice, Werth et al. 2002; Baehr, Eastman et al. 2003; Pandi-Perumal, Smits et al. 2007; Parry, Meliska et al. 2011). Regular sampling every 30-60 min from late afternoon to late evening in a dim light environment should show the rise of melatonin from baseline levels under the detectable limit to peaks of approximately 20-30 pg/ml (Wetterberg, Bergiannaki et al. 1999; Mahlberg, Tilmann et al. 2006). The sampling begins around four to five hours before the regular bedtime, commonly around 6.00 p.m. (Pandi-Perumal, Smits et al. 2007). The rise in plasma melatonin is considered normal when it begins between 7.00 p.m. and 10.30 p.m. (Lewy and Sack 1989). Melatonin declines near sleep offset (Lewy, Sack et al. 1995). When sampling to determine dim light melatonin onset, the saliva samples must be timed to avoid meals, with nothing consumed for 30 min before the sample, including water, so as not to contaminate or dilute the sample (Middleton 2006; Benloucif, Burgess et al. 2008). Saliva sampling also requires that the patients predict their bedtime and remain awake throughout their sampling time, which is not always possible postoperatively. Patients can also suffer from “dry mouth” after their operations, which can make the process of collecting the saliva difficult. There are several foods and medications which affect melatonin levels. Caffeine, chocolate and bananas (serotonin containing) raise melatonin levels. Monoamine oxidase inhibitors stimulate melatonin production. Aspirin has been shown to suppress melatonin levels. In the hospital setting, particularly with cardiac patients, medications such as aspirin are regularly used. Blood sampling for the measurement of melatonin may be more practical in a postoperative hospital environment. Postoperative haemodilution should be considered when plasma sampling in surgical patients (Linden 2003), but the amount of blood sampled is typically small (a minimum of 1.5 ml every 30 min) and not clinically important in adults. Immediate refrigeration of saliva and blood samples is critical because of the instability of melatonin.
Urinary 6-sulphatoxymelatonin sampling is ideal for determining 24 h overall output levels and adequately estimates the peak of the circadian rhythm (Middleton 2006). Sampling can be timed in large “bins”, every four hours during the day and a larger overnight bin (± 8 h). Urinary 6-sulphatoxymelatonin sampling is not as restrictive as plasma and saliva sampling; the metabolite is stable at room temperature for up to five days (Middleton 2006). This low frequency, stable sampling method is ideal for the clinical environment. The frequency of the collections makes it difficult to estimate phase as there can be up to eight hours between measurements in a complete, correct data collection. Other researchers have used catheters with some success, but that depends on the patient population and postoperative patient mobility (Gogenur, Middleton et al. 2007a). In cardiac patients, for example, the catheters are removed as soon as possible to encourage recovery and mobility.

Ambulatory measurement of core body temperature as a marker presents a number of options, of which two are most useful. The rectal temperature probe is very accurate and has a good range, but it is invasive and may even be intimidating equipment. Rectal temperature monitoring is considered the gold standard of ambulatory core body temperature monitoring, but patient compliance can be a problem. A more user-friendly option is the non-invasive ingestible temperature probe (although some patients may have difficulty swallowing the device). This probe, about the size of a large tablet (20 millimetres (mm) x 8 mm x 8 mm), is a radio transmitter which transmits core body temperature information (at 40.86 MHz) to a monitor (usually on the subject’s belt). The patient needs only to be able to swallow in order to have the unit collecting core body temperature data over several days.

**1.2.4. The consequences of circadian clock disruption**

The effects of circadian disruption on health are still being studied; to date prolonged circadian disruption has been shown to lead to sleep deprivation, stress, mood disruption, digestive disturbances, cardiovascular disease, infertility and immune dysfunction (Mahoney; Van Dongen and Belenky 2009; Viswanathan and Schernhammer 2009; Waage, Moen et al. 2009). Two common activities that have been shown to disrupt the circadian clock through a
change in the timing of zeitgeber are shift work and air travel (Brown, Pandi-Perumal et al. 2009; Coste and Lagarde 2009; Sack 2009).

Two prospective cohort studies, of 69269 women aged 42-67 y and of 107915 women aged 25-42 y (without diabetes, cardiovascular disease or cancer at baseline) found that rotating shift work was associated with increased incidences of self-reported type II diabetes, and elevated body weight (Pan, Schernhammer et al. 2011). A trial of 33 shift workers aged 27-62 y (compared with 89 controls aged 19-63 y) showed that shift workers had significantly higher hair cortisol levels (47.32 pg per milligram (mg) versus 29.72 pg/mg, \( p < .001 \)) (Manenschijn, van Kruysbergen et al. 2011). Further investigation showed that the significant differences were present in the younger shift workers (<40 y) (Manenschijn, van Kruysbergen et al. 2011). They reported higher cortisol levels (48.53 pg/mg hair cortisol versus 26.42 pg/mg hair cortisol, \( p < .001 \)) and a higher mean BMI (27.2 kilograms (kg) per square metre (m) versus 23.7 kg/m\(^2\), \( p < .001 \)) (Manenschijn, van Kruysbergen et al. 2011).

Travel, both east and west, has been shown to disrupt diurnal cortisol regulation (Doane, Kremen et al. 2010). Seven hundred and sixty-four healthy middle aged men who had travelled across up to three time zones provided cortisol samples the next day (upon waking, 30 min after waking, at 10:00 a.m., at 3:00 p.m., and at bedtime) (Doane, Kremen et al. 2010). These were analysed according to the number of time zones crossed and the direction of travel (Doane, Kremen et al. 2010). Results showed that eastward travel stimulated an increased cortisol awakening response and westward travel decreased cortisol awakening response (Doane, Kremen et al. 2010). Shorter travel distances (two hours) were enough to significantly affect the circadian clock (Doane, Kremen et al. 2010).

In animal studies, mice were subjected to repeated eight hour advances of the light-dark cycle every two days, and compared with a control group of mice kept in a 12 h:12 h light-dark lighting schedule (Filipski, Delaunay et al. 2004). The mice were assessed for differences in plasma corticosterone, clock protein mPer1 expression in the SCN, mouse ribonucleic acid (RNA) expression of clock genes mPer2 and mRev-erbα in liver and Glasgow osteosarcoma tumour growth (Filipski, Delaunay et al. 2004). This induced chronic circadian disruption,
ablated temperature rhythms and 24 h rest-activity cycles. It also led to significantly reduced mPer1 SCN expression \((p = .01)\) and serum corticosterone \((p < .001)\), as well as significantly reduced \(mPer2\) and \(mREV-erba\) in the liver (Filipski, Delaunay et al. 2004). Tumour growth in the mice subjected to circadian disruption was also accelerated \((p < .001)\) (Filipski, Delaunay et al. 2004).

### 1.2.4.1. Light therapy for seasonal affective disorder and depression

Therapy with light of varying wavelengths has been recommended as a treatment for some illnesses for over a century (Finsen 1895). In 1969, William Zung (of Zung Depression Scale fame) described the results of photic stimuli on depressed patients undergoing electroconvulsive therapy (Zung 1969). The first clinical trial of light therapy for the treatment of seasonal affective disorder (SAD) was in 1984 (Rosenthal, Sack et al. 1984). Since then light therapy has also been trialled as a treatment for other mood disorders (Wirz-Justice, Bucheli et al. 1986; Byerley, Brown et al. 1987). Severe bipolar depression and unipolar depression have been shown to respond to changing light levels and to active light therapy (Beauchemin and Hays 1996; Benedetti, Colombo et al. 2001; Lieverse, Van Someren et al. 2011).

The mechanisms of action of light therapy have not been fully elucidated, but some have been proposed. The basis of SAD is not exclusively circadian, but SAD is the most extensively studied target of light therapy, and thus is often the primary focus of mechanistic theories. The principal theories of the mechanisms of action are discussed below.

Lewy et al. (1987) first proposed that light therapy successfully treats SAD by phase advancing the circadian clock (Lewy, Sack et al. 1987).

Daytime serum melatonin levels have been shown to be higher in patients with SAD. Morning light therapy and seasonal change cause phase advances and decreases in the amplitude of the secretion of melatonin (Burgess, Fogg et al. 2004). Evening light therapy delays the secretion of melatonin. These effects are predictable according to the PRC (Section 1.2.2.1). Morning and evening bright light therapy both result in positive therapeutic outcomes for SAD, though (Avery, Kizer et al. 2001). It has been proposed by
Partonen et al. (1994) that the endogenous mediating effects of melatonin and serotonin may underscore both SAD and the efficacy of light therapy, independent of phase or time of day (Partonen 1994). Serotonin has been shown to increase in patients with non-seasonal and seasonal depression after light therapy (Partonen 1994). Patients with SAD have been shown to have enhanced serotonin transporter (a key pharmacological target in depression treatment) function (Willeit, Sitte et al. 2008). This has been shown to be ameliorated through bright light therapy (Willeit, Sitte et al. 2008). After light therapy, tryptophan depletion is associated with rebound depression (Lam, Zis et al. 1996).
1.3. The hospital environment

The hospital environment contains many factors that disrupt sleep and circadian rhythms.

1.3.1. Hospitalisation and sleep

Sleep disruption and deprivation has been identified as a problem in hospital, although the reported incidence varies. In three studies of adult ICU patients, subjective sleep complaints ranged from 42.9% to 59% of patients (Ayllon Garrido, Alvarez Gonzalez et al. 2007; Lee, Low et al. 2007; Hofhuis, Spronk et al. 2008). In a study by Little et al. (2012) of 116 patients, the patients were also assessed postdischarge, and 24% of patients reported lasting sleep disruption (Little, Ethier et al. 2012).

In-hospital sleep and circadian disruption can be triggered or exacerbated by multiple factors (Table 1:2).

<table>
<thead>
<tr>
<th>Influencing factors</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Environmental</td>
<td>Lighting, treatments and observations, and noise.</td>
</tr>
<tr>
<td>Psychosocial</td>
<td>Fear, anxiety, bereavement, financial stress, boredom and hyperarousal.</td>
</tr>
<tr>
<td>Physical/ Mental</td>
<td>Depression, presenting complaint, comorbidities, pain, medication, surgery and anaesthesia.</td>
</tr>
<tr>
<td>Demographic</td>
<td>Age, sex and ethnicity.</td>
</tr>
<tr>
<td>Behavioural</td>
<td>Routine, daytime napping, feeding times, meal quality and quantity.</td>
</tr>
</tbody>
</table>

Table 1:2
A list of factors, ranging from inherent to environmental, that have been shown to correlate with the sleep disruption of patients in hospital (Griffiths and Peerson 2005; Krishnan and Hawranik 2008).

Behavioural, environmental and psychosocial factors can adversely affect sleep architecture and timing of sleep-wake cycles (Griffiths and Peerson 2005). For example, the timing of sleep-wake cycles, influenced in part by activity and meal times, can be directly affected by a change in routine (Griffiths and Peerson 2005). It may be difficult for patients to adapt to unfamiliar surroundings (Missildine, Bergstrom et al. 2010; Lee, Hwang et al. 2011). The hospital also differs from the home setting in that it is a 24 h working environment (Meyer, Eveloff et al. 1994; Young, Bourgeois et al. 2008). There may be efforts to reduce the noise levels at night, but patient monitoring and standard care take priority. Psychosocial stressors
such as fear, anxiety, bereavement or boredom, can affect the initiation and maintenance of sleep. This may, in turn, disrupt circadian rhythms.

Noise disruption in the hospital setting has been shown, logically, to cause awakenings and arousals. Noise levels of between 45 and 85 decibels, comparable with office or traffic noise, have been recorded (Woods and Falk). Staff activity in the ICU, in particular, has been shown to negatively influence sleep in 81.9% of patients (Woods and Falk; Freedman, Gazendam et al. 2001).

Sedatives such as benzodiazepines have been shown to reduce the time required for sleep onset and to reduce the number of awakenings through the night (Knill, Moote et al. 1990). Benzodiazepines have been shown to cause SWS suppression and high doses of sedatives can change patients’ sleep quality (Knill, Moote et al. 1990). Changes in sleep architecture (such as decreased SWS) reduce sleep quality, although sleep quantity may increase. Sedation in mechanically ventilated patients may increase ventilator time, which can lengthen postoperative recovery (Kress, Pohlman et al. 2000). Patients on mechanical ventilators have been shown to suffer from sleep disruption despite (and possibly because of) the use of sedatives and analgesics (Gottschlich, Jenkins et al. 1994; Cooper, Thornley et al. 2000). Sleep disruption in these patients is found to be unaffected by severity of illness, age, sex or duration of stay; all patients may be at risk in the ICU (Freedman, Gazendam et al. 2001). More than twice the number of arousals and awakenings per hour were recorded in ICU patients, than in healthy subjects (Parthasarathy and Tobin 2004). Freedman et al. (2001) showed that all of the 20 mechanically ventilated patients they monitored showed changes in their sleep architecture (Freedman, Gazendam et al. 2001).

1.3.2. Pain in hospital

Pain in hospitalised patients is, of course, common, particularly in postsurgical patients. A direct relationship between pain and sleep has been shown. Sleep deprivation increases sensitivity, while pain disrupts sleep (Lautenbacher, Kundermann et al. 2006). In nine healthy male volunteers aged 26-43 y, sleep deprivation was shown to affect pain perception, with total sleep deprivation and selective sleep stage deprivation (SWS and REM) both
lowering mechanical pain thresholds (-8 % from baseline) in healthy volunteers (Onen, Alloui et al. 2001). Slow wave recovery sleep leads to an increase in mechanical pain threshold (+15.8 % from baseline), a result which is higher than the 2-12 % increase in pain threshold reported from the analgesics aspirin, ibuprofen, paracetamol and dipyrrone (Forster, Anton et al. 1988; Forster, Magerl et al. 1992; Onen, Alloui et al. 2001). A trial of 27 patients with rheumatoid arthritis showed a significant increase in self-reported pain (p < .01) and painful joint reports (p < .02) following a night of partially disturbed sleep (11:00 p.m. to 03:00 a.m.) (Irwin, Olmstead et al. 2012). Patients suffering from intense chronic pain were shown to have difficulty with sleep initiation and maintenance. A survey of 105 study participants described self-reported sleep disturbances, mood disturbances (anxiety and depression) and pain (intensity and unpleasantness) (Morin, Gibson et al. 1998). Of the 105 patients surveyed, 65 % described themselves as poor sleepers, with pain interfering with sleep onset in 67 % of nights monitored and pain interfering with sleep maintenance in 74 % of the nights monitored (Morin, Gibson et al. 1998). Those subjectively rated “good sleepers” found pain interfered with sleep onset (29 % of nights) and with sleep maintenance (26 % of nights) to a far lesser degree (Morin, Gibson et al. 1998). The poor sleepers also reported greater pain intensity (measured using visual analogue scales) than the self-reported good sleepers (7.67 ± 3.62 cm versus 4.59 ± 4.56 cm, p < .05) (Morin, Gibson et al. 1998).

These results indicate a reciprocal relationship between pain and sleep, but the potential mechanisms are yet to be elucidated. Serotonergic neurotransmission is vital in both nociception and sleep-wake cycle control, and has been proposed as a vital link (Frank, Niesler et al. 2004; Enomoto, Yamashita et al. 2012). In patients with fibromyalgia syndrome, disturbances in the serotonin pathway such as low levels of serotonin and tryptophan have been identified (Frank, Niesler et al. 2004). The role of tryptophan as a precursor to melatonin, a marker of circadian clock activity that exerts considerable influence on the timing of sleep-wake cycles, was discussed in Section 1.2.3.1. The mechanistic pathways of the circadian clock, pain and sleep appear to overlap. In cardiac patients, pain may depend on the type of surgery. Patients who have a coronary artery bypass graft have considerable additional pain where the grafts are harvested, such as in the arms and legs.
Patients with chest drains also report more pain. Postoperative pain management follows a standard procedure of paracetamol every four hours and a daily prescription of aspirin. It also includes opioids if the patients require more pain relief. It should also be noted that the pain medication that the patients use, for example a combination of morphine, paracetamol and aspirin, may affect the amount of melatonin produced, and the subsequent metabolism thereof (see Section 1.2.3.1). The medications may, thus, affect the patients’ sleep and their circadian rhythms.

1.3.3. Hospitalisation and circadian rhythms

The hospital environment alone may be disruptive to sleep architecture and circadian rhythms (see Section 1.3.1). Aspects such as noise, monitoring through the night and additional treatments could potentially disrupt sleep-wake cycles, and in turn disrupt circadian rhythms. For example, mechanical ventilation has been shown to abolish the circadian rhythms of melatonin and cortisol altogether (Olofsson, Alling et al. 2004). In eight patients undergoing mechanical ventilation, Olofsson et al. (2004) found an average ratio of 1 for day/night serum melatonin (Olofsson, Alling et al. 2004). There may be multiple factors influencing the patients’ behaviour and physiology, but hospital lighting is a potentially important factor which is often overlooked. The primary zeitgeber in the entrainment of the human circadian clock is light (see Section 1.2.1). Hospital light cycles may be darker during the day and lighter at night than natural light cycles (refer to Chapter 3). A weak light-dark cycle environment can directly affect sleep-wake cycles and the entrainment of the circadian clock, leading to sleep and circadian disruption.

1.3.3.1. Hospital lighting

Hospital lighting is designed to facilitate constant 24 h activity, and thus may differ from an outdoor natural lighting environment. Daytime hospital light measurements reported in the literature vary (Chapter 3, Table 3:2). In one study, measurements of a Northern hemisphere hospital ward reported light levels ranging from a minimum of 200 lux (north facing room at 9:45 a.m.) to 2000 lux (east facing room at 9:45 a.m.) in June (Beauchemin and Hays 1998). In another, hospital room lighting ranged from a minimum of 1400 lux (west facing room at
9:00 a.m. on a cloudy day) to 15500 lux (east facing room at 5:00 p.m. on a clear day) (Benedetti, Colombo et al. 2001). It is possible that in some rooms the hospital light-dark cycle that patients are exposed to is not ideal for the entrainment of the circadian clock. Kozaki et al. (2011), for example, found that healthy young males needed light exposure of over 750 lux to entrain their circadian clocks (Kozaki, Toda et al. 2011).

In fact, the hospital environment can cause circadian disruption even in healthy subjects when confounding factors such as pathology, surgery and anaesthesia, and medications are not present. Healthy volunteers showed an increase in cortisol levels in a hospital environment (Scheer, Van Paassen et al. 2002). The environment was sound and temperature controlled (Scheer, Van Paassen et al. 2002). Salivary cortisol levels increased the morning after one night in hospital (5.6 nanograms (ng) per ml versus home control cortisol levels of 3 ng/ml ($p < .05$)) (Scheer, Van Paassen et al. 2002). Elderly patients who had been hospitalised for six weeks ($n = 8$) or more showed higher daytime plasma melatonin levels than community controls ($n = 15$) (Baskett, Cockrem et al. 1991). The alteration in rest-activity and posture can also contribute to changes in sleep-wake cycles. In a cohort study of 67 adults in a chronic disease care facility, the number of 24 h periods individuals spent in bed over one week were monitored (Fox, Sidani et al. 2010). Those who spent five to seven days in bed were more likely to suffer from insomnia than those who spent two to four days in bed (Fox, Sidani et al. 2010). It is possible that the change in rest-activity in bedridden patients is influenced by changes in light-dark cycles. These results illustrate the potential for circadian disruption in hospitalised patients. There may be potential for circadian-based interventions such as light therapy to be used in hospital to facilitate entrainment, and perhaps improve sleep and patient recovery.
1.4. Surgery and anaesthesia

Patients in hospital may undergo various treatments, including surgery and anaesthesia. The effects of surgery and anaesthesia on sleep and circadian rhythms are therefore relevant to my research.

1.4.1. Surgery, sleep and circadian rhythms

An operation may involve a number of techniques and treatments (including pharmacological treatments) that could, individually or collectively, cause sleep and circadian disruption. The size of the surgical intervention, whether major or minimally invasive, may impact on the extent of the effects (Gogenur, Rosenberg-Adamsen et al. 2001). The timing (morning, afternoon or night, for example) and the duration of the surgery may influence postoperative sleep and circadian rhythms. It is also possible that the operation may require painful postoperative care, such as drains or dressing changes, which can influence sleep and circadian rhythms.

In a study on the effects of major abdominal surgery on sleep architecture in adults \((n = 6)\), patients were monitored for up to six days postoperatively using a modified EEG (Knill, Moote et al. 1990). During postoperative nights one and two, Knill et al. (1990) identified REM and SWS suppression. Subsequent sleep (postoperative days 2 to 6) resulted in REM rebound (Knill, Moote et al. 1990). Aurell et al.(1985) studied the sleep architecture of a small group of patients \((n = 9)\) for two to four days after major surgery (Aurell and Elmqvist 1985). The mean total sleep time (TST) (excluding stage 1) for the first two days was less than two hours a day (Aurell and Elmqvist 1985). Stage 3 (formerly stages 3 and 4) and REM sleep were suppressed (Aurell and Elmqvist 1985). These results indicate that sleep architecture may be disrupted postoperatively. The disturbances may be attributable to the procedure and/ or the hospital environment.

Postoperative changes in 6-sulphatoxymelatonin levels have been shown after major abdominal surgery for gastrointestinal cancer \((n = 36)\) (Gogenur, Middleton et al. 2007a). Patients’ postoperative excretion levels were shown to be significantly higher during the day, changing the day-night ratio (preoperative day 2.07 micrograms per ml \((\mu g/ml)\), preoperative
night 2.97 µg/ml, postoperative night 1.64 µg/ml, postoperative day 3.97 µg/ml; \( p = .05 \) (Gogenur, Middleton et al. 2007a). Minimally invasive surgery (laparoscopic cholecystectomy, \( n = 12 \)) was also found to disturb postoperative core body temperature rhythms (12 h postoperative phase shift, \( p = .01 \) and 6-sulphatoxymelatonin (6.1ng/mg creatinine postoperative decrease in amplitude (\( p < .005 \), 1h17 phase delay (\( p < .05 \)) when measured during the first postoperative day (Gogenur, Middleton et al. 2007b).

The variability of postoperative circadian clock activity is usually measured using the primary circadian markers (melatonin, cortisol and core body temperature; Section 1.2.3). There are many examples of circadian disruption following surgery, but it is interesting to note the work of Gogenur et al. (2002) on the effects of major abdominal operations on the autonomic nervous system (\( n = 44 \)) (Gogenur, Rosenberg-Adamsen et al. 2002). They found significant postoperative disruption in normal diurnal heart rate variability (Gogenur, Rosenberg-Adamsen et al. 2002). This may indicate that postoperative circadian disruption could extend beyond that measured by standard circadian markers and sleep-wake cycles.

### 1.4.2. Anaesthesia, sleep and circadian rhythms

Postoperative patients show both subjective and objective indicators of sleep and circadian disruption. There is also some evidence to indicate that anaesthesia alone disrupts sleep and circadian rhythms. There are similarities between general anaesthesia and sleep. General anaesthesia, like sleep, is a state of quiescence, with minimal processing of sensory information and no interaction with the environment (refer to Section 1.1). It is thus possible that sleep and general anaesthesia may share some mechanistic pathway.

The activity of “GABAergic” hypnotic agents (such as propofol and barbiturates) has been shown to involve tuberomamillary nucleus (TMN) GABA\(_A\) neurons, much like sleep promoting pathways (Figure 1:3) (Nelson, Guo et al. 2002). Nelson et al. (2002) showed that the sedative effects of general anaesthetics that were considered “GABAergic” were ameliorated in rats through the use of GABA agonist, gabazine (Nelson, Guo et al. 2002). Sedation was achieved through a direct injection of GABAergic anaesthetics into the TMN, indicating that there may be a connection between the sleep promoting TMN centralised
pathway and the mechanism of action of GABAergic anaesthetics (Nelson, Guo et al. 2002). The concurrent administration of gabazine with ketamine or nitrous oxide, which are not shown to have GABA activity, did not affect the level of sedation (Nelson, Guo et al. 2002).

The effects of surgery and anaesthesia on sleep and the circadian clock are difficult to separate. Surgery (with anaesthesia) is thought to disrupt sleep architecture, sleep-wake cycles and circadian rhythms, but anaesthesia alone has also been shown to disrupt circadian rhythms in animal models. The administration of certain anaesthetics has the potential to modify the timing of the sleep-wake cycles much the way a prolonged nap or time zone crossing travel would (Cheeseman, Winnebeck et al. 2012).

Challet et al. (2007) found that daytime general anaesthesia with propofol in rats induced phase advances of 60-90 min in their rest-activity rhythms in the subjective evening (Challet, Gourmelen et al. 2007). A four-hour daytime sevoflurane anaesthetic phase delayed activity by approximately one hour in mice (Ohe, Iijima et al. 2011). In hamsters, the opioid analgesic fentanyl caused both phase advances and delays in activity depending on the time of administration (Vansteensel, Magnone et al. 2005). These phase shifts were successfully blocked by the administration of naloxone (an opioid antagonist) (Vansteensel, Magnone et al. 2005). Dispersyn et al. (2009) showed that general anaesthesia (with propofol) in rats \((n = 40)\) caused a phase-shift of 60-80 min in the rest-activity rhythm and core body temperature, and dampened the amplitude of the rest-activity rhythm (Dispersyn, Pain et al. 2009). It should be noted that these results are tempered by the fact that the subjects are nocturnal. It may be that the reason changes are notable in nocturnal animals during the day is because the anaesthetics are having downstream effects on the synthesis and release of melatonin, which is still released during the night in nocturnal rodents. However, surgeries in humans, with the exception of some acute emergencies, are performed during the day. It is particularly useful then to consider the results of the work of Cheeseman et al. (2012) with the honeybee \((Apis mellifera)\) as an animal model. They studied the effects of general anaesthesia with isoflurane on circadian clock activity (Cheeseman, Winnebeck et al. 2012). A six-hour daytime anaesthetic altered the time-compensated sun compass orientation of the bees and the timing of foraging by 4.3 h (Cheeseman, Winnebeck et al. 2012). The timing of
the administration of external stimuli is essential to their effect on the clock (see Section 1.2.2.1). For example, isoflurane anaesthesia given at night does not affect circadian rhythms in bees (Cheeseman, Winnebeck et al. 2012). Cheeseman et al. were also able to show that the effect of anaesthesia on the behaviour of the bees was attributable to concurrent phase delays in the molecular clockwork (Cheeseman, Winnebeck et al. 2012).

In sedated and mechanically ventilated patients \((n = 16)\), 6-sulphatoxymelatonin excretion was markedly lower than in periods without intubation \((18 \text{ ng/h versus } 555 \text{ ng/h, } p < .0001)\) (Frisk, Olsson et al. 2004). In 31 % of patients, 6-sulphatoxymelatonin excretion was immeasurably low for a minimum of 24 h (Frisk, Olsson et al. 2004). The administration of adrenergic drugs was shown to increase the excretion of the urinary metabolite (Frisk, Olsson et al. 2004). In my master’s program I conducted a pilot study in 12 elective postoperative cardiac patients and found evidence of sleep-wake cycle and circadian disruption (Jardim 2008). All the participants displayed three or more indicators of sleep disruption when compared to preoperative scores (defined in Table 5:2) (Jardim 2008). Patients were found to spend 18.1 % more time in bed asleep preoperatively than postoperatively in hospital \((p = .05)\) (Jardim 2008). There were also significant changes in two non-parametric circadian rhythms variables (Van Someren, Lijzenga et al. 1997; Van Someren, Swaab et al. 1999). Postoperative intradaily variability, which measures the extent of fragmentation in the activity rhythm, increased significantly \((p = .05)\) (Jardim 2008). Postoperative interdaily stability, which measures the variability of the activity rhythm between days, decreased significantly \((p = .05)\) (Jardim 2008).

The data available on the effect of general anaesthesia on the circadian clock indicate that it may contribute to postoperative sleep-wake cycle and circadian disruption. A therapeutic intervention to potentially ameliorate these symptoms is worthy of investigation.
1.5. Outline of my thesis

The overall goal of the work I describe in this thesis was to establish whether increasing light exposure can improve postoperative sleep-wake cycle and circadian disruption in cardiac patients. The subsequent chapters contain the details of a series of studies into:

1. the validity of wrist-level ambulatory light monitoring devices,
2. the hospital lighting environment,
3. the effects of hospitalisation, surgery and anaesthesia on patients’ lengths of stay in hospital and
4. the efficacy of morning light therapy as a treatment for postoperative sleep-wake cycle and circadian disruption in postoperative cardiac patients.

The first step in these investigations was to validate the measurement of light levels with ambulatory equipment. Wrist actigraphy is widely used in circadian rhythms research. It assumes that wrist-level light measurements are representative of eye-level light exposure. In Chapter 2, I describe a methodological investigation of the agreement between wrist-level and eye-level light measurements. Twenty-one postoperative patients were asked to concurrently wear a wrist-level light measurement device (ActiWatch-L) and an eye-level light measurement device (Daysimeter). Twelve patients provided usable data, and the measurements from the two devices were compared. There was agreement between eye- and wrist-level light measurements, with differences of less than 10 lux at eye-level light intensities less than 5000 lux. With respect to time of day, the differences between the devices were on average 50 lux higher at eye-level during the day, and 50 lux lower during the night. The agreement between the devices was acceptable for the purposes of my research.

In Chapter 3, I describe the lighting environment in the cardiothoracic ward at Auckland City Hospital, Auckland, New Zealand. As light-dark cycles are central to the entrainment of the circadian clock, an accurate description of the environment is important. Individual bedspaces were monitored using fixed actigraphs. At each bedspace, 72 h of continuous
lighting data were collected. The bedspaces were all categorised as low or moderately lit, with median daytime light levels at each bedspace less than 500 lux. None of the bedspaces were classified as brightly lit.

The comprehensive description of the ambient hospital lighting in the cardiothoracic ward was used to determine if there was a relationship between ambient lighting in this hospital environment and the length of stay of postoperative cardiac patients. A prospective audit, over one year, was conducted on 654 postoperative cardiac patients admitted to the Cardiovascular Intensive Care Unit (CVICU) and consequently transferred to the cardiothoracic ward. Data were collected on patient demographics, length of stay, bedspace and medications. I found no relationship between ambient light intensity and length of ward stay in postoperative cardiac patients. This may have been because none of the bedspaces in this cardiothoracic ward had ambient light levels that were bright enough for the entrainment of the patient’s circadian clocks. This result indicated an opportunity to increase patient light exposure and subsequently assess the efficacy of light therapy as an intervention to decrease circadian and sleep disruption in postoperative cardiac patients.

At the beginning of my doctoral program, I designed an extensive randomised placebo controlled trial examining the effects of morning light therapy on postoperative sleep-wake cycles and circadian rhythms. Participants were identified from elective cardiac surgical lists at Auckland City Hospital between August 2010 and July 2011. Participants were asked to provide data assessing sleep-wake cycles, circadian rhythms, length of hospital stay, chronotype and mood for four weeks at four different timepoints. Collections occurred preoperatively (baseline data of one week), postoperatively for the duration of their hospital stay, postoperatively at home in the week postdischarge from hospital and for one week three months after their surgery. The trial design was ambitious, and unfortunately progress was slow. The complexity of the sampling process and the large number of variables proved to be too difficult to complete in the timeframe of a doctoral program. The process played an important role in the subsequent development and design of the main, abbreviated randomised controlled trial which could be completed in the time available. In Chapter 5, I
describe the subsequent single blind randomised placebo controlled trial in 61 patients scheduled for cardiothoracic surgery.

The primary outcome of this study was to determine whether morning light therapy significantly improves postoperative sleep-wake cycle and circadian disruption. Patients were randomised to placebo light therapy or morning light therapy. They were asked to wear an ActiWatch (to monitor sleep-wake cycles) and to provide urine samples (to measure 6-sulphatoxymelatonin excretion, using it as a marker of the circadian clock) for 72 h postoperatively. Results showed no calculable circadian rhythm in the mean 6-sulphatoxymelatonin excretion rates in the placebo treatment arm. In the light therapy arm, there was an identifiable rhythm in mean 6-sulphatoxymelatonin excretion rates on the second and third therapy days. There were no significant differences between groups in sleep quality, sleep quantity, sleep timing, length of hospital stay or mood.

In Chapter 6 I discuss the investigations presented in this thesis, reviewed in light of the current literature and draw some overall conclusions. I suggest possible directions for future research into the treatment of postoperative sleep-wake cycle and circadian disruption.

The work presented in this thesis forms part of a departmental initiative exploring the interactions between hospitalisation, surgery and anaesthesia and the circadian clock. It builds on the information available in the current body of literature, including work presented in my Master’s thesis (Jardim 2008). This series of investigations contributes to our understanding of the interaction between ambient lighting, therapeutic lighting, sleep-wake cycles and circadian rhythms in the clinical setting.
Chapter 2. Validating the use of wrist-level light monitoring for in-hospital circadian studies.

Chapter summary

Background

Wrist-worn light measurement devices are common in circadian studies. The assumption that light measured at the wrist is equivalent to light measured at the eye has not been validated in the hospital setting. Confirming the efficacy of these wrist-level monitors will provide confidence for the use of these tools in the clinical setting.

Methods

Postoperative cardiac patients were asked to simultaneously wear a wrist-level light monitoring device and an eye-level light monitoring device. The overall agreement between light measurements recorded by the two devices was assessed using a modified Bland-Altman plot using a LOESS smoother, and differences were evaluated with regards to time of day using a non-linear mixed effects model.

Results

At eye-level light intensities of less than 5000 lux, the differences between the two devices were less than 10 lux. At eye-level light intensities of 5000 lux or more, the differences between the devices were greater than 100 lux. Agreement between the eye- and wrist-level light measurements appears to be influenced by time of day. During the day wrist-level measurements were on average 50 lux lower than eye-level measurements. At night wrist-level measurements were on average 50 lux higher than eye-level measurements.

Conclusion

The results show that wrist-level light monitoring devices provide an estimate of patients’ light exposure at eye-level that is adequate for the purposes of research, although agreement between the devices was found to decrease as eye-level light exposure increased. This study

2 The findings in the chapter have been published in a peer-reviewed journal: Jardim, A.C. , M.D. Pawley, et al. (2011). "Validating the use of wrist-level light monitoring for in-hospital circadian studies." Chronobiology international 28(9): 834-840. I have expanded on the paper in this chapter.
is the first to evaluate the relationship between wrist-level light-monitoring devices and eye-level light exposure in the clinical setting.
2.1. Introduction

A first step in the investigation into the efficacy of morning light therapy for the treatment of postoperative sleep and circadian disruption is the evaluation of tools available for the measurement of individual light exposure. There is a paucity of data, especially in the clinical setting, confirming that light-monitoring devices at wrist-level accurately estimate eye-level light exposure. Consequently, I set out to establish the agreement between light measured at the wrist and light measured at the eye.

Actigraphy is considered a useful tool for the measurement of rest-activity rhythms (Brown, Smolensky et al. 1990). It is an objective form of measurement which, when combined with patient sleep diaries to improve data quality, can accurately distinguish between wake and sleep in an activity profile. Wrist actigraphy has been repeatedly validated against EEG-based diagnostic tools in multiple settings and populations since Kupfer et al. (1972) first reported a significant correlation between rest-activity rhythms measured using measurements derived from wrist-level actigraphs and rest-activity measurements derived from EEG-based devices (Kupfer, Detre et al. 1972). Actigraphy is not limited to wrist placement; it has also been studied at the trunk, on the ankle and at the eye. Wrist actigraphy usage is widespread and actigraphs can incorporate accelerometers and light meters. The use of wrist-level actigraphy when assessing lighting environment is predicated on the assumption that the measurements of light intensity at the wrist reflect light at the eye. However, it is possible that the angle and the intensity of the light levels measured may not be entirely accurately representative of those entering the eye. For example, in hospital wrist-level monitors can be occluded by sleeves and blankets.

Light-monitoring devices worn at the wrist are commonly used in clinical studies where light levels are important (Ancoli-Israel, Cole et al. 2003; Alessi, Martin et al. 2008; Missildine, Bergstrom et al. 2010), but eye-level light monitors, which in theory provide a more accurate estimate of light entering the eye, are less common (Savides, Messin et al. 1986; Schernhammer, Laden et al. 2001; Grundy, Sanchez et al. 2009; Higgins, Hornick et al. 2010). There are no published data on the agreement between wrist- and eye-level light
exposure in hospital settings, and there have been only two previous studies attempting to validate the use of wrist-worn light-monitoring devices.

The first of these studies (an abstract in Sleep Research in 1990) reports good overall agreement ($R^2 = 0.93$) between 24 h wrist and forehead measurements in 10 healthy student volunteers (Cole, Kripke et al. 1990); however, “there are sometimes large discrepancies, since the wrist actigraph may be aimed in a very different direction from the forehead” (personal communication, Dan Kripke, 2011). The second study, which was conducted in a hospital setting, compared 24 h wrist-level light exposure to 480 single measurements of vertical room light (Higgins, Winkelman et al. 2007). In this study no attempt was made to measure eye-level light exposure. The limitations of using stationary light meters to measure light entering the eye are perhaps obvious, but are noteworthy. The orientation of a stationary light meter will affect the illuminance measured. Given that almost all of the artificial light sources in hospital are ceiling lights, vertical measurements are likely to be higher than horizontal measurements. Similar problems exist with the use of wrist-level measurements, given that wrist position does not reliably reflect angle of gaze.

In this chapter, I describe the results from a validation study to determine the agreement between wrist- and eye-level light monitoring in a hospital environment by simultaneously measuring light exposure at the wrist (ActiWatch-L) and at the eye (Daysimeter) (Bierman, Klein et al. 2005). The latter allows the accurate measurement of entraining light in the clinical setting. This is a preliminary step in a series of investigations to determine the efficacy of morning light therapy for the amelioration of postoperative sleep and circadian disruption.
2.2. Aims

The aim of this study was to validate the use of wrist-level light measurements for estimating eye-level light exposure in the clinical setting.

2.3. Materials and Methods

2.3.1. Ethics Approval

Ethics approval for this study was given by the Ministry of Health Northern Y Ethics Committee (NTY/08/09/086; Appendix A) and locality approval given by the Auckland District Health Board (A+4228).

2.3.2. Participants

I aimed to collect data from 20 patients scheduled for elective cardiac surgery. Patients were recruited the day prior to their surgery while in the cardiothoracic ward. Patients were asked to wear an Actiwatch-L (Philips Respironics) and a head-worn Daysimeter (Rensselaer Polytechnic Institute, N.Y.) (described in Bierman et al., 2005) (Bierman, Klein et al. 2005). Patients were asked to wear both devices continuously from placement of the devices until discharge. Following cardiac surgery, patients were transferred to the CVICU. Thirty minutes after arrival in the CVICU, both devices were positioned and secured to the patients by an investigator. The ActiWatch and the Daysimeter were set to begin collecting data as soon as they were attached and activated. Once patients are stable, awake and are no longer mechanically ventilated (usually within 24 h), they are transferred from the CVICU to the cardiothoracic ward. Patients typically spend between three and seven days convalescing in the cardiothoracic ward before being discharged.
2.3.3. Study devices

2.3.3.1. The Daysimeter

The Daysimeter, worn at eye-level by a volunteer.

Note: A plastic hook sits over the ear. The eye-level light monitor is visible protruding just above the eye and the recording device is visible behind the ear. The hanging string secures the unit to the user’s clothing.

The Daysimeter was considered the gold standard in this study. The Daysimeter attaches to the ear. It protrudes at eye-level to monitor photopic illuminance in lux from 400-700 nanometres (nm) at the approximate angle of gaze (Figure 2:1). The data were downloaded and handled with Daysimeter V4 v. 8.2.1 (Rensselaer Polytechnic Institute, N.Y.).
2.3.3.2. The ActiWatch-L

Figure 2:2
The ActiWatch-L, worn at wrist-level by a volunteer.

Note: The light meter is visible on the face.

The ActiWatch-L records photopic illuminance from 400-900 nm at the wrist (Figure 2:2). Data were downloaded and handled with ActiWatch Activity and Sleep Analysis 5 Version 5.54 (Cambridge Neurotechnology). Daysimeters and Actiwatches were calibrated using a standard 10000 lux fluorescent light source (Pharos, Lumie, Cambridge, U.K.) and a Li-Cor LI-185B spectrophotometer (Li-Cor Biosciences). Light intensity was logged in lux every 30 seconds (s) for the duration of the patients’ hospital stay. Patients were visited between two and four times daily to confirm their compliance, and to monitor the position of equipment.

2.3.4. Study environment

All artificial light sources at Auckland City Hospital are fluorescent, and all external-facing windows are tinted and shaded. The CVICU is a 24-bed unit (four beds per room) with west-facing windows. Bedspaces are illuminated by individual ceiling lights. In addition, during the day a central room-length ceiling light is permanently on. Patients also control a
second personal light source, a ceiling light bank directly above the bed space. The cardiothoracic ward is a 22-room unit (a combination of private and four-bed shared rooms) with west-facing or internally rotated windows (Chapter 3, Figure 3:1). Artificial light is provided by ceiling light sources. Patients can control curtains, window blinds and a wall-mounted down light. The fluorescent corridor lighting is on permanently. This provides a mean illumination at the angle of gaze (semi-recumbent) during the day of 139 lux (SEM = 20 lux) and during the night of 12 lux (SEM = 3 lux) (Jardim 2008).

2.3.5. Analysis

Data were analysed using Microsoft Excel and the statistical package R v. 2.12 (R Development Core Team, 2011). Night and day were differentiated using local sunrise and sunset times for each study day. Mean lux values, taken over 10 min, were calculated for each device and used to compare light measurements between individual patients.

2.3.5.1. Agreement between the devices

Agreement between the light measurements from the ActiWatch and the Daysimeter was assessed using a modified Bland-Altman plot, with the difference between the two devices displayed as a function of the eye-level light measurements (Bland and Altman 1999; Krouwer 2008). The data were log transformed for the modified Bland-Altman plot (Figure 2:5) to account for the variation and the spread in the large dataset when comparing all the paired data points (Higgins, Winkelman et al. 2007). A non-parametric locally weighted smoother (LOESS) accounted for the non-linear relationship between the difference (Daysimeter minus ActiWatch) and the eye-level measurements (Bland and Altman 1999; Krouwer 2008).

2.3.5.2. Time of day

It was also important to assess whether there were differences in agreement between the devices because of ambient light intensity or whether time of day also influenced the difference between the devices. Thus, the effect of time of day on agreement between the two devices was investigated using a non-linear mixed-effects model with an AR1
auto-correlated error structure and a periodic spline. The AR1 auto-correlated error structure was used because the wrist- and eye-level observations were not independent. The effect of time of day on the agreement between the two devices was calculated using the raw data.
2.4. Results

Twenty-one patients scheduled for elective cardiac surgery at Auckland City Hospital, Auckland, New Zealand provided written informed consent to participate in this observational study. Patients were recruited the day prior to their surgery while in the cardiothoracic ward (Figure 2:3). Nineteen patients wore both a wrist-worn ActiWatch (Philips Respironics) and a head-worn Daysimeter (Rensselaer Polytechnic Institute, N.Y.) from one to six days (24 h) postoperatively (Bierman, Klein et al. 2005).

![Flowchart showing patient recruitment and data collection](image)

Figure 2:3
The flow of patient recruitment and data collection through the trial.

*Note:* Four patients withdrew and two operations were cancelled. The Daysimeters that were worn by six patients malfunctioned and no data were collected from those devices.

Of the 21 subjects recruited, 19 underwent scheduled surgery, and of those, 12 provided sufficient data for analysis (Daysimeter download failures in six patients and study withdrawal of one patient accounted for the difference) (Figure 2:3). These patients provided data from their arrival in the CVICU following surgery until their discharge from the cardiothoracic ward, representing a total of 29 subject days of data or 86399 light
measurements. Individual subject data showing concurrently recorded wrist- and eye-level light data (collected from December 2008 to March 2009) are displayed in Figure 2.4. Upon visual inspection, the devices appear to show good agreement, with a few notable exceptions (Patient 2, day 3; Patient 3, day 2; Patient 10, day 2 and Patient 11, day 2).
Figure 2:4
Concurrently measured eye-level and wrist-level light exposure for 12 postoperative cardiac patients.

*Note:* Eye-level light measurements (Daysimeter) are displayed in black and wrist-level light measurements (ActiWatch) are displayed in blue. The grey shading indicates night and the number one through 12 indicate the patients who provided data. All the patients were monitored from 7:00 p.m. (except for Patient 4, who started monitoring at 07:00 a.m.) and were monitored for one to seven days.
Mean eye-level light during the day is higher in the cardiothoracic ward than in the CVICU (Table 2:1).

<table>
<thead>
<tr>
<th>Light levels</th>
<th>CVICU</th>
<th>Cardiothoracic Ward</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Eye-level</td>
<td>Wrist-level</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.34</td>
<td>0.11</td>
</tr>
<tr>
<td>Maximum</td>
<td>1068</td>
<td>12778</td>
</tr>
<tr>
<td>Daytime mean (SEM)</td>
<td>156 (24)</td>
<td>246 (119)</td>
</tr>
<tr>
<td>Nighttime mean (SEM)</td>
<td>28 (7)</td>
<td>12 (3)</td>
</tr>
</tbody>
</table>

Table 2:1
The descriptive statistics indicating the minima, the maxima and the mean light levels (lux) at wrist- and eye-levels in the cardiovascular intensive care unit and cardiothoracic ward settings.

Note: CVICU indicates the cardiovascular intensive care unit and SEM indicates standard error of the mean.

2.4.1. Agreement between the devices

Figure 2:5 shows the difference between the eye-level and wrist-level light measurements plotted as a function of eye-level light measurements. This includes a locally weighted smoother (LOESS) to show the mean difference between the wrist- and eye-level measurement as a function of the eye-level measurement.
The mean difference between eye-level and wrist-level light exposure is positive, indicating that levels recorded at the eye are higher than at the wrist. This bias is low (< 10 lux) when light levels are below 5000 lux (as indicated by the Loess smoother). For values of 5000 lux or more, the bias increases. Only 286 eye-level measurements of 5000 lux or greater were recorded (representing 0.3 % of the data). These eye-level measurements over 5000 lux were recorded only in the datasets of patients two and four (Figure 2:4).
2.4.2. Time of day

A non-linear mixed effects model was used to model the difference between eye-level and wrist-level measured light with respect to time of day. The periodic spline fitted to the data showed a small but statistically significant relationship between time of day and the difference between wrist- and eye-level light values (Figure 2:6).

![Figure 2:6](image)

Figure 2:6
A mixed-effects model of the difference between eye- and wrist-level light measurements expressed as a function of time of day.

*Note:* The solid line (periodic spline) indicates the mean difference. At night, the variance decreases. The grey shading indicates nighttime (8:00 p.m. to 7:00 a.m.) and inset A shows a clearer portion of the main figure indicating the periodic spline and clearly showing the change in the mean difference from night to day.

The variance between the two devices was greater during the day (between 7:00 a.m. and 8:00 p.m.) than at night (8:00 p.m. and 7:00 a.m.), with a maximum day-time difference of over 6000 lux recorded (Figure 2:6). During the day wrist-level measurements were on
average 50 lux lower than eye-level measurements. At night wrist-level measurements were on average 50 lux higher than eye-level measurements. They were statistically significant ($p < .001$), but in the context of the overall data spread, this time of day effect is minimal. There were differences in the peak light values between the CVICU and the cardiothoracic ward, but there were no significant differences in mean light exposure between the CVICU and the ward. Location (CVICU versus ward) was fit as a covariate in the model and was found to have no effect on the difference between the devices. Thus, no separate analyses based on location were indicated. In the CVICU, individual light recordings were occasionally higher (almost double) at the wrist than the eye. In the cardiothoracic ward, the maximum single light value measured was at eye-level (12778 lux versus 6602 lux at wrist-level). The highest single maximum light value recorded in the CVICU was recorded by the wrist-worn device (1961 lux versus 1068 lux at eye-level).
2.5. Discussion

2.5.1. Agreement between the devices

In this clinical setting, wrist-level light measurements show good agreement with eye-level light measurements. The differences between the devices were small (< 10 lux) at eye-level light less than 5000 lux. At higher light levels, wrist-level measurements underestimated eye-level light exposure. Wrist-level measurements were less sensitive to both high (> 5000 lux) and low light levels (< 10 lux) than eye-level measurements. Ninety-four percent of the data recorded indicated light intensities of less than 300 lux, and 69 % of all values recorded by the two devices varied less than 50 lux. Those differences at very high and very low light levels may be explained by light sensor occlusion by bedding and clothing, or wrist positioning; factors which are difficult to control. The different angles of the two devices are reflected in the difference between wrist- and eye-derived light measurements.

2.5.1. Time of day

During the day wrist-level measurements were on average 50 lux lower than eye-level measurements. At night wrist-level measurements were on average 50 lux higher than eye-level measurements. This finding is not surprising given there is more light during the day than at night. However, there is typically light at night in hospital settings, and it is important to note that this is overestimated by wrist-level measurements. The higher light levels recorded at the eye during the day probably reflect the use of clothing and bedding. The lower levels recorded at the eye during the night are probably attributable to a combination of head and wrist positioning. Patients are encouraged to be mobile during the day, while at night they are predominantly semi-recumbent. In the semi-recumbent position, the eye-level monitor measures at the angle of gaze while the wrist-level monitor is perpendicular to the ceiling, where there is a light source. The time of day effect is relatively minor compared to the overall spread of the data.

The finding that in the CVICU wrist-level light measurements were sometimes much higher than those recorded at the eye can be explained by the fact that in the CVICU patients are
semi-recumbent and, for a majority of their stay, immobile. It is also worth noting that there is a constant light source in the CVICU to enable safe, 24 h patient care. This is not the case in the ward where patients are stable and do not require around-the-clock monitoring.

The pertinent question raised by these results is whether the differences found between eye- and wrist-level light measurements have consequences for in-hospital circadian studies? This depends on the assumed sensitivity of the circadian system to light. In controlled laboratory conditions, a single broad spectrum 6.5 h pulse of 100 lux can phase shift the circadian clock half as much as a 9000 lux pulse (Zeitzer, Dijk et al. 2000). Phase shifts of the human circadian clock have also been shown in response to shorter pulses, with one hour of 500 lux (Laakso, Hatonen et al. 1993) or four hours of eight lux of blue light (at 436 - 456 nm, with dilated pupils) (Warman, Dijk et al. 2003) eliciting shifts. The lowest broad spectrum white light level shown to suppress nocturnal melatonin is again 6.5 h of 100 lux (Zeitzer, Dijk et al. 2000). However, moderately higher intensities (285 lux for three hours and 396 lux for 30 min can also cause suppression (Aoki, Yamada et al. 1998). For subjects with dilated pupils exposed to monochromatic blue light (456 nm), as little as 10 lux for 45 min can induce melatonin suppression (Thapan, Arendt et al. 2001). The light sources in our hospital are exclusively fluorescent. Unless the circadian system is proven to be more sensitive to light than has been reported previously, a time of day influenced difference of 50 lux between the wrist- and eye-level measurements may have little relevance.

2.5.2. Strengths and limitations

The main limitation of our study is the relatively small number of participants providing useful data; only 12 patients provided concurrent data from both devices to enable comparisons to be made. The primary factor influencing the number of patients providing useful data was data download failures with the Daysimeter. Despite this, concurrently recorded light levels at the wrist and head in patients for 24 h per day for the duration of their stay yielded a large data set (29 subject-days or 86399 concurrent measurements). Practically, measuring eye-level light exposure with the equipment described here is problematic. Patient compliance is already a challenge as patients are burdened by a large
number of clinical monitoring devices during their postoperative stay. In addition, the eye-level device used in this study is impractical and was found to be technically unreliable. The device may also negatively influence the patients’ sleep as it was considered cumbersome for the patients. When studying sleep-wake cycles and circadian rhythms, the potential for a monitoring device to disrupt patients’ sleep is a risk. It remains up to each researcher to decide whether the convenience of the actigraph outweighs the bias in the agreement between the wrist-level and eye-level measurements.

This study is the first of its kind in the clinical setting to confirm the validity of wrist-level actigraphy as a tool for estimating light levels entering the patient eye. The development of smaller and less invasive personal light meters would further facilitate the accurate measurement of eye-level light exposure in the clinical setting, but given the results presented here this may not proffer any great advantage over wrist-level monitoring devices. The results therefore provide some confidence that wrist-level actigraphy will adequately quantify patient light exposure, as well as the rest-activity rhythms measured by the accelerometer.

2.5.3. Conclusion

There was adequate agreement, for the purposes of research, between light measurements recorded by the wrist-level and eye-level light monitoring devices at eye-level light measurements less than 5000 lux in the clinical setting.
Chapter 3. Lighting in hospital

Chapter summary

Background

Light is important for the entrainment of the circadian clock. An accurate assessment of the lighting environment in our hospital may help to explain the postoperative disruption of circadian rhythms and sleep-wake cycles. An understanding of the environmental light in this clinical setting is helpful to determine the effects of lighting on patients’ lengths of hospital stay and subsequently for the design of a randomised controlled trial examining the effects of morning light therapy on patients’ sleep-wake cycles and circadian rhythms. The aim of this chapter was to profile the lighting environment in our cardiothoracic ward.

Methods

Light intensity (lux) was measured at all thirty-five bedspaces in a cardiothoracic surgical ward. Continuous measurements were recorded for 72 h, in one-minute epochs. Daytime and nighttime median light intensities were calculated for each bedspace. Light levels were defined according to categories outlined by Scheuermaier et al. (2010). Bedspaces with windows were compared to bedspaces without windows using a Wilcoxon-Mann-Whitney test. Street-facing bedspaces were compared to internal bedspaces using a Wilcoxon-Mann-Whitney test.

Results

All the bedspaces were categorised as low or moderately lit. None were brightly lit. Median daytime light levels ranged from 8 lux to 406.7 lux. Eighty-one percent of all data collected were less than 100 lux, classified as “dim to moderate indoor light”. Sixty-four percent of the data collected during the day were less than 100 lux. Street-facing bedspaces were significantly brighter (median = 145 lux, IQR = 50.2-211.5) than internal bedspaces (median = 31.3 lux, IQR = 16.3-65.7, p = .015). Bedspaces with windows (median = 68.3 lux, IQR = 43.3-164) were significantly brighter than bedspaces without (median = 29.7 lux, IQR = 17.5-37.4, p = .001).
Conclusion

Street-facing bedspaces were significantly brighter than internal bedspaces and bedspaces with windows were significantly brighter than bedspaces without windows. The light levels in the cardiothoracic ward were found to be predominantly “low to moderate”. These data can be used to establish whether there is a relationship between the hospital lighting environment and the lengths of hospital stay of the postoperative patients.
3.1. Introduction

General anaesthesia and surgery may disrupt sleep-wake cycles and circadian rhythms. Ambient hospital lighting may also exacerbate these disturbances (Beauchemin and Hays 1996; Beauchemin and Hays 1998). We already know that cardiothoracic surgical patients \( n = 12 \) are exposed to light levels that are predominantly less than 5000 lux (refer to Chapter 2). However, ambient light levels may vary across our cardiothoracic ward. I sought to categorise the ambient light levels in the cardiothoracic ward, to see whether the light intensity at different bedspaces could be sufficient to affect patients’ lengths of hospital stay.

For an interventional trial examining the effects of increased light exposure on sleep-wake cycles and circadian rhythms to be well-designed and effective, it is important to understand how the ambient light levels in this hospital environment affect these patients.

Before proceeding, it would be useful to categorise low, moderate and bright light levels. Scheuermaier et al. (2010) defined ambient light level categories when determining the effects of ambient light on the circadian clock of healthy adults (Table 3:1) (Scheuermaier, Laffan et al. 2010).

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very dim indoor light</td>
<td>&lt; 10 lux</td>
</tr>
<tr>
<td>Dim to moderate indoor light</td>
<td>10 to 99 lux</td>
</tr>
<tr>
<td>Moderate to bright indoor light</td>
<td>100 to 1000 lux</td>
</tr>
<tr>
<td>Outdoor light</td>
<td>&gt; 1000 lux</td>
</tr>
</tbody>
</table>

Table 3:1
A broad categorisation of light exposure levels (in lux).

*Note: These categories were used to define the light levels in this hospital environment (Scheuermaier, Laffan et al. 2010).*

This working definition provides a contextual framework for the light levels profiled in our cardiothoracic ward.

3.1.1. Hospital lighting environments

Eleven studies have described hospital lighting environments. These are detailed in Table 3:2. Mean daytime light levels ranging from 23.9 lux to 15500 lux were reported, indicating
<table>
<thead>
<tr>
<th>Ward</th>
<th>Measurement</th>
<th>Light levels (Lux)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical ICU</td>
<td>Compass orientation</td>
<td>( N = 34.1 \text{ (SEM = 3)} ) ( E = 30.6 \text{ (SEM = 1.3)} ) ( S = 399.2 \text{ (SEM = 146)} ) ( W = 45.9 \text{ (SEM = 5.9)} )</td>
<td>(Verceles, Liu et al. 2012)</td>
</tr>
<tr>
<td>Old and new ICU</td>
<td>Compass orientation</td>
<td><strong>Old Ward</strong> ( N = 5428.8 ) ( E = 9420.5 ) ( S = 5673.6 ) ( W = 4103.2 ) ( New Ward ) ( N = 1890.8 ) ( E = 12476.3 ) ( S = 23625.3 ) ( W = 3695.3 )</td>
<td>(Shepley, Gerbi et al. 2012)</td>
</tr>
<tr>
<td>Old Psychiatric Ward, New Secure Psychiatric Unit</td>
<td>Cloudless day between 11:00 a.m. and 12:00 p.m.</td>
<td><strong>Old Ward</strong> Bedroom = 190 Lounge = 165 Recreation area = 170 Dining area = 900 <strong>Secure Psychiatric Unit</strong> Bedroom = 1800 Lounge = 2700 Recreation area = 400 Dining area = 1600</td>
<td>(Olver, Love et al. 2009)</td>
</tr>
<tr>
<td>ICU (Medical, Cardiothoracic, Neuroscience), Acute Care Rooms</td>
<td>Light meter versus Sleepwatch (24 h mean)</td>
<td><strong>Intensive Care Unit</strong> Light meter = 31.3 Sleepwatch = 23.9 <strong>Acute Care Unit</strong> Light meter = 72.6 Sleepwatch = 39.1</td>
<td>(Higgins, Winkelman et al. 2007)</td>
</tr>
<tr>
<td>Surgical unit</td>
<td>Compass orientation</td>
<td>( E = 50410 \text{ lux-hours} ) ( W = 73537 \text{ lux-hours} )</td>
<td>(Walch, Rabin et al. 2005)</td>
</tr>
<tr>
<td>Psychiatric ward</td>
<td>Cloudy and bright days at 9:00 a.m. and 5:00 p.m.</td>
<td>( E = 140 – 15500 ) ( W = 150 – 3000 )</td>
<td>(Benedetti, Colombo et al. 2001)</td>
</tr>
<tr>
<td>Chest disease ward</td>
<td>Compass orientation</td>
<td>( N = 50 – 300 \text{ lux} ) ( S = &gt; 3000 \text{ lux (fair weather)} )</td>
<td>(Wakamura and Tokura 2001)</td>
</tr>
<tr>
<td>Cardiovascular ICU</td>
<td>Compass orientation</td>
<td>( N = 200 – 400 ) ( E = 400 – 2000 ) ( S = 1200 – 2500 )</td>
<td>(Beauchemin and Hays 1998)</td>
</tr>
<tr>
<td>Psychiatric ward</td>
<td>Cloudy and bright days</td>
<td>Bright room = 500 – 5000 Dim room = 200 – 300</td>
<td>(Beauchemin and Hays 1996)</td>
</tr>
<tr>
<td>Neonatal ICU</td>
<td>At 1:00 p.m. and 12:30 a.m.</td>
<td>Daytime = 184 Nighttime = 34</td>
<td>(Bullough, Rea et al. 1996)</td>
</tr>
<tr>
<td>Neonatal ICU</td>
<td>40 inches from the floor (24 h mean)</td>
<td>NICU = 300 Nursery = 164</td>
<td>(Glotzbach, Rowlett et al. 1993)</td>
</tr>
</tbody>
</table>

Table 3:2
Light intensities recorded in 14 hospital environments, during different days and at different times.

*Note:* In five of these studies, measurements were taken on the basis of the direction of the room (in the table this is recorded as “compass orientation”). ICU indicates Intensive Care Unit, N indicates North, E indicates East, S indicates South and W indicates West.
A disparity in light intensity at different hospitals is to be expected, but the intra-hospital variability is noteworthy (Table 3:2). Glotzbach et al. (1993) coined the term “microenvironments” to describe the different light sources and room structures resulting in a large range of light intensities (Glotzbach, Rowlett et al. 1993). They report considerable variation within one room, from bedspace to bedspace, with a 0-1500 lux range (Glotzbach, Rowlett et al. 1993).

3.1.2. The Cardiothoracic Ward

Olver et al. (2009) recorded higher light levels in their “newer” psychiatric unit than they did in their “older” psychiatric unit (Olver, Love et al. 2009). This is interesting from our perspective because our hospital building is a newer building. One specific goal in the design of this building was the increasing of natural light levels in the wards. It was designed with a window in each patient room. To make this possible the building has a “void”, free space from the ground floor to the roof sky-lights (Figure 3:2). Internal rooms and offices wrap around the space, with windows facing it (Figure 3:1). There are 22 rooms, with five four-bed shared rooms and 15 single-bed private rooms (35 bedspaces, Figure 3:1).
Figure 3:1
The cardiothoracic ward layout. The beds spaces are numbered.

Note: The blank areas are additional facilities such as kitchens, nursing stations, storage rooms and sluice rooms. The eastern garden area (the green trees) is a walled off area. All the windows (blue) are tinted, and have sunshades and curtains. The ward is on the ground floor at street level. There is a building with 12 floors to the East and a building with 6 floors across the street to the West.

The cardiothoracic ward faces south-west (rooms six to 18, Figure 3:2).
Figure 3:2
Three photographs, taken without flash, of empty bedspaces in the cardiothoracic ward.

Note: The window coverings are open and no artificial light sources were used.
Picture A: Two bedspaces in a south-west street facing four-bed shared room (Room 15, bedspaces A and B).
Picture B: Room seven, a private south-west street facing room.
Picture C: Two bedspaces in an internal four-bed shared room, with a view into the “void” (Room 21, bedspaces B and C).

The light sources, described in Chapter 2, Section 2.3.4, predominantly provide broad-spectrum, white artificial light and natural light.
3.2. Aims

The aim of this prospective observational study was to describe the lighting environment in the cardiothoracic ward, in order to determine the levels of potentially entraining light that the postoperative cardiac patients could be exposed to.

3.3. Materials and Methods

Light levels were prospectively measured in each occupied bedspace in the cardiothoracic ward (Auckland City Hospital, Auckland, New Zealand) using actigraphs (ActiWatch 2, Philips Respironics, Bend, Oregon, USA). Devices were secured to the wall behind the head of the hospital bed, positioned horizontally to record vertical light levels. Light levels (lux) were monitored continuously in one-minute epochs for 72 h.

3.3.1. Analysis

Data were retrieved using Actiware v.5.5 (Philips Respironics, Bend, Oregon, USA). Data were handled and analyses were conducted using Microsoft Excel (Microsoft Office 2010), GraphPad Prism 6 Version 6.01 (GraphPad Software Inc., La Jolla, CA, USA) and IBM SPSS Statistics Version 19 (IBM Corporation, Armonk, NY, USA). Bedspaces were analysed individually. Light level measurements were analysed as light intensity per minute. Median light intensities during the night (7:00 p.m.–7:00 a.m.) and day (7:00 a.m.–7:00 p.m.) were calculated. Night and day times were defined according to approximate sunset and sunrise times.

3.3.1.1. Bedspace orientation and structure

Data were analysed to determine whether there were differences in the median daytime light levels on the basis of ward structure and bedspace position. The hypothesis was that bedspaces that are street-facing or have a window are significantly brighter. Bedspaces with windows were compared with bedspaces without windows using a Wilcoxon-Mann-Whitney test, to establish whether the light levels in the bedspaces with windows were brighter. Street-facing bedspaces were compared with internal bedspaces using a Wilcoxon-Mann-Whitney test, to establish whether the light levels in the bedspaces that are
street-facing were brighter. On the basis of two tests, the Bonferroni correction was used to adjust the test level from 0.05 to 0.025.
3.4. Results

3.4.1. Light measurements

Light measurement data were collected in one-minute epochs for 72 h, at 35 bedspaces. A total of 151200 (4320 datapoints, or 4320 min, per bedspace) data points contributed to the final dataset.

<table>
<thead>
<tr>
<th>Range of light levels (lux)</th>
<th>Contribution (%)</th>
<th>Night (7:00 p.m. – 7:00 a.m.; %)</th>
<th>Day (7:00 a.m. – 7:00 p.m.; %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1000</td>
<td>0.2</td>
<td>0.05</td>
<td>0.3</td>
</tr>
<tr>
<td>500 - 999</td>
<td>1.3</td>
<td>0.1</td>
<td>2.4</td>
</tr>
<tr>
<td>100 – 499</td>
<td>17.9</td>
<td>3</td>
<td>32.9</td>
</tr>
<tr>
<td>50 - 99</td>
<td>10.6</td>
<td>6</td>
<td>15.2</td>
</tr>
<tr>
<td>&lt; 50</td>
<td>63.1</td>
<td>77.2</td>
<td>49</td>
</tr>
<tr>
<td>0</td>
<td>6.9</td>
<td>13.8</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Table 3:3
The range of light levels recorded (lux) in all the bedspaces.

Eighty-one percent (80.6 %) of all the data collected were less than 100 lux (classified as “dim to moderate indoor light”); of the daytime data, 34.6% were greater than 100 lux (classified as “moderate to bright indoor light”) (Table 3:3). Sample plots of the light measurements at bedspaces in different sections of our cardiothoracic ward are presented below (Figure 3:3). The plots showing light intensities over 72 h for all the bedspaces are displayed in Appendix B.
Chapter 3: Lighting in hospital

Figure 3:3
The raw data of the light levels measured in six typical cardiothoracic ward bedspaces.

Note: The raw light intensity data (y+1, log_{10}lux) is expressed here as a function of time for bedspaces 1B (internal bedspace), bedspace 3 (bedspace with a garden-facing window), bedspace 6 (street-facing bedspace with a window), bedspace 10A (internal bedspace), bedspace 19 (void-facing bedspace with a window) and bedspace 21A (internal bedspace without a window). These data were log transformed to facilitate visual analysis, with 1 lux added to each datapoint to account for the 0 lux values. The shaded areas indicate nighttime (7:00 p.m. – 7:00 a.m.). The light intensities for each bedspace in the cardiothoracic ward are presented in Appendix B.

The median daytime (7:00 a.m.-7:00 p.m.) light intensities range from eight lux (IQR = 5.7-12.9; bedspace 15A) to 406.7 lux (IQR = 265.2-526.7; bedspace 10B) (Figure 3:4). Bedspace 15A can be classified as “very dim indoor light” and bedspace 10B as “moderate to bright light” (Scheuermaier, Laffan et al. 2010).
The median daytime (7:00 a.m.-7:00 p.m.) light levels (log_{10}\text{lux}) in each bedscape in the cardiothoracic ward, from darkest to brightest.

Note: The boxes show the median and interquartile range and the whiskers show the full range, from minimum to maximum. These data were log transformed to facilitate visual analysis, with 1 lux added to each datapoint to account for the 0 lux values. In 23 of 35 bedspaces (65.7 %) the median light levels ranged from 8 to 85.7 lux, while in 12 of the 35 bedspaces (34.3 %) median daytime light intensities of greater than 100 lux were recorded.

Sixty-six percent (65.7 %) of bedspaces had a median daytime light level of less than 100 lux. Forty-three percent had a daytime median greater than 100 lux, which can be considered “moderate to bright indoor light” (Scheuermaier, Laffan et al. 2010), and in only 14.2 % of the bedspaces median daytime light levels greater than 200 lux were recorded. In two bedspaces, median daytime light levels of greater than 300 lux were recorded (7 and 10B, 393 lux (IQR = 250.8-508.7) and 406.7 lux (IQR = 265.2-526.7), respectively). None of the median light levels recorded during the day met the criteria for “outdoor light”. The median nighttime light intensities ranged from zero lux (IQR = 0-0, bedscape 7, IQR = 0-0.6,
bedspace 21D and IQR = 0-9, bedspace 21B) to 11.8 lux (IQR = 11.1-70.3, bedspace 13) (Figure 3:5).

Figure 3:5
The median nighttime (7:00 p.m. - 7:00 a.m.) light levels (log_{10}lux) in each bedspace in the cardiothoracic ward.

Note: The boxes show the median and interquartile range and the whiskers show the full range, from minimum to maximum. These data were log transformed to facilitate visual analysis, with 1 lux added to each datapoint to account for the 0 lux values. In 34 bedspaces, median nighttime light levels were less than 10 lux; in one bedspace the median nighttime light level was 11.8 lux (bedspace 13).

In all of the bedspaces save one (bedspace 13, 11.8 lux), the median nighttime light levels fell within the “very dim indoor light” category (Scheuermaier, Laffan et al. 2010).
3.4.2. Ward structure and bedspace position

Light intensities at the street-facing bedspaces (Figure 3:1; bedspaces 6, 7, 8, 9, 10B, 10C, 11, 12, 13, 14, 15B, 15C, 16, 17 and 18) were compared to the internal bedspaces, orientated into the building. The daytime median light intensity at the street-facing bedspaces was 145 lux ($n = 16$, IQR = 50.2-211.5). The daytime median light intensity at the internal bedspaces was 31.3 lux ($n = 19$, IQR = 16.3-65.7). There was a statistically significant difference between the daytime (7:00 a.m. – 7:00 p.m.) median light levels in street-facing rooms and internal bedspaces ($p = .001$). Median light levels in the bedspaces facing the street were categorised as “moderate to bright” and median light levels in the internal bedspaces were categorised as “dim to moderate”.

Light intensities at the bedspaces with windows (Figure 3:1; Bedspaces 1B, 1C, 3, 4, 6, 7, 8, 9, 10B, 10C, 11, 12, 13, 14, 15B, 15C, 16, 17, 18, 19, 20, 21B and 21C) were compared to bedspaces without windows. The daytime median light intensity at bedspaces with windows was 68.3 lux ($n = 25$, IQR = 43.3-164). The daytime median light intensity at the bedspaces without windows was 29.7 lux ($n = 10$, IQR = 17.5-37.4). There was a statistically significant difference between the daytime (7:00 a.m. – 7:00 p.m.) median light levels at bedspaces with windows and bedspaces without windows ($p = .015$). Median light levels in bedspaces with windows were categorised as “moderate to bright” and median light levels in bedspaces without windows were categorised as “dim to moderate”.
3.5. Discussion

The primary objective of this chapter was to describe the lighting environment in the cardiothoracic ward. In the cardiothoracic wards at Auckland City Hospital, the broad spectrum white light levels were of “very-dim-to-moderate-to-bright” intensity (Scheuermaier, Laffan et al. 2010). Light intensities at bedspaces that have windows (median = 68.3 lux, IQR = 43.3-164) were significantly brighter than bedspaces without windows (median = 29.7 lux, IQR = 17.5-37.4, \( p = .015 \)). Bedspaces that are street-facing (median = 145 lux, IQR = 50.2-211.5) were significantly brighter than internal bedspaces (median = 31.3 lux, IQR = 16.3-65.7, \( p = .001 \)). The median was used rather than the mean due to the extensive spread of the data.

The effects of the hospital lighting environment on the circadian clock, and thus on sleep-wake cycle timing, are dependent on the sensitivity of the circadian clock to light. Intensity, wavelength and duration (particularly of broad spectrum white light) have been shown to influence the clock’s response (Dewan, Benloucif et al. 2011; Chang, Santhi et al. 2012). In two studies on the phase-shifting effects of light on the clock, intensities less than 10 lux and 30 lux, respectively, were considered too low to affect the clock (Boivin, Duffy et al. 1996; Aoki, Yamada et al. 1998). On the basis of the criteria of Aoki et al. (1998) for categorising dim light (< 10 lux) two bedspaces (bedspace 15A and 2C) had daytime median light levels insufficient for entrainment. According to the criteria for dim light set by Boivin et al. (1996) (< 30 lux), nine bedspaces (25.7 %) had daytime median light levels that were insufficient for entrainment of the circadian clock (Boivin, Duffy et al. 1996).

Kozaki et al. (2011) found no significant circadian response with a three-hour morning fluorescent light pulse up to 1500 lux, but reports show that five hours of 180 lux light for three consecutive days can phase advance the clock (+1.16 h) (Boivin, Duffy et al. 1996). In 29 bedspaces (82.8 %) the median daytime light exposure recorded was less than 180 lux, but there were four bedspaces (11.4 %) that exceeded a median of 180 lux for five hours (7:00 a.m. – 12:00 p.m.). Light levels in these four bedspaces may effectively advance the clock.
The response to very dim and very bright light in older and younger subjects is similar because of the limits of sensitivity of the pacemaker (Benloucif, Green et al. 2006). Evidence suggests that the circadian clock in older subjects is less sensitive to moderate light (Zeitzer, Dijk et al. 2000; Duffy, Zeitzer et al. 2007). In subjects 65 y and older, Duffy et al. (2007) reported decreased sensitivity to light with aging, with decreased responsiveness to light levels at moderate to bright light levels (Duffy, Zeitzer et al. 2007). Patients in this cardiothoracic ward, with a mean age of 63.2 y (SD = 10.1, recorded in 654 cardiac patients, Chapter 4), may be less sensitive to these ambient light levels.

In many of the bedspaces, light at night was evident throughout the monitoring period. The lighting at each bedspace can be controlled by the patients or by the clinical staff. Thus, the duration and intensity of the blocks of nighttime light are dependent on the activity of the patients and staff. For example, the light could be due to the required monitoring of the patients, or it may be that the patients are having trouble sleeping anyway and are turning the lights on themselves. Three hundred and fifty lux of bright light during the evening has been shown to suppress 92 % of melatonin production in young adults, while in older adults the response ranged from no suppression to a maximum of 76.8 % (Zeitzer, Dijk et al. 2000). The lowest broad spectrum white light level shown to suppress nighttime melatonin is six and a half hours of 100 lux (Zeitzer, Dijk et al. 2000). The nighttime light levels recorded here do not reach these light intensities, suggesting that the nighttime ambient light levels may be low enough to avoid impacting patients’ circadian clocks.

3.5.1. Strengths and limitations

The bedspaces were not monitored simultaneously, as there were insufficient devices and only occupied bedspaces were monitored. Considering the “microenvironment”, it is possible that light levels in other areas of the rooms, such as closer to the window, are higher (Section 3.1.1). The light levels recorded are, to a certain extent, reflective of self-selected light exposure. The lighting in the room is controlled by patients and staff, not centrally regulated. These results are consequently a reflection of the range of light levels available to
the patients, which are still very low considering the presumed sensitivity of the circadian clock.

Speculation on the potential effect of this lighting on sleep and the circadian clock is limited by the number of factors. The minimum required intensity for entrainment varies depending on, for example, interindividual differences in sensitivity of the clock, previous lighting exposure and pupillary response. However, this description of our hospital environment, using 72 h of continuous measurements is comprehensive and defining the lighting environment in this hospital provides the basic information required to examine the impact of different bedspaces on patient outcome, the subject of the next chapter. This sets the scene to determine whether a significant increase in bright light exposure in this environment would ameliorate the effects of hospitalisation, surgery and anaesthesia on sleep-wake cycles and circadian rhythms.

3.5.2. Conclusions

The ambient light levels recorded at the bedspaces in this cardiothoracic ward can be classified as “dim to moderate”. There was a significant difference between the ambient light levels in bedspaces with windows and bedspaces without windows. There was a significant difference between the ambient light levels in bedspaces that are street-facing and bedspaces that are internally rotated. In Chapter 4, I describe the use of these recorded light levels to assess the relationship between ambient lighting and the lengths of hospital stay of postoperative cardiac patients.
Chapter 4. Light environment and length of hospital stay

Chapter summary

Background
Studies have indicated that there may be a relationship between bright ambient hospital lighting and a decreased length of hospital stay in patients. This may be because light is central to the entrainment of the circadian clock, and entrainment may influence the well-being and recovery of patients. In our hospital setting, median daytime ambient light levels were found to range from 8 lux to 406.7 lux. The question remains of whether patients’ durations of hospital stay are related to ambient light levels, in spite of the light levels in this hospital setting being low. The aim of this audit was to determine if there is a relationship between ambient bedspace light level and postoperative patients’ lengths of stay in this cardiothoracic ward.

Methods
A prospective audit of 654 postoperative cardiac patients was conducted to investigate the relationship between the ambient light intensity (described in Chapter 3) and patients’ lengths of postoperative ward stay. The impact of light intensity on length of stay in the ward was tested using a generalised linear model. Factors that may influence recovery, such as surgery type, physical status and age, were included in the model.

Results
The median length of stay was the same in patients in dim to moderately lit rooms (0-99 lux; 5 d, IQR = 4-7) and in moderate to brightly lit rooms (100-1000 lux; 5 d, IQR = 4-7). The median length of stay of patients in bedspaces with windows (5 d, IQR = 4-7) and in bedspaces without windows (5 d, IQR = 4-7) did not differ. The median length of stay of patients in street-facing bedspaces (5 d, IQR = 4-7) and in internal bedspaces (5 d, IQR = 4-7) did not differ.

Conclusion
There was no identifiable relationship between ambient light intensity and length of stay in the ward in this group of postoperative cardiac patients. This finding may indicate that...
higher light intensities are required to influence sleep-wake cycles in postoperative cardiac patients.
4.1. Introduction

In Chapter 1, evidence for hospital inpatient sleep and circadian disruption was discussed. Postoperative circadian disruption may be attributable primarily to the effect of general anaesthesia and surgery on the circadian clock, but low hospital lighting may also have an effect. In Chapter 3, I describe the hospital lighting environment in the individual bedspaces in the cardiothoracic ward. The median daytime (7:00 a.m. – 7:00 p.m.) light levels in the ward bedspaces ranged from very dim (< 10 lux; minimum value 8 lux) to moderately lit (100-1000 lux, maximum value 406.7 lux). In this poorly lit hospital environment, a lack of entraining light signal may exacerbate sleep and circadian disruption. If patients are deprived of a substantial amount of light they may be at subsequent risk of destabilised mood, sleep disruption, circadian disruption and prolonged hospital stay.

Seven studies have investigated the effects of room lighting on patients’ lengths of hospital stay. These are summarised in Table 4:1 (Diffey and Storey 1988; Beauchemin and Hays 1996; Beauchemin and Hays 1998; Benedetti, Colombo et al. 2001; Wunsch, Gershengorn et al. 2011; Shepley, Gerbi et al. 2012; Kohn, Harhay et al. 2013). Three retrospective studies identified a statistically significant difference in patients’ lengths of hospital stay (Beauchemin and Hays 1996; Beauchemin and Hays 1998; Benedetti, Colombo et al. 2001). Patients in rooms with increased light exposure, and in rooms that are predominantly exposed to morning sunlight, had a shorter length of hospital stay (Beauchemin and Hays 1996; Beauchemin and Hays 1998; Benedetti, Colombo et al. 2001). The statistically significant differences in lengths of stay of the patients in the darker and the lighter rooms reported in those studies ranged from one day to 3.7 days. The remaining four studies presented no supporting evidence of an effect of light on patients’ lengths of stay (Table 4:1) (Diffey and Storey 1988; Wunsch, Gershengorn et al. 2011; Shepley, Gerbi et al. 2012; Kohn, Harhay et al. 2013).

In two of the three audits in which an effect of light on patients’ lengths of hospital stay was shown, the sample populations were depressed inpatients (Beauchemin and Hays 1996; Benedetti, Colombo et al. 2001). Patients with depression have been shown to be susceptible
to lighting environment changes (Partonen 1995; Postolache and Oren 2005; Fonken, Finy et al. 2009). Shepley et al. (2012) found no effect of light levels on patients’ lengths of stay in cardiac surgical and chronic obstructive pulmonary disease patients (COPD) (Shepley, Gerbi et al. 2012). Wunsch et al. (2011) studied patients suffering from head injuries (critically ill with subarachnoid haemorrhage), a pathology which may decrease the circadian response to light (Wunsch, Gershengorn et al. 2011).

<table>
<thead>
<tr>
<th>Environment</th>
<th>Population</th>
<th>Measurement</th>
<th>n</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital*</td>
<td>All patients</td>
<td>Season</td>
<td>334828</td>
<td>-</td>
<td>(Diffey and Storey 1988)</td>
</tr>
<tr>
<td>Psychiatric ward*</td>
<td>Severe depression</td>
<td>Light levels</td>
<td>174</td>
<td>↑</td>
<td>(Beauchemin and Hays 1996)</td>
</tr>
<tr>
<td>Cardiac ICU*</td>
<td>Myocardial infarction</td>
<td>Compass orientation²</td>
<td>628</td>
<td>↑,↑</td>
<td>(Beauchemin and Hays 1998)</td>
</tr>
<tr>
<td>Psychiatric ward*</td>
<td>Bipolar, unipolar depression</td>
<td>Compass orientation², season</td>
<td>187 (bi); 415 (uni)</td>
<td>↑ (bi)</td>
<td>(Benedetti, Colombo et al. 2001)</td>
</tr>
<tr>
<td>Neurological ICU</td>
<td>SAH</td>
<td>Window</td>
<td>789</td>
<td>-</td>
<td>(Wunsch, Gershengorn et al. 2011)</td>
</tr>
<tr>
<td>Cardiovascular ICU</td>
<td>Cardiac surgical, COPD</td>
<td>Light levels</td>
<td>110</td>
<td>-</td>
<td>(Shepley, Gerbi et al. 2012)</td>
</tr>
<tr>
<td>Medical ICU*</td>
<td>Mixed</td>
<td>Window</td>
<td>6336</td>
<td>-</td>
<td>(Kohn, Harhay et al. 2013)</td>
</tr>
</tbody>
</table>

Table 4:1
An overview of studies investigating the effects of lighting environment on patient recovery.

Note: An asterisk (*) indicates a retrospective study, ICU indicates Intensive Care Unit, a dash (-) indicates no change seen, an ↑ indicates light positively influencing outcome, 1 indicates north versus south, 2 indicates east versus west, ‘bi’ indicates bipolar, ‘uni’ indicates unipolar, SAH indicates subarachnoid haemorrhage and COPD indicates chronic obstructive pulmonary disease. Three of seven studies found a relationship between light levels and length of hospital stay.

Benedetti et al. (2001) reported differences between compass orientations (east-facing rooms and west-facing rooms) ranging from 500 lux (cloudy day) to 14100 lux (bright day, avoiding sunlight) (Benedetti, Colombo et al. 2001). Beauchemin et al. (1996) reported differences between the room categories (sunny and dark rooms), ranging from 300 lux (cloudy day) to 4700 lux (bright day) as positively affecting patients’ lengths of hospital stay and mortality (Beauchemin and Hays 1996). This same group was able to show a similarly significant effect in a second ward (and a different patient population) with a difference in the range of illuminance from 1000 lux (summer) to 2300 lux (winter) between the room categories (Beauchemin and Hays 1998). It should be noted that the light levels reported in these studies were measured at specific time points (described in Table 3:2), rather than the 72 h
continuous monitoring results presented in Chapter 3. In studies showing no significant
differences in patients’ lengths of stay, only one reported light intensity measurements
(Shepley, Gerbi et al. 2012). In the studies comparing rooms with windows to rooms without
windows (assuming increased light exposure in rooms with a window), researchers found no
significant effect on patients’ lengths of hospital stay (Diffey and Storey 1988; Wunsch,

4.1.1. Factors known to affect length of hospital stay

There are a number of factors that may influence postoperative cardiac patients’ lengths of
stay which are difficult to account for. In this public hospital setting, aspects such as
socioeconomic status may not directly affect the decision to discharge the patient. Bedspaces
are at a premium, so patients are encouraged to mobilise and work hard so that they may be
discharged as soon as it is safe to do so. Conversely, elective patients may face an extended
wait for their surgeries. This example indicates that there are systemic issues inherent to the
hospital environment which cannot be predicted, but which may affect length of stay. Bed
shortages, staffing and hospital policy may affect the preoperative health state and
consequent recovery of postoperative patients. Length of stay may also be impacted by
individual complications such as infection, or may be strongly influenced by the strategies of
the consultant surgeon, as some surgeons may advocate a longer hospital stay than others.

However, there are a number of influencing factors which have been shown to affect length
of hospital stay which can be quantified and possibly controlled for in the context of a
statistical analysis.

The physical status of patients can be used to predict their postoperative outcomes. One
measure of patient status that is used to assess these cardiac patients is the American Society
of Anesthesiologists’ physical status classification system (ASA) (Table 4:2) (Wolters, Wolf
et al. 1996; Anesthesiologists 2008). There are now more developed measures available, but
this physical status classifier is available for all cardiac patients (Daabiss 2011).
ASA Physical status | Definition
--- | ---
ASA 1 | A normal healthy patient
ASA 2 | A patient with mild systemic disease
ASA 3 | A patient with severe systemic disease
ASA 4 | A patient with severe systemic disease that is a threat to life
ASA 5 | A moribund patient whose survival depends on the surgery
ASA 6 | A “brain dead” patient whose organs are being harvested for donor purposes

Table 4:2
The categories and definitions for the American Society of Anesthesiologists’ classification system for patients’ physical statuses.

The number of medications prescribed before hospital admission may also be related to physical health (Vyas, Pan et al. 2012). Polypharmacy (defined as the use of multiple medications by a patient) in patients older than 21 y has been shown to correlate with multiple comorbidities (Vyas, Pan et al. 2012). In elderly patient populations medication quantity has also been shown to correlate with patient mortality (Clark 2001; Jyrkka, Enlund et al. 2009).

Evidence regarding age-related predictors of postoperative recovery is inconsistent, with some studies showing no age-related postoperative complications, and others finding older patients have higher rates of reintubation and ICU readmission (Benetis, Sirvinskas et al. 2013; Rylski, Hoffmann et al. 2013).

A higher body mass index (BMI > 30kg/m²) may also negatively influence patient recovery. Patients with higher body mass indices have been shown to have higher ICU readmission rates and increased lengths of hospital stay (Drain, Gerrard et al. 2006; Benetis, Sirvinskas et al. 2013).

Differences have been shown in recovery and neurological outcomes in men and women after cardiac surgery (Hogue, Barzilai et al. 2001; Alam, Bandeali et al. 2013). Women have been shown to be at greater risk for complications (Hogue, Barzilai et al. 2001; Alam, Bandeali et al. 2013).

The ambient light levels shown to relate to a decrease in patients’ lengths of hospital stay are considerably higher than those measured in this hospital setting (Chapter 3). However, there
is some evidence to show that exposure for five hours of 180 lux light for three consecutive days can phase advance the clock (Boivin, Duffy et al. 1996). It is possible that having controlled for the measurable factors that could affect length of hospital stay, we may see some difference in lengths of stay between postoperative patients admitted to darker bedspaces and postoperative patients admitted to brighter bedspaces in this cardiothoracic ward.
4.2. Aims

The aim of this audit was to determine if there is a relationship between daytime ambient light levels in the bedspaces and the lengths of stay of postoperative patients in a cardiothoracic ward.

4.3. Methods

Ethics approval for this observational audit was given by the Ministry of Health Northern X Regional Ethics Committee (NTX/10/129) and locality approval was given by the Auckland District Health Board (A+4831) (Appendix C).

4.3.1. Participants

Postoperative patients aged 40 y-80 y admitted to the CVICU, and subsequently to the cardiothoracic ward, following cardiac surgery were included in this prospective audit (Figure 4:1). The audit was conducted between the 1st January 2011 and the 31st December 2011. Participants who died, moved rooms during their ward stay or were readmitted into the CVICU were excluded.

4.3.2. Hypothesis

The hypothesis was that in bedspaces in the cardiothoracic ward with brighter ambient light levels patients would have a shorter postoperative stay.

4.3.3. Data collection

Patients were identified from the CVICU admission lists on a weekly basis. Data on patient demographics, surgery type, medication, room and length of hospital stay were collected from the CVICU and ward records, from patient files and from the online patient record viewing system, CRIS.

4.3.4. Analysis

All data were handled and analysed using Microsoft Excel (Microsoft Office 2010) and IBM SPSS Statistics Version 19 (IBM Corporation, Armonk, NY, USA). A generalised linear
model (GLM) with a log link function was used to determine whether there was a relationship between light levels and patients’ lengths of stay in the ward. The response variable was length of stay in the cardiothoracic ward (measured as the number of nights spent in the ward). In order to determine whether a relationship existed, five predictor variables that relate to light levels were analysed separately (Table 4:3).

<table>
<thead>
<tr>
<th>Response variable</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay</td>
<td>The number of nights spent in the ward.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Predictor variables</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedspace light level</td>
<td>“Dim to moderate” bedspaces (0-99 lux) and “moderate to bright” bedspaces (100-1000 lux), as categorised and described in Chapter 3.</td>
</tr>
<tr>
<td>Bedspace structure</td>
<td>Bedspaces with windows versus bedspaces without windows.</td>
</tr>
<tr>
<td>Bedspace orientation</td>
<td>Street-facing bedspaces versus internal bedspaces.</td>
</tr>
<tr>
<td>Season</td>
<td>Three months per season, four in total.</td>
</tr>
<tr>
<td>Daylight saving time</td>
<td>Daylight saving dated from 1st January 2010 to the 4th April 2010, and from the 26th September 2010 to the 31st December 2010.</td>
</tr>
</tbody>
</table>

Table 4:3
The predictor variables tested to determine the relationship between light levels and length of stay.

Note: The response variable “length of stay” was used as a proxy for patient outcome. Five predictor variables were analysed to establish whether bedsight light levels statistically influenced patients’ lengths of postoperative stay in the ward. The predictor variables were modelled against length of hospital stay individually, in five separate models. The “very dim indoor light” category and the “low to moderate light” category were combined, as there were only two bedspaces in which the light levels were categorised as “very dim indoor light”

A separate GLM was constructed for each of the predictor variables listed in Table 4:3, resulting in five separate models. In addition, the relationship between patients’ lengths of stay and ambient light levels was modelled in a subset of patients who had had the same operation. The effects of light levels on length of stay in coronary patients (CABG) were tested using a univariate linear regression. The relationship between patients’ lengths of ward stay and environmental lighting was also tested in a subset of patients who spent only one night in the CVICU.

The relationship between patients’ total lengths of hospital stay and ward light levels were also tested using another GLM, to confirm that the effects of cardiothoracic ward light levels, if any, only influenced patients’ lengths of stay in the cardiothoracic ward.
The Wald Chi-Square was reported as the indicator of model effects. On the basis of eight tests performed, the Bonferroni correction was used and it was determined that a \( p < .006 \) would be considered significant. All \( p \) values were presented uncorrected.

A number of factors that may influence postoperative cardiac patients’ lengths of ward stay were included in the models to increase the probability of accurately assessing the effects of hospital lighting on length of stay (Section 4.1.1). The factors that have been shown to correlate with length of hospital stay were used to build a base GLM. All the additional factors were modelled against patients’ lengths of hospital stay (Table 4:4).

<table>
<thead>
<tr>
<th>Additional factors</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation type</td>
<td>The operations were categorised as: 1. CABG, 2. Mitral or aortic valve, 3. Combination operations, 4. Other, 5. Redone operations</td>
</tr>
<tr>
<td>Preoperative medications (before hospitalisation)</td>
<td>The number of preoperative medications listed for each patient. The three categories were less than 6, 6-9, greater than 10 (Jyrkka, Enlund et al. 2009).</td>
</tr>
<tr>
<td>Length of stay in the CVICU</td>
<td>The number of nights spent in the CVICU.</td>
</tr>
<tr>
<td>Time to extubation</td>
<td>The number of days during which the patients were intubated.</td>
</tr>
<tr>
<td>ASA</td>
<td>The possible categories range from I to VI (Table 4:2).</td>
</tr>
<tr>
<td>Age</td>
<td>The patients’ ages were restricted to 40 y–80 y for inclusion into the audit. The population was reflective of the patients included in the randomised controlled trial reported in Chapter 5.</td>
</tr>
<tr>
<td>Sex</td>
<td>Males and females.</td>
</tr>
<tr>
<td>BMI</td>
<td>kg/m(^2)</td>
</tr>
</tbody>
</table>

Table 4:4
The additional factors selected to improve the accuracy of the model. These factors have been shown to correlate with patients’ lengths of stay (Section 4.1.1).

Note: CABG indicates coronary artery bypass grafting, Combination operations indicates operations during which more than one technique was used, Other indicates the less common operation types, Redo operation indicates operations that are being redone, CVICU indicates cardiovascular intensive care unit, ASA indicates the American Society of Anesthesiologists’ patient physical status classification system, y indicates years, BMI indicates body mass index and kg/m\(^2\) indicates kilograms per metre squared.

The factors that did not significantly influence length of hospital stay were systematically excluded from the base model. The significant predictors of length of hospital stay were retained and were included, along with predictor variables relating to light exposure, in the eight independent models reported in the results.
4.4. Results

4.4.1. Patient population

Six-hundred and eighty-two patients were eligible for inclusion into the audit (Figure 4:1).

Twenty-three patients did not have a bedspace number recorded and six patients did not have their extubation time or preoperative medications listed in the records that I was able to access. Six hundred and fifty-four patients were included in the audit (Table 4:5).
Chapter 4: Light environment and length of hospital stay

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>71</td>
<td>10.9</td>
</tr>
<tr>
<td>50-59</td>
<td>159</td>
<td>24.3</td>
</tr>
<tr>
<td>60-69</td>
<td>223</td>
<td>34</td>
</tr>
<tr>
<td>70-80</td>
<td>201</td>
<td>30.7</td>
</tr>
<tr>
<td><strong>Mean (SD)</strong></td>
<td>63.2</td>
<td>(10.1)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>465</td>
<td>71</td>
</tr>
<tr>
<td>Female</td>
<td>189</td>
<td>29</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NZ European</td>
<td>321</td>
<td>49.1</td>
</tr>
<tr>
<td>Maori</td>
<td>68</td>
<td>10.4</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>87</td>
<td>13.3</td>
</tr>
<tr>
<td>Other European</td>
<td>73</td>
<td>11.2</td>
</tr>
<tr>
<td>Other ethnicity</td>
<td>99</td>
<td>15.1</td>
</tr>
<tr>
<td>Not stated</td>
<td>6</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Operation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>353</td>
<td>54</td>
</tr>
<tr>
<td>Valve replacement</td>
<td>120</td>
<td>18.3</td>
</tr>
<tr>
<td>Combination operations</td>
<td>60</td>
<td>9.2</td>
</tr>
<tr>
<td>Other</td>
<td>72</td>
<td>11</td>
</tr>
<tr>
<td>Redo operation</td>
<td>49</td>
<td>7.5</td>
</tr>
</tbody>
</table>

Table 4:5
A summary of audit participant characteristics and treatment.

Note: SD indicates standard deviation, NZ indicates New Zealand, CABG indicates coronary artery bypass grafting, Combination operation indicates an operation where more than one technique is used, Other indicates the less common operation types and Redo operation indicates operations that are being redone.

4.4.2. Length of hospital stay

The median total length of stay for all the patients following surgery was 7 days, (IQR = 6-9). The median length of stay for all the patients, following the transfer from the CVICU to the ward, was 5 d (IQR = 4-7). Patients in the “low to moderate” light intensity rooms (0-99 lux) had a median ward stay of 5 d (IQR = 4-7), while patients in the “moderate to bright” rooms had a median ward stay of 5 d (IQR = 4-7) (Scheuermaier, Laffan *et al.* 2010). Distribution of bedspace allocation in the ward was unremarkable, with the exception of bedspace 18, to which only six audit patients were allocated (median = 5 d, IQR = 4-7). The median length of stay according to bedspace light level is presented below (Figure 4:2).
Chapter 4: Light environment and length of hospital stay

Figure 4:2
The median length of stay (d) and median daytime light intensity (lux; Chapter 3) expressed as a function of bedspace number.

Note: Graph A shows the median lengths of ward stay in each bedspace. The red boxes show the median and interquartile range and the whiskers show the full range, from minimum to maximum. Graph B shows the median daytime light levels. The black boxes show the median and interquartile range and the whiskers show the full range, from minimum to maximum. The bedspaces in both graphs are ordered in increasing median daytime light intensity (refer to Chapter 3).

Upon visual inspection, there was no obvious relationship between light level expressed by bedspace and the length of stay of postoperative patients in the cardiothoracic ward (Figure 4:2).

The distribution of the response variable (length of stay in the cardiothoracic ward) was skewed and positively overdispersed (Figure 4:3). This negative binomial distribution was analysed using a generalised linear model with a log link function.
Chapter 4: Light environment and length of hospital stay

4.4.2.1. The baseline model

Of the eight external factors included in the baseline GLM, only operation type was found to significantly affect patients’ length of hospital stay ($p = .003$). Of the five operation categories, the parameter estimates of the baseline model indicated that patients who had a combination operation or a redone operation had a longer length of ward stay. Operation type was the only factor included in the subsequent models assessing the relationship between bedspace lighting and patients’ lengths of hospital stay.

Figure 4:3
The frequency distribution of length of stay in the ward (number of nights (d)), including a single outlying datapoint.

Note: The histogram indicates an overdispersed Poisson distribution, with the length of stay ranging from 2 d-72 d.

A single 72 d outlier was excluded to reduce overdispersion in the GLM (Figure 4:3).
4.4.2.2. The effects of bedspace lighting on length of stay

First, light levels (separated into two levels, 0-99 lux and 100-1000 lux) and operation type were modelled against length of hospital stay. Light levels were not found to significantly affect patient length of stay (Wald Chi-square = 0.00, df = 1, $p = .99$; Table 4:6).

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>$n$</th>
<th>SE</th>
<th>95% Confidence Intervals</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation types</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>323</td>
<td>0.16</td>
<td>-0.92 - 0.29</td>
<td>.000*</td>
</tr>
<tr>
<td>Valve</td>
<td>120</td>
<td>0.18</td>
<td>-0.8 - 0.1</td>
<td>.01</td>
</tr>
<tr>
<td>Combination</td>
<td>60</td>
<td>0.2</td>
<td>-0.73 0.07</td>
<td>.1</td>
</tr>
<tr>
<td>Other</td>
<td>72</td>
<td>0.2</td>
<td>-0.86 - 0.08</td>
<td>.02</td>
</tr>
<tr>
<td>Redo – ref.</td>
<td>48</td>
<td>-</td>
<td>- -</td>
<td>-</td>
</tr>
<tr>
<td>Light levels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-99 lux</td>
<td>384</td>
<td>0.09</td>
<td>-0.18 0.18</td>
<td>.99</td>
</tr>
<tr>
<td>100-1000 lux – ref.</td>
<td>269</td>
<td>-</td>
<td>- -</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 4:6
The parameter estimates of the generalised linear model of the relationship between light levels and operation type, and the response variable “length of stay”.

Note: SE indicates standard error, CABG indicates coronary artery bypass grafting, Redo indicates redone operations, an asterisk (*) indicates significance at an adjusted $\alpha$ of .006 and ref. indicates the predictor variable reference category. Coronary artery bypass grafting operations differed significantly in their effects on postoperative patients’ lengths of stay in the ward from the predictor variable reference category (redone operations), but the light levels in the bedspaces did not contribute to the model.

A subset analysis of only CABG patients ($n = 353$) was conducted. The relationship between length of stay and lighting in that specific population was tested using a univariate linear regression. The results indicate no relationship between bedspace light levels and length of ward stay in patients who underwent coronary artery bypass grafting ($F(1) = 0.24$, $p = .63$, $R^2 = 0.03$). There is no significant effect of bedspace lighting on length of stay in coronary patients.
To account for the patients with extended CVICU stays, a subset analysis was conducted on patients who spent only one night in the CVICU ($n = 425$). The relationship between light levels and length of stay was tested using a GLM (Table 4:7). Light levels were not found to significantly affect patients’ lengths of stay (Wald Chi-square = 0.02, df = 1, $p = .89$; Table 4:7).

<table>
<thead>
<tr>
<th>Variables</th>
<th>$n$</th>
<th>SE</th>
<th>95% Confidence Intervals</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Operation types</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>257</td>
<td>0.25</td>
<td>-1.41 -0.44</td>
<td>.000*</td>
</tr>
<tr>
<td>Valve</td>
<td>78</td>
<td>0.27</td>
<td>-1.38 -0.33</td>
<td>.001*</td>
</tr>
<tr>
<td>Combination</td>
<td>34</td>
<td>0.3</td>
<td>-1.26 -0.08</td>
<td>.03</td>
</tr>
<tr>
<td>Other</td>
<td>37</td>
<td>0.3</td>
<td>-1.47 -0.31</td>
<td>.003*</td>
</tr>
<tr>
<td>Redo – ref.</td>
<td>19</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Light levels</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-99 lux</td>
<td>262</td>
<td>0.11</td>
<td>-0.16 0.26</td>
<td>.89</td>
</tr>
<tr>
<td>100-1000 lux – ref.</td>
<td>163</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 4:7
The parameter estimates of the generalised linear model assessing the relationship between the ambient light levels and operation type, and the response variable “length of stay” in patients who stayed in the cardiovascular intensive care unit for one night only.

Note: SE indicates standard error, CABG indicates coronary artery bypass grafting, Redo indicates redone operations, an asterisk (*) indicates significance at an adjusted $\alpha$ of .006 and ref. indicates the predictor variable reference category. Coronary artery bypass grafting operations, valve operations and “other” operations differed significantly in their effects on postoperative patients’ lengths of stay in the ward from the predictor variable reference category (redone operations), but the light levels in the bedspaces did not contribute to the model.
As the light levels were measured in the cardiothoracic ward, the response variable was specific to length of stay in the ward because it was thought that ward light would only affect ward stay. To ensure that this assumption was not incorrect, the effect of ward light levels on total postoperative stay was also tested using a GLM. It was not found to be statistically significant (Wald Chi-square = 0.53, df = 1, $p = .47$; Table 4:8).

<table>
<thead>
<tr>
<th>Variables</th>
<th>$n$</th>
<th>SE</th>
<th>95% Confidence Intervals</th>
<th>Significance</th>
</tr>
</thead>
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<tr>
<td>Operation types</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>257</td>
<td>0.16</td>
<td>-1</td>
<td>-0.37</td>
</tr>
<tr>
<td>Valve</td>
<td>78</td>
<td>0.18</td>
<td>-0.87</td>
<td>-0.17</td>
</tr>
<tr>
<td>Combination</td>
<td>34</td>
<td>0.2</td>
<td>-0.79</td>
<td>0.001</td>
</tr>
<tr>
<td>Other</td>
<td>37</td>
<td>0.19</td>
<td>-0.84</td>
<td>-0.08</td>
</tr>
<tr>
<td>Redo – ref.</td>
<td>19</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Light levels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-99 lux</td>
<td>262</td>
<td>0.09</td>
<td>-0.24</td>
<td>0.11</td>
</tr>
<tr>
<td>100-1000 lux – ref.</td>
<td>163</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 4:8
The parameter estimates of the generalised linear model assessing the relationship between the ambient light levels and operation type, and the response variable “total postoperative stay”.

Note: SE indicates standard error, CABG indicates coronary artery bypass grafting, Redo indicates redone operations, an asterisk (*) indicates significance at an adjusted $\alpha$ of .006 and ref. indicates the predictor variable reference category. Coronary artery bypass grafting operations and valve operations differed significantly in their effects on total postoperative stay from the predictor variable reference category (redone operations), but the light levels in the bedspaces do not contribute to the model.
4.4.2.3. The effect of bedspace structure and position on length of stay

Data were analysed using a GLM to establish whether being in a bedspace with a window or without a window affected patients’ length of stay (Table 4:9). The presence of a window in the bedspaces did not significantly affect patients’ lengths of stay (Wald Chi-square = 0.15, df = 1, \( p = .7 \); Table 4:9).

<table>
<thead>
<tr>
<th>Variables</th>
<th>( n )</th>
<th>SE</th>
<th>95% Confidence Intervals</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation Type</td>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>CABG</td>
<td>353</td>
<td>0.16</td>
<td>-0.92</td>
<td>-0.29</td>
</tr>
<tr>
<td>Valve</td>
<td>120</td>
<td>0.18</td>
<td>-0.81</td>
<td>-0.1</td>
</tr>
<tr>
<td>Combination</td>
<td>60</td>
<td>0.21</td>
<td>-0.74</td>
<td>0.06</td>
</tr>
<tr>
<td>Other</td>
<td>72</td>
<td>0.2</td>
<td>-0.86</td>
<td>-0.09</td>
</tr>
<tr>
<td>Redo – ref.</td>
<td>48</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Window presence</td>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>Window</td>
<td>458</td>
<td>0.1</td>
<td>-0.15</td>
<td>0.22</td>
</tr>
<tr>
<td>No window – ref.</td>
<td>195</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 4:9
The parameter estimates of the generalised linear model of the relationship between the presence of a window in the bedspace and operation type, and the response variable “length of stay”.

\textit{Note:} SE indicates standard error, CABG indicates coronary artery bypass grafting, Redo indicates redone operations, an asterisk (*) indicates significance at an adjusted \( \alpha \) of .006 and \textit{ref.} indicates the predictor variable reference category. Coronary artery bypass grafting operations differed significantly in their effects on patients’ postoperative lengths of stay in the ward from the predictor variable reference category (redone operations), but the presence of a window did not contribute to the model.
Patients’ lengths of ward stay were also analysed against bedspace orientation using a GLM (Table 4:10). Whether the bedspaces were street-facing or internal did not significantly affect patients’ length of stay (Wald Chi-square = 0.003, df = 1, \( p = .86 \); Table 4:10).

<table>
<thead>
<tr>
<th>Variables</th>
<th>n</th>
<th>SE</th>
<th>95% Confidence Intervals</th>
<th>Significance</th>
</tr>
</thead>
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<tr>
<td>Operation Type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>353</td>
<td>0.16</td>
<td>-0.92 -0.29</td>
<td>.000*</td>
</tr>
<tr>
<td>Valve</td>
<td>120</td>
<td>0.18</td>
<td>-0.8 -0.1</td>
<td>.01</td>
</tr>
<tr>
<td>Combination</td>
<td>60</td>
<td>0.21</td>
<td>-0.74 0.07</td>
<td>.1</td>
</tr>
<tr>
<td>Other</td>
<td>72</td>
<td>0.2</td>
<td>-0.86 -0.08</td>
<td>.02</td>
</tr>
<tr>
<td>Redo – ref.</td>
<td>48</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variables</th>
<th>n</th>
<th>SE</th>
<th>95% Confidence Intervals</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedspace orientation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Street</td>
<td>285</td>
<td>0.09</td>
<td>-0.15 0.18</td>
<td>.86</td>
</tr>
<tr>
<td>Internal – ref.</td>
<td>368</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 4:10
The parameter estimates for the generalised linear model of the relationship between bedspace orientation and operation type and the response variable “length of stay”.

Note: SE indicates standard error, CABG indicates coronary artery bypass grafting, Redo indicates redone operations, an asterisk (*) indicates significance at an adjusted \( \alpha \) of .006 and ref. indicates the predictor variable reference category. Coronary artery bypass grafting operations differed significantly in their effects on patients’ postoperative lengths of stay in the ward from the predictor variable reference category (redone operations), but the bedspace orientation did not contribute to the model.
4.4.2.4. The effect of daylight saving time on length of stay

Daylight saving time was modelled against patients’ lengths of stay to determine whether it influenced their lengths of stay in the cardiothoracic ward (Table 4:11). The results were not statistically significant (Wald Chi-square = 0.1, df = 1, p = .76).

<table>
<thead>
<tr>
<th>Variables</th>
<th>n</th>
<th>SE</th>
<th>95% Confidence Intervals</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Operation Type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>353</td>
<td>0.16</td>
<td>-0.92 -0.29</td>
<td>.000*</td>
</tr>
<tr>
<td>Valve</td>
<td>120</td>
<td>0.18</td>
<td>-0.8 -0.1</td>
<td>.01</td>
</tr>
<tr>
<td>Combination</td>
<td>60</td>
<td>0.21</td>
<td>-0.74 0.07</td>
<td>.1</td>
</tr>
<tr>
<td>Other</td>
<td>72</td>
<td>0.2</td>
<td>-0.86 -0.09</td>
<td>.02</td>
</tr>
<tr>
<td>Redo – ref.</td>
<td>48</td>
<td></td>
<td>- -</td>
<td></td>
</tr>
<tr>
<td><strong>Daylight Saving Time</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NZST</td>
<td>332</td>
<td>0.09</td>
<td>-0.19 0.14</td>
<td>.76</td>
</tr>
<tr>
<td>NZDT – ref.</td>
<td>321</td>
<td></td>
<td>- -</td>
<td></td>
</tr>
</tbody>
</table>

Table 4:11
The parameter estimates for the generalised linear model determining the relationship between daylight saving time and operation type, and the response variable “length of stay”.

Note: SE indicates standard error, CABG indicates coronary artery bypass grafting, Redo indicates redone operations, an asterisk (*) indicates significance at an adjusted α of .006, NZST indicates New Zealand standard time, NZDT indicates New Zealand daylight saving time and ref. indicates the predictor variable reference category. Coronary artery bypass grafting operations differed significantly in their effects on patients’ postoperative lengths of stay in the ward from the predictor variable reference category (redone operations), but daylight saving time did not contribute to the model.
4.4.2.5. The effect of season on length of stay

Patients’ lengths of stay in the ward were also analysed according to season. Season did not significantly affect length of stay (Wald Chi-square = 0.12, df = 3, p = 1; Table 4:12).

<table>
<thead>
<tr>
<th>Variables</th>
<th>n</th>
<th>SE</th>
<th>95% Confidence Interval</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>353</td>
<td>0.16</td>
<td>-0.92 -0.28</td>
<td>.000*</td>
</tr>
<tr>
<td>Valve</td>
<td>120</td>
<td>0.18</td>
<td>-0.80 -0.09</td>
<td>.01</td>
</tr>
<tr>
<td>Combination</td>
<td>60</td>
<td>0.21</td>
<td>-0.73 0.08</td>
<td>.11</td>
</tr>
<tr>
<td>Other</td>
<td>72</td>
<td>0.2</td>
<td>-0.86 -0.08</td>
<td>.02</td>
</tr>
<tr>
<td>Redo – ref.</td>
<td>48</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Season</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summer</td>
<td>142</td>
<td>0.12</td>
<td>-0.23 0.24</td>
<td>.96</td>
</tr>
<tr>
<td>Autumn</td>
<td>144</td>
<td>0.12</td>
<td>-0.26 0.21</td>
<td>.82</td>
</tr>
<tr>
<td>Winter</td>
<td>184</td>
<td>0.11</td>
<td>-0.25 0.2</td>
<td>.83</td>
</tr>
<tr>
<td>Spring – ref.</td>
<td>183</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 4:12
The parameter estimates for the generalised linear model determining the relationship between season and operation type, and the response variable “length of stay”.

Note: SE indicates standard error, CABG indicates coronary artery bypass grafting, Redo indicates redone operations, an asterisk (*) indicates significance at an adjusted α of .006 and ref. indicates the predictor variable reference category. Coronary artery bypass grafting operations differed significantly in their effects on length of stay from their reference category (redone operations), but season did not contribute to the model.
4.5. Discussion

There is no relationship between patients’ lengths of ward stay and light intensity in this study. This is perhaps not surprising given that while the bedspaces with windows and bedspaces facing the street were significantly brighter than bedspaces without windows and internal bedspaces, the light levels were still only categorised as “low to moderate” (Scheuermaier, Laffan et al. 2010). The light level differences in comparable trials reporting significant differences in patient length of stay were greater than those reported in this ward (Section 4.1). Benedetti et al. (2001) reported a difference between east and west rooms on a bright day (14100 lux) that is more than double the single highest value recorded in our ward (6277.6 lux) (Benedetti, Colombo et al. 2001).

As discussed in Chapter 3, the sensitivity of the human circadian pacemaker to moderate light decreases with age (Duffy, Zeitzer et al. 2007). Sixty-five percent of the patients in this audit were older than 60 y, with a mean age of 63.2 y (SD = 10.1). These cardiac patients are older, are immunocompromised and are exposed to multiple operative, pharmacological and pathological factors. It is possible that to see a significant relationship between length of hospital stay and lighting environment in this patient population, we would require greater differences in light exposure (> 1000 lux). However, it is also possible that we do not see an effect of light on patients’ lengths of hospital stay because the patients are not being affected by light. The literature indicates otherwise, but a finding that brighter light does not affect patients at all might be clinically relevant.

4.5.1. Strengths and limitations

The audit sample population was restricted to patients aged 40 y to 80 y to match the age range criteria for inclusion into the randomised controlled trial (Chapter 4). It is possible that by including patients younger than 40 y, we may see an effect of these lower light levels on patient length of stay.
The lighting environment was profiled comprehensively, but the nature of the lighting in this facility meant that the patients could select their bedspace light levels using light switches. Thus, the lighting may have changed for the individual patients. However, the range of bedspace light levels and the presumed sensitivity of the circadian pacemaker are such that a difference in length of stay may only have been identifiable between patients in the darkest possible bedspaces and those in the brightest possible bedspaces. Also, light intensity was measured at the head of the bed, but it is possible that patients spend more time out of bed than anticipated.

Light levels in the CVICU were not included in this audit as they could not be reliably and continuously monitored because of the nature and structure of the CVICU. There was nowhere to reliably place a monitor that was at head level and that did not impede the treatment of the patients. For the 427 patients who were transferred to the ward on the first postoperative morning, ward light is probably the primary entraining light signal. However, the inclusion of CVICU light levels would improve any future analyses.

This audit was conducted using a comprehensive light measurement profile. The results are difficult to extrapolate to other hospitals and other patients populations unless their ambient lighting levels are similar. However, the study is a real life prospective study which is reflective of our clinical environment. Several patient characteristics and external factors inherent to surgery and anaesthesia were controlled for in the analysis, but it should be noted that factors may be unaccounted for and that this may limit the interpretation of the results. The results may be explained by the low overall light levels in the cardiothoracic ward, or they may be because light does not affect these postoperative patients. The question raised by these findings provides a further basis for the design of a randomised placebo controlled trial to determine whether a substantial increase in ambient light levels could affect the patients.
4.5.2. Conclusion

Light levels in our cardiothoracic ward bedspaces did not appear to influence postoperative patients’ lengths of ward stay.
Chapter 5. Morning light therapy in postoperative cardiac patients

A randomised placebo controlled trial determining the effects of light therapy on sleep-wake cycles and the circadian clock

Chapter summary

Background

In Chapter 4, no relationship was identified between the ambient light levels in this cardiothoracic ward and the lengths of stay in the ward of postoperative patients. This result may be because light does not affect patients’ lengths of stay in this clinical setting, or it may be because the light levels at the bedspaces were too low to entrain patients’ circadian rhythms. To establish whether increasing light levels could decrease sleep and circadian disruption, I conducted a randomised placebo controlled trial where morning bright light therapy was administered to postoperative cardiac patients.

Methods

I aimed to recruit 60 cardiac surgical patients. Patients were evenly randomised to either morning light therapy or placebo light therapy. Patients were monitored for one night preoperatively and for 72 h postoperatively. Sleep disruption was assessed using eight actigraphically derived sleep variables monitoring sleep quantity and sleep quality, and circadian disruption was assessed using 24 h urinary 6-sulphatoxymelatonin collections. Postoperative mood was assessed at the end of study participation using the Beck Depression Inventory. Actigraphically derived rest-activity data were analysed using non-parametric circadian rhythms analysis and 6-sulphatoxymelatonin data were analysed using cosinor analysis.

Results

Sixty-one cardiac patients participated. In the light therapy group there were identifiable circadian rhythms in the mean 6-sulphatoxymelatonin excretion rates on postoperative days two and three (acrophases of 5:35 a.m. and 3:59 a.m., respectively). There were no calculable circadian rhythms in the placebo mean 6-sulphatoxymelatonin excretion rates over the 72 h of monitoring. Postoperatively, placebo patients excreted significantly less
6-sulphatoxymelatonin overnight than they did preoperatively (mean difference 261.1 ng/h, 95 % CI = 18.4-503.9, p = .03). There was no significant difference in preoperative and postoperative excretion rates in the light therapy group (mean difference = 111, CI = -95.1-417.1, p = .7). There were no significant differences between groups in the eight actigraphically derived sleep variables. There were no significant differences between groups in Beck Depression Inventory scores or patients’ lengths of hospital stay.

Conclusion
These results indicate morning light therapy influences the circadian rhythms of postoperative cardiac patients. Morning light therapy does not appear to ameliorate sleep disruption in these postoperative cardiac patients.
5.1. Introduction

The results of the audit of the relationship between ambient light levels and lengths of ward stay of postoperative cardiac patients reported in Chapter 4 indicated no relationship in this clinical setting (Beauchemin and Hays 1996; Beauchemin and Hays 1998). This finding could be attributable to low ambient light levels, with little difference in light levels between the bedspaces (Chapter 3), or it could be because there is no effect of light on these patients. I therefore designed a randomised placebo controlled trial to determine whether exposure to high intensity artificial morning light can alleviate circadian and sleep disruption after hospitalisation, surgery and anaesthesia in postoperative cardiac patients.

5.1.1. Postoperative mood disturbances

Postoperative depression has been identified as a problem in cardiac patients (Gallagher, McKinley et al. 2004; Goyal, Macfadyen et al. 2005; Yin, Luo et al. 2005; Broadbent, Ellis et al. 2006; Doering, Magsarili et al. 2006). Patients report postoperative social, emotional and physical problems (Gallagher, McKinley et al. 2004). These symptoms correlate significantly with postoperative complications, nausea, pain, poor appetite and, most importantly, with sleep disturbances (Gallagher, McKinley et al. 2004; Goyal, Macfadyen et al. 2005).

The cause has not been definitively determined, but there is an established connection between sleep disruption and mood disturbances. In a study of 59 patients diagnosed with bipolar disorder, for example, irregular sleep-wake cycles correlated with significant mood disturbances in 41% of patients (Bauer, Grof et al. 2006). In our population of postoperative cardiac patients, the potential impact of surgery and anaesthesia on emotional well-being is worthy of investigation.

5.1.2. Postoperative in-hospital light therapy

There have been two randomised controlled trials conducted examining the effects of morning light therapy in postoperative patients (Taguchi, Yano et al. 2007; Ono, Taguchi et al. 2011). Taguchi et al. (2007) studied the effects of 5000 lux of postoperative morning
light therapy in 11 oesophagectomy patients. They determined the effects on activity, delirium and length of stay in hospital. Increased exposure to light resulted in lower delirium scores at the start of light therapy, but there was no significant difference between patients in the light therapy group and the control group at the end of patients’ hospital stays. They found no differences between patients’ lengths of hospital stay or activity level. Ono et al. (2011) studied gradually increased morning light therapy (to a maximum of 6000 lux) in 20 postoperative oesophagectomy patients. They found no effect on delirium, but a frequency analysis of rest-activity rhythms found a “circadian spectrum cycle” of 24.1 h (SD = 3.2) in the light group 21.9 h (SD = 1.5) in the control group. They took these results to indicate that light therapy patients were entrained. It should be noted that the frequency analysis used in this study assumes a sinusoidal rhythm in the rest-activity data and this is not always the case. Patients in the interventional group moved less during the night. They also found morning light therapy significantly decreased arrhythmias.
5.2. Aims

The primary objectives of this trial were:

- to determine whether morning bright light therapy can reduce postoperative circadian disruption in postoperative cardiac patients,
- to determine whether morning bright light therapy can reduce postoperative sleep disruption in postoperative cardiac patients,
- to determine whether morning bright light therapy can decrease mood disturbances in postoperative cardiac patients,
- and to determine whether morning bright light therapy can decrease the lengths of hospital stay of postoperative cardiac patients.

5.3. Materials and Methods

Ethics approval for a randomised controlled trial was given by the Ministry of Health Northern Y Ethics Committee (NTX09/09/083) and locality approval given by the Auckland District Health Board (A+4505) (Appendix E). An amendment to the original long form randomised controlled trial was approved by the Ministry of Health Northern Y Ethics Committee (NTX09/09/083) and by Auckland District Health Board (A+4505) on the 6 April 2011.

Unless otherwise stated, data analyses were performed using Microsoft Excel (Microsoft Office 2010), IBM SPSS Statistics v. 19 (IBM Corporation, Armonk, NY, USA) and GraphPad Prism 6 Version 6.01 (GraphPad Software Inc., La Jolla, CA, USA).

5.3.1. Participants

Participants were identified from acute and elective cardiac surgical lists at Auckland City Hospital between April 2011 and August 2012. Patients aged 40 y-80 y scheduled for first time cardiac surgery (not reoperations) were invited to participate (Figure 5:2). Participants gave informed consent and were not paid for their participation.
5.3.2. The hospital stay

After their surgeries patients are immediately admitted to the ICU. During their stay in the ICU patients are allocated either a room shared with three other people or one shared with one other person. Patients are monitored continuously. They have a urinary catheter and are sometimes postoperatively ventilated overnight. On the first postoperative day patients are moved to the ward, where they are allocated either a private room or a room shared with three other people. In the ward patient monitoring occurs regularly throughout the night for the first two nights, and patients often wake up during these periods. If recovery is uneventful the patients are then monitored overnight without being disturbed until discharge. The urinary catheter is removed as soon as possible to encourage mobility and recovery. Patients are encouraged to mobilise hourly for short distances throughout their postoperative ward stay.

5.3.3. Randomisation to treatment

Subjects were randomised preoperatively in blocks of four. In the event of the withdrawals of participants (due, for example, to non-compliance or cancellation of surgery), the next participant that was recruited was randomised to replace them. The results of the analyses presented in chapters three and four indicated that the ambient light levels in each bedspace did not significantly affect the patients’ lengths of stay in the cardiothoracic ward, so it was not deemed necessary to also randomise participants to specific bedspaces.

5.3.4. Light therapy

Morning light therapy was administered to patients in the interventional group using fluorescent white light boxes (Pharos, Lumie, UK). The Pharos projects an illuminance of 10000 lux at 50 cm (with a diffuser). Placebo light therapy was administered to patients in the control group using modified Pharos light boxes. The fluorescent light sources were removed and replaced with four battery-operated 5 mm red light emitting diodes (LEDS), with a wavelength range of 620-660 nm.
Chapter 5: Morning light therapy in postoperative cardiac patients

Figure 5:1
A placebo (left) and an interventional (right) light box, both lit.

Note: The placebo light box was modified by removing the fluorescent light bulbs replacing them with battery operated red light LEDs.

Light therapy was administered for two hours (beginning at 7:30 a.m.) for three consecutive postoperative mornings. This time was selected because: (a) activities in the ward usually begin around 7:00 a.m., so it was reasonable to assume that patients would be awake before therapy started and (b) as patients were restricted to their bedspaces during breakfast and ward rounds, this was thought likely to increase patient compliance. Light boxes were placed in front of the patient, angled to the side (left or right side depended on the orientation of the room and the space available), at an approximate distance of one metre. If participants were still sleeping at 7:30 a.m., the light box was turned on anyway without deliberately waking the patient. Participants were asked to remain next to the light box. I monitored the patients periodically during their therapy sessions. The light levels were monitored using the Actiwatch 2 worn postoperatively by the individual patients.

5.3.5. Chronotype

To establish chronotype, patients were asked to complete the Munich Chronotype Questionnaire after informed consent was obtained (Appendix F).
5.3.6. 6-Sulphatoxymelatonin

5.3.6.1. Hypothesis
Postoperative disruption of the circadian rhythm of 6-sulphatoxymelatonin caused by hospitalisation, surgery and anaesthesia can be reduced in participants given morning bright light therapy. This was measured using 6-sulphatoxymelatonin and cosinor analysis.

5.3.6.2. Data collection
6-sulphatoxymelatonin was collected as a marker of circadian phase and rhythmicity (0, Section 1.2.3.1). The 6-sulphatoxymelatonin sampling protocol requires the collection of all urine expelled by a participant over 24 h. These samples are collected in time bins (Table 5:1). This is a commonly accepted practice used in published field studies (Midwinter and Arendt 1991; Deacon and Arendt 1994; Barnes, Deacon et al. 1998; Arendt, Middleton et al. 2006). Participants were asked to provide one preoperative overnight “total” urine sample where all the urine voided from bed time to wake time was collected. Postoperatively, patients were asked to provide three days of urine samples, beginning at their admission to the ward after their overnight stay in the ICU (five sample bins per day) (Table 5:1).

<table>
<thead>
<tr>
<th>Preoperative</th>
<th>Postoperative (3 d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop Sample 1</td>
<td>Postop Sample 1</td>
</tr>
<tr>
<td>Overnight</td>
<td>8 a.m. - 12 p.m.</td>
</tr>
</tbody>
</table>

Table 5:1
The urine collection profile requested from each participant.

Note: Preop indicates the preoperative sampling period, Postop indicates the postoperative sampling period and d indicates days. The postoperative sampling period took place over three days. During each sampling time bin, participants were asked to collect all the urine they produced in a portable plastic urinal.

The time bins were selected to maximise the resolution of the circadian rhythms with a low frequency sampling rate. In this case, the times were selected to account for the hospital staff rounds and to coincide with the end of patient visiting hours (8:00 p.m.). The total amounts voided were collected at the end of each time bin, the volumes recorded, and samples
aliquoted into 2 ml safe-lock microcentrifuge tubes (Eppendorf AG, Germany). The tubes were labelled according to participant number and time bin, and stored at -20°C.

Concentrations of 6-sulphatoxymelatonin were determined using competitive binding enzyme linked immunosorbent assays (ELISA, Bühlmann laboratories AG, Switzerland). An external quality control was included in each assay. The mean intraassay coefficient of variation of the external control was 5.7 %, with an interassay coefficient of variation of 13.8 %.

5.3.6.3. Analysis: Cosinor analysis

The 6-sulphatoxymelatonin sample concentrations, in nanograms per millilitre (ng/ml), were converted into total 6-sulphatoxymelatonin excreted per time bin sample (ng), for each patient. The total volume of urine voided was multiplied by the concentration, as determined by the assay, and divided by the duration of the time bin (in hours). These were expressed as an excretion rate, in ng/h, for each time bin. Throughout this dataset, samples are missing because of missed collections (where patients discarded or forgot to collect a sample) or lack of urination (where patients were unable to produce a sample during a particular time bin). In the event of a missed collection, where the sample was somehow discarded, the time bin is treated as a “blank”. In the event of the patient being unable to urinate, the time bin was combined with that of the next sample and the volume divided by the sum of the hours of the two time bins.

The analysis of the circadian marker was conducted using cosinor analysis. Cosine curve analysis enables the calculation of circadian variables that accurately identify the rhythmicity of melatonin excretion. These variables include circadian phase, amplitude and mesor. Cosinor analysis was performed using Chronos-Fit v 1.06 (Zuther, Gorbey et al. 2009). According to the sampling protocol (Table 5:1), for each patient there are a maximum of five samples per day. To accurately fit a curve using cosinor analysis, a minimum of four datapoints is required. With fewer datapoints, it becomes easier to fit a curve but more points are needed to be confident in the results. The maximum number of time bins per day (five),
and the fact that the patients were assumed to be entrained to 24 h, limits the possible equations to a single harmonic. Resulting values were only accepted if the coefficient of determination (or the “goodness of fit”) was greater than 0.5, with a significance at an \( \alpha \) of .05. Patients with five datapoints or less were excluded from the overall analysis of the circadian rhythms. Individual samples that were greater than 2 standard deviations from the overall mean were excluded as outliers in keeping with the work of Wetterberg et al. (1999) indicating normal 6-sulphatoxymelatonin excretion levels (Wetterberg, Bergiannaki et al. 1999).

5.3.6.4. Analysis: Amplitude of the raw data

The amplitude of the raw data was calculated in two different ways. The 6-sulphatoxymelatonin data were analysed to determine the peak-to-trough amplitude (the difference between the peak and the nadir) and the day-night amplitude (comparing the sum of the daytime (8:00 a.m.-8:00 p.m.) and nighttime (8:00 p.m.-8:00 a.m.) values).

Only the data representing the days where the patients collected all their urine for the full 24 h collection period were used, and the analysis was conducted with all those subsequent data from the full postoperative period (72 h) grouped together. The differences between the peak-to-trough raw data amplitudes recorded in the two groups were compared using an independent sample Student’s \( t \)-test.

The data collection began at 8:00 a.m., so for the amplitude analysis I considered daytime to be from 8:00 a.m. to 8:00 p.m. Only the data from participants who provided full urine samples for daytime and nighttime urine collections were used for the day-night amplitude analysis. The analysis was conducted with all those subsequent data from the full 72 h postoperative period grouped together. The differences between the day-night raw data amplitudes recorded in the two groups were compared using an independent sample Student’s \( t \)-test.

The Bonferroni correction was used to adjust the test level considered significant from .05 to .025, on the basis of two tests.
5.3.6.5. Analysis: Overnight 6-Sulphatoxymelatonin excretion levels

Preoperative nighttime 6-sulphatoxymelatonin production was compared to the three postoperative overnight production levels (10 p.m. to wake) in each group using an analysis of variance. The patients who provided all four overnight samples were the only ones included in the analysis.

5.3.7. Actigraphy

5.3.7.1. Hypothesis

The quantity and quality of postoperative sleep can be improved in participants given morning bright light therapy treatment. This was measured using eight variables derived from rest-activity data collected using actigraphy (Table 5:2).

5.3.7.2. Data collection

Patients wore a wrist actigraph (ActiWatch 2, Mini Mitter Philips Respironics, USA) to record rest-activity rhythms. These were used to determine the timing of the sleep-wake cycles and to calculate variables indicating sleep duration and quality. Patients wore actigraphs for one preoperative night. The actigraphs were replaced on their wrists once patients were postoperatively admitted into the CVICU. Patients kept them for their stay in the CVICU and for 72 h in the cardiothoracic ward, until the morning after their final light therapy treatment day (or until 24 h after their final light therapy treatment). Data were collected in one-minute epochs. Actigraphic analysis sensitivity was set to a threshold of 20 counts. This low threshold ensured that we could differentiate between sleep and the “quiet wake” resulting from reduced postoperative activity. Patients were asked to wear the watch on the non-dominant wrist preoperatively, but where it was necessary, it was moved to the dominant wrist postoperatively (Sadeh, Sharkey et al. 1994).

5.3.7.3. Analysis: Actigraphy

The raw actigraphic data were scored using Actiware software Version 5.5 (Mini Mitter Philips Respironics, USA). Variables derived from the actigraphic data were calculated
(Table 5:2). These variables were chosen because they were thought to be the most important indicators of the presence and extent of sleep disruption in the hospital environment. They provide a measure of sleep quantity and sleep quality.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Sleep Time (TST)</td>
<td>Total time scored “sleep” – number of immobile bouts greater than one minute.</td>
</tr>
<tr>
<td>Total Activity Score (TAS)</td>
<td>Activity counts between sleep start and sleep end.</td>
</tr>
<tr>
<td>Mean Activity Score (MAS)</td>
<td>Mean value of the activity counts per minute for the assumed sleep period.</td>
</tr>
<tr>
<td>Sleep Bouts (SB)</td>
<td>Number of sleep episodes. The lower the number, signifying long periods of uninterrupted sleep, the better the sleep quality.</td>
</tr>
<tr>
<td>Fragmentation Index (FI)</td>
<td>Wake time (mobile bouts)/Sleep time (immobile bouts). A score greater than 50 shows great restlessness; less than 20 shows little restlessness.</td>
</tr>
<tr>
<td>Wake After Sleep Onset (WASO)</td>
<td>The total time (min) spent awake between the start time and the end time of the sleep interval.</td>
</tr>
<tr>
<td>Sleep Onset Latency (SOL)</td>
<td>The time between the start of a rest interval and the sleep start time.</td>
</tr>
<tr>
<td>Sleep Efficiency (SE)</td>
<td>The ratio of the time spent asleep to the interval duration, excluding the “invalid” time (expressed as a percentage).</td>
</tr>
</tbody>
</table>

Table 5:2

The sleep variables indicating sleep quantity and sleep quality, and an explanation for how each is derived from the actigraphic rest-activity data.

Note: The grey shaded variables were also used in a pilot study that formed the basis for this interventional trial (Jardim 2008).

The eight variables were calculated for the full postoperative period (72 h), and for the last night alone (Night 3). In addition to the eight variables, sleep timing was calculated using the actigraphically derived times and the times I recorded in sleep diaries. Differences were assessed for each sleep parameter using a univariate linear regression analysis. The categorical factors used as independent variables in the analysis were: randomisation (placebo or light) and zopiclone (prescribed or not prescribed). Patients who had had redone surgeries were excluded from recruitment, so surgery type was not indicated as an additional independent variable in the analyses.

The Bonferroni correction was used to adjust the test level from 0.05 to 0.004, based on twelve tests performed for the each of the two overall time periods, the full 72 h period of monitoring postoperatively and the final night of monitoring alone. Eight tests were performed on the sleep variables assessing quality and quantity and four tests were performed assessing the timing of the sleep-wake cycles. All p values were presented uncorrected.
5.3.7.4. Analysis: Non-parametric circadian rhythms analysis

Postoperative actigraphic data were also analysed using non-parametric circadian rhythms analysis (NPCRA) software written by Dr Eus van Someren, ActiWatch Activity and Sleep Analysis 5 Version 5.54 (Cambridge Neurotechnology Ltd). (Lewy and Sack 1989; Van Someren, Swaab et al. 1999). NPCRA is used to determine the coupling of the non-sinusoidal rest-activity rhythm to the underlying sinusoidal circadian rhythm.

The non-parametric circadian rhythm analysis variables are intradaily variability (IV), interdaily stability (IS) and relative amplitude (RA) (Van Someren, Swaab et al. 1999). Intradaily variability measures the extent of fragmentation of the rhythm – the frequency and extent of transitions between rest and activity (Van Someren, Lijzenga et al. 1997; Van Someren, Swaab et al. 1999). This score ranges from zero to two, with higher scores indicating a more fragmented rhythm. Interdaily stability, based on the Chi-square periodogram, quantifies variability between days, or the strength of the coupling of the rhythm to the zeitgebers (Van Someren, Lijzenga et al. 1997; Van Someren, Swaab et al. 1999). This score ranges from zero to one, where zero is totally arrhythmic and one is a perfect sine wave. Relative amplitude is the ratio of the difference between the most active ten-hour period and the least active five-hour period, and the sum of the most active ten-hour period and the least active five-hour period. As patients are hospitalised and spend a large amount of time in bed, this measurement allows us to differentiate between a reduction in physical activity and circadian disruption through dampening of the activity of the clock. This score ranges from zero to one, with higher scores indicating higher amplitude in the rest-activity rhythm.

The NPCRA variables were compared between groups using independent sample Student’s t-tests. The Bonferroni correction was used to adjust the test level from 0.05 to 0.017, based on three tests performed for each of the two time periods, the full 72 h period of monitoring postoperatively and the final night of monitoring. All p values were presented uncorrected.
5.3.8. Clinical outcomes: Mood

The hypothesis pertaining to mood scores was that there was a significant difference between the mood scores in the two groups. At the end of their participation in the trial, patients were asked to complete a self-rating mood scale, the Beck Depression Inventory (BDI, Appendix G) (Beck, Steer et al. 1996). The BDI is scored additively; high scores indicate depression. The two groups were compared to test whether morning light therapy decreases postoperative mood disturbances using a Wilcoxon-Mann-Whitney test.

One of the questions of the BDI is a subjective rating of sleep pattern change (Table 5:3).

<table>
<thead>
<tr>
<th>Score</th>
<th>Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>I have not experienced any change in my sleeping pattern.</td>
</tr>
<tr>
<td>1a</td>
<td>I sleep somewhat more than usual.</td>
</tr>
<tr>
<td>1b</td>
<td>I sleep somewhat less than usual.</td>
</tr>
<tr>
<td>2a</td>
<td>I sleep a lot more than usual.</td>
</tr>
<tr>
<td>2b</td>
<td>I sleep a lot less than usual.</td>
</tr>
<tr>
<td>3a</td>
<td>I sleep most of the day.</td>
</tr>
<tr>
<td>3b</td>
<td>I wake up 1-2 hours early and I can’t get back to sleep.</td>
</tr>
</tbody>
</table>

Table 5:3
Question 16 of the Beck Depression Inventory is a self-reported description of sleep quality. The related scores increase with a perceived change in sleep quantity.

The statements patients selected regarding their perception of their postoperative sleep patterns were compared between the two groups using a Chi-square test.

5.3.9. Clinical outcomes: Length of Stay

The hypothesis pertaining to length of stay in hospital was that there was a significant difference between the lengths of stay of the patients in the two groups. Lengths of stay in the ward were compared between the two groups using an independent sample Student’s t-test.
5.4. Results

One hundred and fifteen preoperative cardiac patients were approached until the quota of 60 evaluable patients specified in the protocol was met. Eighty-three men consented to take part in the trial (Figure 5:2).

Men and women were approached, but only men were recruited. Men outnumber women in the cardiac operative setting (71% and 29%, respectively in an audit of 654 surgical patients, Chapter 4, Table 4:5) but the fact that women did not participate may also be due, in part, to the nature of sampling for the urinary metabolite, 6-sulphatoxymelatonin. Originally, there were to be 30 patients in each treatment arm, but one actigraph malfunctioned. That patient’s 6-sulphatoxymelatonin data were usable and were retained; hence in the light treatment arm 31 patients were included.

Finally, sixty-one patients were included in the randomised controlled trial (Table 5:4). The mean participant age was 61.3 y (SD = 8.9).
5.4.1. 6-Sulphatoxymelatonin

6-sulphatoxymelatonin was the circadian marker used to monitor the effects of morning light therapy on the circadian clock. The raw data showing the complete postoperative excretion rates of 6-sulphatoxymelatonin in the placebo group (Table 5:5) and the morning light therapy group (Table 5:6) are presented here. The overall mean preoperative excretion rates were similar in the two groups. The placebo treatment arm mean excretion was 561 ng/h (SD = 399.03 ng/h, 95 % CI = 293.6 – 586.4), while the light therapy treatment arm overall excretion rate was 440 ng/h (SD = 602.2 ng/h, 95 % CI = 336.1 – 785.9).
Table 5.5
The 6-sulphatoxymelatonin excretion rates (ng/h) of participants in the placebo light therapy group (n = 30).

Note: Preop indicates preoperative samples, blank spaces indicate discarded samples, * indicates a sample that is repeated from the following time bin due to the lack of urination by the patient, patients highlighted in grey were excluded because they provided insufficient samples and samples highlighted in grey were excluded as outliers.
The 6-sulphatoxymelatonin excretion rates (ng/h) of participants in the morning light therapy group (n = 31).

Note: Preop indicates preoperative samples, blank spaces indicate discarded samples, * indicates a sample that is repeated from the following time bin due to the lack of urination by the patient, patients highlighted in grey were excluded because they provided insufficient samples and samples highlighted in grey were excluded as outliers.

Table 5:6

<table>
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<th>Patient Index</th>
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<td>31</td>
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</tbody>
</table>

Chapter 5: Morning light therapy in postoperative cardiac patients
A visual representation of the raw data showing the excretion rates of 6-sulphatoxymelatonin (ng/h) is presented (Figure 5:3). The individual raw data show a range of daytime and nighttime values in melatonin excretion, and no clear daily rhythm in either the treatment or the placebo groups. However, the values in the placebo group (Figure 5:3, A: Placebo group) appear to vary more than those in the light therapy group (Figure 5:3, B: Light group).
Figure 5:3
The raw 6-sulphatoxymelatonin excretion data for each participant in the placebo and light therapy groups.

Note: Graph A shows the placebo arm (n = 30) and graph B the light therapy arm (n = 31). Raw 6-sulphatoxymelatonin excretion data for each participant is expressed as a function of three consecutive (72 h) postoperative sampling days, from day one of morning light therapy (Postoperative Day 1). The times on the x-axis are the midpoint times of the time bins the data were collected in. Outlying datapoints and patients with five datapoints or less are excluded (Table 5:5, Table 5:6).
The mean results over the 72 h period show five peaks at different times of the day in the placebo arm (Figure 5:4). In the light therapy group there are four peaks, three of which occur after morning light therapy treatment begins, at night. This may indicate a consolidated rhythm in the morning light therapy group (Figure 5:4).
Figure 5:4
The mean 6-sulphatoxymelatonin excretion rates over the 72 h postoperative sampling period for the placebo (A) and light therapy (B) groups.

Note: Histogram A represents the placebo arm (n = 30) and histogram B represents the light therapy arm (n = 31). The mean 6-sulphatoxymelatonin excretion rates (ng/h) for each time bin are expressed as a function of three consecutive 72 h postoperative sampling days, from day one of data collection (Postoperative Day 1). The error bars indicate standard error of the mean. Outlying datapoints and patients with five datapoints or less are excluded (Table 5:5, Table 5:6).
5.4.1.1. Analysis of phase

Surgery and anaesthesia may cause a phase shift in the circadian rhythm of melatonin. If light therapy is effective in entraining the circadian clock and re-establishing robust rhythmicity, a number of days of therapy may be required to elicit an effect. I would anticipate the effect to be most evident on day three, the final therapy day. When the individual raw data for day three are presented, in a subjective visual analysis it appears that more patients in the light treatment group show a circadian rhythm in melatonin production than in the placebo group (Figure 5:5). This may indicate that patients in the morning light treatment arm may show a more consolidated rhythm.
Figure 5:5
The raw 6-sulphatoxymelatonin data for each participant across the final 24 h of data collection.

Note: The raw data from each participant, presented for the final sampling day and sampled from 8:00 a.m. for 24 h (Postoperative Day 3), are plotted as a function of time. Graph A shows the patients in the placebo arm and graph B the patients in the light therapy arm. Outlying datapoints and patients with five datapoints or less are excluded (Table 5:5, Table 5:6)
In order to determine if there is a difference in rhythmicity between the two groups, patients’ data were analysed individually. There were 19 patients in the placebo group and 20 patients in the light therapy group with sufficient datapoints for analysis on the last day of data collection. On analysis, two patients show a calculable cosinusoidal rhythm on day 3 in the light group. These patients had a mean acrophase time of 3:59 a.m. (SEM = 1:17). No patients in the placebo group had a calculable cosinusoidal rhythm.

The next step was an objective analysis of the rhythmicity of the mean 6-sulphatoxymelatonin data for placebo and light treatment groups using cosinor analysis (Figure 5:6).
Figure 5.6
The curves resulting from the cosinor analyses on the mean 6-sulphatoxymelatonin excretion rates (ng/h) for the postoperative 72 h monitoring period in the placebo group and in the light therapy group.

Note: The first three graphs (blue squares, A graphs) show the placebo group excretion rates for postoperative days one, two and three. The last three graphs (red triangles, B graphs) show the light therapy group excretion rates for postoperative days one, two and three. The excretion rates are expressed as a function of time. In the light therapy group the n ranged from a minimum of 19 to a maximum of 27 patients supplying data to any one point. In the placebo group the n ranged from a minimum of 18 to a maximum of 28 patients supplying data to any one point. In the placebo group, there were no resultant curves and day one of the light therapy group also did not result in a curve. The curve for postoperative day two in the light therapy group resulted in an acrophase time of 5:35 a.m., an amplitude of 127.1 ng/h and a mesor of 218.9 ng/h. The curve for postoperative day three in the light therapy group resulted in an acrophase time of 3:59 a.m., an amplitude of 53.3 ng/h and a mesor of 273.2 ng/h.
Chapter 5: Morning light therapy in postoperative cardiac patients

There was no identifiable cosinor rhythm for the placebo group means in any of the three days, but a cosinor rhythm was calculable in postoperative days two and three in the light therapy group means. An acrophase time of 5:35 a.m. (coefficient of determination of 0.97) on postoperative day two and an acrophase of 3:59 a.m. (coefficient of determination of 0.98) in postoperative day three were calculated (Figure 5:6). The amplitude on postoperative day two (127.1 ng/h) reduced to (53.3 ng/h) on postoperative day three in the light therapy group. The mesor on postoperative day two (218 ng/h) increased to (273.2 ng/h) on postoperative day three.

5.4.1.2. Analysis of amplitude using raw data

There were no statistically significant differences between the two treatment groups’ treatment arms’ peak-to-trough amplitudes across the postoperative 72 h period (placebo group n = 21 and light group n = 17) (Table 5:7). There were no statistically significant differences between the two treatment groups in the day-night amplitudes (placebo group n = 14 and light group n = 14) (Table 5:7).

<table>
<thead>
<tr>
<th>Mean Amplitude</th>
<th>Placebo (SEM)</th>
<th>95 % Confidence Interval</th>
<th>Light (SEM)</th>
<th>95 % Confidence Interval</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak-to-trough</td>
<td>570.4 (88.1)</td>
<td>393.9-746.9</td>
<td>533.7 (77.2)</td>
<td>378.4-688.9</td>
<td>.76</td>
</tr>
<tr>
<td>Day-night</td>
<td>-63.2 (215.6)</td>
<td>-499.7-373.2</td>
<td>-38.8 (122)</td>
<td>-286.7-209.1</td>
<td>.92</td>
</tr>
</tbody>
</table>

Table 5:7
The mean amplitudes, calculated using the raw 6-sulphatoxymelatonin excretion values.

Note: The mean peak-to-trough amplitudes were calculated using the days where patients collected all the samples in the 24 h period. The mean day-night amplitudes were calculated using the days where patients collected all the daytime (8:00 a.m. - 8:00 p.m.) and nighttime (8:00 p.m. - 8:00 a.m.) urine. The test level is an adjusted α of .025.

5.4.1.3. Nighttime 6-sulphatoxymelatonin excretion

Patients were asked to provide one overnight 6-sulphatoxymelatonin sample the night before their scheduled surgery. These preoperative samples were compared with the three postoperative overnight samples using an analysis of variance (Figure 5:7).
Figure 5.7
The mean preoperative overnight 6-sulphatoxymelatonin excretion (10:00 p.m. to 8:00 a.m.), and the mean overnight postoperative 6-sulphatoxymelatonin excretion (nights one, two and three of data collection) in the placebo and light therapy groups.

Note: The grey bars represent the placebo group and the white bars the light therapy group. Error bars indicate standard error of the mean. The graph is a representation of the means of all the overnight samples available in both groups. The statistical analysis was performed using only the data from the patients who provided all four overnight samples.

Using only the patients who provided all four overnight samples (placebo, \( n = 19 \) and light, \( n = 13 \)), the placebo group patients were found to have a significantly reduced 6-sulphatoxymelatonin excretion on their third postoperative ward night (\( F = 4.62, p = .03 \), mean difference = 261.1, 95% CI = 18.4 – 503.9), while in the light therapy group, the difference between the preoperative and postoperative excretion was not significant (\( F = 4.38, p = .7 \), mean difference = 111, CI = -95.1 – 417.1). There were no significant differences in preoperative values between groups (refer to Section 5.4.1).
5.4.2. Actigraphy

The actograms of two patients, one from each treatment arm, are presented below. The actograms show the preoperative night, and the postoperative nights. The actograms of all the patients are presented in Appendix H.

Figure 5:8
Two sample actograms, one from the placebo group (Patient 32) and one from the light therapy group (Patient 1).

Note: The actograms show the preoperative night and the postoperative follow up period. The grey shaded bars separate the preoperative and the postoperative monitoring periods.

To illustrate rest-activity rhythms of all the patients, the activity of all the participants in the groups was averaged over each postoperative day in the 72 h monitoring period to generate a form estimate (Figure 5:9).
Figure 5:9
The mean level of activity across the full 72 h postoperative monitoring period in both the placebo group (A) and the light therapy group (B).

Note: Mean activity derived from actigraphy is expressed as a function of time (hh:mm). Thirty patients were included in postoperative days one, two and three in both treatment groups.

There is no visible difference in mean rest-activity rhythms between the two groups on postoperative days one, two and three (Figure 5:9). However, the form estimates of mean activity presented are only a visual aid, they do not account for the difference in phase of the rest-activity rhythms of the individual patients.

The rest-activity data derived using actigraphy were used to calculate the eight sleep variables describing sleep quantity and sleep quality (Table 5:2). The individual mean results for each patient’s sleep variables (calculated from the three postoperative nights following start of the administration of light therapy, Table 5:8) and those calculated for each patient’s final night following light therapy (Night 3, Table 5:9) are tabulated individually. The group means and standard errors of the mean are presented separately (Table 5:10, Table 5:11).
Table 5:8
The means of each sleep variable for the participants (in both the light therapy and placebo group) across the 72 h postoperative monitoring period.

Note: TST indicates total sleep time, TAS indicates total activity score, MAS indicates mean activity score, SB indicates sleep bouts, FI indicates fragmentation index, WASO indicates wake after sleep onset, SOL indicates sleep onset latency, SE indicates sleep efficiency, min indicates minutes, c indicates counts and an asterisk (*) indicates that the patient was administered sedatives. Patient 35, patient 48 and patient 9 only supplied two nights of data. The means for each parameter are expressed in Table 5:10.
The sleep variables on the final therapy night (Night 3) for participants in both the light therapy and the placebo groups.

Note: TST indicates total sleep time, TAS indicates total activity score, MAS indicates mean activity score, SB indicates sleep bouts, FI indicates fragmentation index, WASO indicates wake after sleep onset, SOL indicates sleep onset latency, SE indicates sleep efficiency, min indicates minutes, c indicates counts and an asterisk (*) indicates that the patient was administered a sedative on night three. Blanks indicate missing patient data. The mean values for each parameter are expressed in Table 5:11.

<table>
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<tr>
<th>Placebo</th>
<th>TST (min)</th>
<th>TAS (c/min)</th>
<th>MAS (%/%)</th>
<th>SB (count)</th>
<th>FI (count)</th>
<th>WASO (min)</th>
<th>SOL (min)</th>
<th>SE (%)</th>
</tr>
</thead>
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<td>Patient</td>
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<td>(c/min)</td>
<td>(%)</td>
<td>(count)</td>
<td>(count)</td>
<td>(count)</td>
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Table 5:9
The sleep variables on the final therapy night (Night 3) for participants in both the light therapy and the placebo groups.

Chapter 5: Morning light therapy in postoperative cardiac patients
### 5.4.2.1. The effects of light therapy on sleep variables

The patients’ sleep variables over the 72 h monitoring period were compared first (Table 5:10).

<table>
<thead>
<tr>
<th>Indicates</th>
<th>Variable</th>
<th>Placebo (SEM)</th>
<th>Light (SEM)</th>
<th>$F$ ($p$)</th>
<th>$R^2$</th>
<th>$\beta$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantity</td>
<td>Total Sleep Time (min)</td>
<td>394.6 (14.34)</td>
<td>351.3 (14.9)</td>
<td>3.02 (.06)</td>
<td>.1</td>
<td>-.28</td>
<td>.03</td>
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<tr>
<td>Quality</td>
<td>Total Activity Score (counts)</td>
<td>12200.2 (1104.8)</td>
<td>13040.8 (1569.8)</td>
<td>0.25 (.78)</td>
<td>.01</td>
<td>.07</td>
<td>.61</td>
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<td>Quantity</td>
<td>Mean Activity Score (counts/min)</td>
<td>23.4 (2.14)</td>
<td>26.1 (2.7)</td>
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<td>.04</td>
<td>.12</td>
<td>.38</td>
</tr>
<tr>
<td>Quality</td>
<td>Sleep bouts (counts)</td>
<td>37.1 (3.9)</td>
<td>38.7 (3.6)</td>
<td>2.13 (.13)</td>
<td>.07</td>
<td>-.13</td>
<td>.33</td>
</tr>
<tr>
<td>Quality</td>
<td>Fragmentation index (%)</td>
<td>48.5 (3.1)</td>
<td>52.8 (3.8)</td>
<td>1.42 (.25)</td>
<td>.05</td>
<td>.14</td>
<td>.28</td>
</tr>
<tr>
<td>Quantity</td>
<td>Wake after sleep onset (min)</td>
<td>131.9 (10.5)</td>
<td>137.8 (14.8)</td>
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<td>.02</td>
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<td>.65</td>
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<td>Quantity</td>
<td>Sleep onset latency (min)</td>
<td>11 (2.6)</td>
<td>8 (1.5)</td>
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<td>.02</td>
<td>-.13</td>
<td>.32</td>
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<tr>
<td>Quality</td>
<td>Sleep efficiency (%)</td>
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<td>69.7 (2.8)</td>
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<td>.03</td>
<td>-.15</td>
<td>.25</td>
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</tbody>
</table>

Table 5:10
The means and standard errors of the mean for the eight sleep variables in the placebo and light therapy treatment arms presented over the three postoperative nights. The results of the linear regressions, and whether the variables are indicate sleep quality or sleep quantity, are also presented.

Note: SEM indicates standard error of the mean, min indicates minutes, $F$ indicates the $F$ statistic, ($p$) indicates the significance of the $F$ statistic, $R^2$ indicates the r squared statistic, $\beta$ indicates the standardised beta coefficients for the treatment the patients received (placebo or light therapy) and $p$ indicates the significance of the treatment in the model. Statistical significance was at an adjusted $\alpha$ of .004.

There were no significant differences in the eight sleep variables (Table 5:10). If light therapy is effective in the amelioration of sleep disruption, a difference between the sleep variables in the light and placebo groups is most likely to be seen on the final night of therapy (Night 3) (Table 5:11).
Table 5:11
The means and standard errors of the mean for the eight sleep variables in the placebo and light therapy treatment arms on the final night of therapy (Night 3). The results of the linear regressions, and whether the variables are indicate sleep quality or sleep quantity, are also presented.

Note: SEM indicates standard error of the mean, min indicates minutes, F indicates the F statistic, (p) indicates the significance of the F statistic, $R^2$ indicates the R squared statistic, $\beta$ indicates the standardised beta coefficients for the treatment the patients received (placebo or light therapy) and $p$ indicates the significance of the treatment in the model. Statistical significance was at an adjusted $\alpha$ of .004.

These results indicate that, on the final postoperative therapy night, there were no differences between the two groups in the sleep variables measured (Table 5:11). (Table 5:11). There was also no significant difference in zopiclone intake between the two groups (6 placebo patients versus 3 light therapy patients, $p = .25$).
5.4.2.2. The effects of light therapy on sleep and wake times

The start (wake time) and end of the active phase (sleep time) are presented here (Table 5:12).

<table>
<thead>
<tr>
<th></th>
<th>Placebo (SEM)</th>
<th>Light (SEM)</th>
<th>$F$ ($p$)</th>
<th>$R^2$</th>
<th>$\beta$</th>
<th>$p$</th>
</tr>
</thead>
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<td></td>
<td></td>
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<td></td>
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<td>21:27:36 (00:15:19)</td>
<td>21:44:24 (00:15:25)</td>
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<td>-.03</td>
<td>.8</td>
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<td>06:43:12 (00:10:48)</td>
<td>06:18:00 (00:17:31)</td>
<td>3.21 (.05)</td>
<td>.12</td>
<td>-.21</td>
<td>.12</td>
</tr>
<tr>
<td><strong>Actigraphy wake time</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative mean</td>
<td>06:39:00 (00:07:33)</td>
<td>06:19:12 (00:10:48)</td>
<td>1.7 (.2)</td>
<td>.06</td>
<td>-.21</td>
<td>.11</td>
</tr>
<tr>
<td>Night 3</td>
<td>06:31:12 (00:11:02)</td>
<td>05:52:36 (00:19:15)</td>
<td>4.67 (.01)</td>
<td>.15</td>
<td>-.33</td>
<td>.01</td>
</tr>
</tbody>
</table>

Table 5:12

The mean postoperative sleep diary and scored sleep-wake times (hh:mm:ss) for the light therapy and placebo groups. The results of the linear regressions are also presented.

Note: The postoperative mean indicates the mean results over the full postoperative monitoring period, Night 3 indicates the standard error of the mean. Statistical significance was at an adjusted $\alpha$ of .004.

The results indicate no statistically significant differences between the placebo and light therapy groups in the sleep and wake times recorded in the sleep diaries and derived from the actigraphy (Table 5:12).
5.4.2.3. Non-parametric circadian rhythms analysis

The NPCRA was calculated over the 72 h postoperative period. In order to approximate a value for the final night of therapy, NPCRA was also calculated using only the last two days of rest-activity data (Table 5:14).

<table>
<thead>
<tr>
<th>Postoperative 72 h</th>
<th>Placebo (SEM)</th>
<th>Light (SEM)</th>
<th>df</th>
<th>t</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interdaily stability</td>
<td>0.5 (0.03)</td>
<td>0.4 (0.03)</td>
<td>51</td>
<td>2.29</td>
<td>.03</td>
</tr>
<tr>
<td>Intradaily variability</td>
<td>1.1 (.06)</td>
<td>1.1 (0.06)</td>
<td>51</td>
<td>-0.49</td>
<td>.63</td>
</tr>
<tr>
<td>Relative amplitude</td>
<td>0.6 (0.02)</td>
<td>0.5 (0.03)</td>
<td>51</td>
<td>1.52</td>
<td>.13</td>
</tr>
</tbody>
</table>

Table 5:13
The postoperative non-parametric circadian rhythms analysis variables, analysed for the full 72 h of postoperative study participation and the last two days of study inclusion for both of the light therapy group and the placebo group.

Note: SEM indicates the standard error of the mean, df indicates degrees of freedom and t indicates the t statistic. Statistical significance was at an adjusted $\alpha$ of .02.

There was no statistically significant difference between the interdaily stability in the treatment arms over the 72 h period, but the results do indicate a trend (Table 5:13). There was no significant difference in the relative amplitude alone of the final 24 h period (placebo = 0.7, SEM = 0.03 and light = 0.62, SEM = 0.03, $t(55) = 1.79, p = .08$).
5.4.2.4. Light exposure

Patients in the interventional group were exposed to higher light levels than those in the placebo group (Table 5:14). This was confirmed with the actigraphy.

<table>
<thead>
<tr>
<th>Light exposure levels (Lux)</th>
<th>Placebo</th>
<th>Light</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Daytime (SEM)</td>
<td>21986.4 (5464)</td>
<td>38346.6 (7433.9)</td>
</tr>
<tr>
<td>7:30 a.m. to 9:30 a.m. (SEM)</td>
<td>33.9 (8.8)</td>
<td>136.6 (27.3)</td>
</tr>
<tr>
<td>Maximum light exposure (SEM)</td>
<td>364.3 (78.4)</td>
<td>867.6 (248.9)</td>
</tr>
</tbody>
</table>

Table 5:14
The mean daytime light exposure calculated using the light exposure recordings derived from the actigraphy data, presented for the two treatment arms over the 72 h postoperative period.

*Note:* The light levels are presented in lux and SEM indicates standard error of the mean.

5.4.3. Mood

At study conclusion, participants were asked to complete a Beck Depression Inventory Score (Appendix G). The placebo group median BDI score of 9.5 (IQR = 6-12.75) and the light therapy group median BDI score of 6 (IQR = 4-14) were not statistically or clinically significantly different ($p = .45$).
5.4.3.1. Subjective sleep patterns

Of the patients in the placebo group, 94.9% reported a change in their sleep patterns (Table 5:15). Of patients in the light therapy group, 77.4% reported a change in their sleep patterns (Section 5.4.2.1).

<table>
<thead>
<tr>
<th>Statement</th>
<th>Placebo (n)</th>
<th>Light (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have not experienced any change in my sleeping pattern.</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>I sleep somewhat more than usual.</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>I sleep somewhat less than usual.</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>I sleep a lot more than usual.</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>I sleep a lot less than usual.</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>I sleep most of the day.</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 5:15
The patients’ perceived postoperative changes in sleep patterns in the placebo and light therapy groups.

Note: The answers were tested for a significant difference in the frequency of the different responses to the statement. The results are reported below.

The results of the Chi-square analysis of the reported frequencies of the statements chosen by the patients in the two treatment groups indicate no significant differences (Chi-square = 4.5, n = 60, df = 5, p = .48).

5.4.4. Length of stay

Patients in the placebo treatment group were hospitalised from surgery to discharge for a mean 6.77 d (SEM = 0.3), while patients in the morning light therapy group were hospitalised for a mean 6.97 d (SEM = 0.6). There were no significant differences between the two treatment groups (t(58) = .3), p = .76).
5.4.5. Medications

A number of participants were administered medications that have been shown to affect the synthesis, release and metabolism of melatonin (Table 5:16).

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Mel</th>
<th>Preop</th>
<th>Operation</th>
<th>Postop ICU</th>
<th>Postop Ward</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P</td>
<td>L</td>
<td>P</td>
<td>L</td>
<td>P</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>↓</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Anti-depressants*</td>
<td>↑</td>
<td>3</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anti-emetics</td>
<td>↓</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Aspirin*</td>
<td>↓</td>
<td>25</td>
<td>25</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>β-blockers*</td>
<td>↓</td>
<td>22</td>
<td>21</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Dopamine*</td>
<td>↑</td>
<td>-</td>
<td>-</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Ketamine*</td>
<td>~</td>
<td>4</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Opioids*</td>
<td>↑</td>
<td>-</td>
<td>-</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>↓</td>
<td>8</td>
<td>12</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>↓</td>
<td>5</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Propofol Inf/Bol*</td>
<td>↑</td>
<td>-</td>
<td>-</td>
<td>17/20</td>
<td>23/21</td>
</tr>
<tr>
<td>Salbutamol*</td>
<td>↑</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 5:16
The number of study participants who were administered principal preoperative, perioperative and postoperative medications. The effects of the medications on the overall quantity of 6-sulphatoxymelatonin excreted are indicated (Dixon, Colthup et al. 1995; Ohyama, Nakajima et al. 2000; Facciola, Hidestrand et al. 2001; Norman, Piccolo et al. 2001; Chetsawang and Govitrapong 2005; Dispersyn, Pain et al. 2010; Mihara, Kikuchi et al. 2012).

Note: P indicates the placebo group; L indicates the light therapy group. Preop indicates the preoperative period, Postop indicates the postoperative period, ICU indicates the intensive care unit. The grey shaded medications affect the metabolism of melatonin and the * indicates medications that affect the synthesis and release of melatonin. ↑ indicates increased excretion of 6-sulphatoxymelatonin, ↓ indicates decreased excretion of 6-sulphatoxymelatonin, ~ indicates effects dependent on the phase of the cycle.
5.4.6. Reported side effects

Four patients in the light therapy group reported problems with: (a) feeling discomfort with the light intensity \( n = 4 \) and (b) discomfort with the high temperature of the box \( n = 3 \). Those four patients withdrew from the trial. Of the remaining patients, five in the light treatment arm reported feeling nauseous, dizzy and overheated. There were no reported side effects in the placebo group.

5.4.7. Treatment arm randomisation process

At the end of their participation in the trial, patients were asked “What group did you think you were in?” (Table 5:17).

<table>
<thead>
<tr>
<th>Answers</th>
<th>Placebo</th>
<th>Light</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Light</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Did not know</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Total n</td>
<td>24</td>
<td>20</td>
</tr>
</tbody>
</table>

Table 5:17
The answers to the question “What group did you think you were in?”

Seventy-five percent of the patients questioned in the light therapy group thought that they were in the placebo group.
5.5. Discussion

5.5.1. 6-Sulphatoxymelatonin and actigraphy

In the light therapy group we see an identifiable circadian rhythm in mean 6-sulphatoxymelatonin excretion rates on the second and third therapy days. The acrophase of the mean rhythm advanced from 5:35 a.m. (day two) to 3:59 a.m. (day three) in the light therapy group. This phase advance is in keeping with previous findings of the effects of morning light therapy on the circadian clock (Eastman, Gazda et al. 2005). There is also a decrease in the cosinor derived amplitude from 127.1 ng/h (day two) to 53.3 ng/h (day three) in the light therapy group. This dampening of the amplitude supports the results indicating a shift in acrophase, as it has been shown that there is a reciprocal relationship between amplitude changes and phase shifts (Pulivarthy, Tanaka et al. 2007). There are no identifiable circadian rhythms in the individual excretion rates of the patients in the placebo group or in the group mean 6-sulphatoxymelatonin excretion rates. Other research indicates that 48 h after major and minor surgery the rhythms of melatonin, cortisol and CBT are yet to return to normal (Gogenur, Middleton et al. 2007b; Gogenur, Ocak et al. 2006). It may be that this postoperative disruption is ameliorated in the morning bright light therapy group.

In the placebo group, overnight 6-sulphatoxymelatonin excretion levels decreased significantly from preoperative levels in the placebo group. In the light therapy patients, we do not see a significant decrease in postoperative melatonin excretion. This result is consistent with the results from studies by Gogenur et al. indicating decreased postoperative melatonin levels on the first postoperative night (Gogenur, Ocak et al. 2007; Gogenur, Middleton et al. 2007a). In our own research group, a student has recently been able to show a similar result in 12 kidney donor patients (De Villiers 2013). Gogenur et al. found that the postoperative 6-sulphatoxymelatonin excretion levels rebound after nights two and three (Gogenur, Ocak et al. 2007; Gogenur, Middleton et al. 2007a). We do not see this in the postoperative cardiac patients in the placebo group. This may be because of the severity of cardiac surgery and the subsequent postoperative treatments, such as mechanical ventilation, sedation, chest drains and painful dressing changes. In the light therapy patients, we do not
see the significant decrease in the overnight postoperative excretion rates. The result is encouraging.

There were a number of drugs administered, such as aspirin and omeprazole, which potentially affected the secretion, metabolism and excretion of the hormone melatonin (Section 1.2.3.1). These medications were, in some cases, prescribed preoperatively but it is possible that baseline 6-sulphatoxymelatonin measurement weeks prior to the hospital stay would indicate what the patients’ true natural melatonin levels were. However, as shown in Table 5:16, the number of medications prescribed were consistently comparable across the two groups and would likely be affecting patients equally.

There were no statistically significant differences in sleep quality or quantity between the two groups. However, patients in the placebo group slept longer by a mean of 64.4 min (Night 3). The direction of this change was of potential clinical importance as it contrasts with the findings of Giménez et al. (2011) when they examined the effects of an interventional dawn simulation room with an overall brighter daytime lighting level (including at least one morning hour of over 750 lux) in 107 stable cardiology patients (Giménez, Geerdinck et al. 2011). They found that total sleep time was greater by a mean of 50.5 min in hospitalised interventional patients. The reduction in total sleep time evident here is of sufficient magnitude that even though it is not statistically significant, it is worthy of discussion and possibly further investigation. It may be interpreted in a number of ways: (a) the patients in the light therapy group do not sleep better and light therapy is causing a phase advance which shortens the sleep time with no positive effects, (b) patients in the light therapy group cycle through all their sleep stages and do not need an increase in sleep time to compensate for disrupted sleep architecture, (c) patients in the placebo group sleep more because their sleep architecture is disrupted and their general sleep quality is poorer due to their low light exposure and (d) this is evidence of a type I error, accounted for by the Bonferroni correction. Gogenur et al. (2001) found that postoperative patients increased their total sleep time significantly after surgery (Gogenur, Rosenberg-Adamsen et al. 2001). Thus, it may be worth considering that the shorter total sleep time could be indicative of consolidated circadian rhythms and a faster return to baseline sleep-wake cycles.
The findings of Walch et al. (2005), indicate that increased light exposure is associated with decreased use of pain and sleep medication postoperatively (Walch, Rabin et al. 2005). We do not see this result here, but the study was not powered for this and it is possible that with greater sample numbers a difference would become evident (Walch, Rabin et al. 2005). Three of patients in the morning light therapy group were administered zopiclone (a non-benzodiazepine hypnotic); six of patients in the placebo group were administered zopiclone. With a greater \( n \) it would be interesting to determine whether patients in the placebo group feel more sleep deprived than those in the morning light therapy group, even though their total sleep time is considerably longer than patients in the interventional group.

5.5.1.1. Non-parametric circadian rhythms analysis

The differences in the NPCRA variables (interdaily stability, intradaily variability and relative amplitude) are not statistically significant. This finding is not unexpected as patients were monitored less than the recommended seven days for NPCRA.

5.5.2. Mood

There were no significant differences in the BDI. Although this result is consistent with the literature (Taguchi, Yano et al. 2007; Ono, Taguchi et al. 2011), the potential consequences of disrupted circadian rhythms for health and recovery from an operation, discussed in detail in Section 1.2.4, indicate that postoperative patients may see a decrease in immune function, a change in their sleep-wake cycle timing and a negative change in mood. It is possible that with greater sample numbers a difference between treatment groups could be identified.

5.5.3. Length of stay in hospital

There was no difference in patients’ lengths of hospital stay between the two groups. The sample size may be too small for us to see a statistically significant difference. However, this result is relevant to the questions raised in Chapter 4. Is it possible that ambient light does not affect patients, or that the light levels patients are exposed are still not strong enough? As the circadian rhythms analysis seems to indicate that the light does affect the patients, it would appear that the environmental light levels are influential. The fact that we do not see
an effect in the length of stay of the patients may indicate that: (a) light therapy of a longer
duration may be needed, (b) light therapy is not strong enough to overcome the illness and
the extensive effects of the surgery, anaesthesia and hospitalisation and (c) the timing or
duration of light therapy could be modified.

5.5.4. Randomisation to treatment

Patients were asked whether they knew which group they were randomised to. The question
was asked to establish whether blinding was successful. Seventy-five percent of the patients
questioned in the light therapy group thought that they were in the placebo group. This may
indicate that the blinding and randomisation were effective and that any results that we do see
are unlikely to be because of a placebo effect. It is interesting to note that patients did not
believe that light could be affecting their sleep, and yet only the light therapy patients
complained of side effects and both staff and patients complained that the light boxes were
sometimes uncomfortably bright.

5.5.5. Strengths and limitations

5.5.5.1. 6-Sulphatoxymelatonin sampling

One limitation of this study is the number of missing datapoints in the 6-sulphatoxymelatonin
dataset. The data were unevenly spaced and the missing data points were frequent. This
limitation is reflective of the processes of collecting data in the clinical environment. For
example, postoperative patients have difficulty with fluid balance and with passing urine after
catheter removal. Urinary 6-sulphatoxymelatonin was chosen as the circadian marker to
avoid the complications encountered with core body temperature and salivary melatonin
collections, but the method brought its own set of challenges.

Cosinor analysis was the method chosen to analyse the 6-sulphatoxymelatonin data. A
limitation of cosinor analysis is that it makes the assumption that the rhythm is sinusoidal.
This is not always the case, and that may be reflected in the results I have presented.
However, if a curve could not be assigned because the rhythm was asymmetrical, that too
may indicate circadian disruption. Cosinor analysis is well suited to dealing with the
unevenly spaced 6-sulphatoxymelatonin data. With the program I used, (Zuther, Gorbey et al. 2009) curve fit is fit when the data are below a certain goodness of fit (Section 5.3.6.3). The method I consequently used to quantify a trend that was visually obvious and to maximise the data available was to use the overall group means at each timepoint. For example, with visual inspection there were indications that in the excretion data of 12 of 20 patients in the light therapy arm (on the third day) there may be a calculable circadian rhythm. A rhythm was only calculable in the data of two of those patients and that may be because of key missing data points, even though there were a minimum of four datapoints for each patient included in the cosinor analysis. So, the overall group means were used. There are admittedly substantial flaws with this method. These data, which could be tactfully described as patchy, highlighted the need for more frequent sampling or for stricter sampling protocols.

There were patients with very high and very low excretion rates, and in particular, one patient with a consistently high excretion rate throughout their postoperative period (Patient 44). Based on the work of Mahlberg et al. and Wetterberg et al. on normative 6-sulphatoxymelatonin excretion profiles, patient 44 excreted two to three times the expected amount for a healthy subject of that age (Wetterberg, Bergiannaki et al. 1999; Mahlberg, Tilmann et al. 2006). Further investigation indicated that patient 44 was administered an infusion of dopamine throughout their postoperative period. Dopamine has been shown to increase the synthesis and release of melatonin by the pineal through binding to the D4 receptors (Gonzalez, Moreno-Delgado et al. 2012).

Patients 38, 59 and 30 had increased, seemingly spontaneous, periods of excretion which stood out amongst the overall low-level production displayed by the patients. In the case of one particular patient (patient 30), their samples were assayed a second time to ensure the result was not spurious. The other samples in the original assay were within the normal range and were considered accurate, so when the second assay supported this result, I accepted that the outlying point was correct. In this case, further investigation revealed that the patients were administered omeprazole, a CYP450 competing substrate, and amiodarone (an inhibitor
of CYP450 function) the day prior to the peaking values. It is possible that this combination may have resulted in delayed metabolism and excretion of melatonin.

The very low values throughout the results are explained by very low urine volumes. Older patients sometimes void very small quantities of very concentrated urine through the day, and sometimes overnight. Once hospital staff are made aware of this, solutions such as an investigation into kidney function or an increase in fluid intake are proposed.

5.5.5.2. Actigraphy

The validity of these actigraphic and NPCR analyses is limited with 72 h of data collection. It is preferable to have seven or more days included in the analysis to be assured of the accuracy of the result. In this study design, the minimum of three days recommended by the American Academy of Sleep Medicine were adhered to, but the results would be more robust if the monitoring period had been extended (Littner, Kushida et al. 2003). Similarly, the minimum three days of light stimuli recommended for a phase shift were adhered to (Zeitzer, Khalsa et al. 2005). In this hospital environment the length of stay in the ward can be as short as three days and in order to standardise the number of days of data, the minimum stay was adhered to. None of the participants left on day three, but 18 of them were discharged on day four, so I would have had a maximum of 96 hours in one third of our dataset. Anecdotally, some of the patients were frustrated with the participation process and with the limitations imposed by the two hours of morning light therapy. I believe that with more than 72 h of monitoring, more patients would have dropped out of the study.

In some cases, the site of actigraph placement changed postoperatively (Section 5.3.7). Agreement between dominant and non-dominant wrist actigraphy is adequate, although standardisation within a study group is recommended (Sadeh and Acebo 2002). Unfortunately, this was not always possible here. Postoperative fluid retention, intra-arterial lines and the removal of the radial artery for coronary artery bypass grafting in coronary patients precipitated the movement of the watch to the dominant wrist in some patients (Sadeh, Sharkey et al. 1994). However, studies have shown good agreement between
rest-activity data from actigraphic devices worn on the non-dominant and dominant wrists (Sadeh, Sharkey et al. 1994).

5.5.5.3. Study population
The population studied was homogeneous. This allowed me some control in a difficult study environment, but it may limit the generalisability of the findings. That only men consented to take part in the study may affect the results, particularly given the findings of Beauchemin et al. (1998). They found that women in brighter rooms stayed one day less in hospital ($p < .012$) after myocardial infarctions (Beauchemin and Hays 1998). Women refused to take part in this randomised controlled trial primarily because the sampling process was impractical for them. Postoperatively, coordination and mobility are considerably limited and women would have required assistance for the sampling collection. Another study assessing postoperative circadian rhythms in women overcame this problem by using a urinary catheter from before the surgery start through to the end of the monitoring period (Gogenur, Middleton et al. 2007b). This was not practical for our patients.

5.5.5.4. Light therapy
The timing of the morning light therapy was chosen partly for practical reasons. Perhaps timed light exposure based on chronotype or circadian time would have been more effective.

5.5.5.5. The study design
One of the limitations of the study is that the preoperative and postoperative data are of short duration. The original study design included four weeks of monitoring using a number of different methods. None of the participants completed the study in its entirety. Problems encountered included equipment faults (actigraphs and temperature monitors), data loss and patient compliance issues. It was determined that the protocol was so extensive that it was too difficult for patients to adhere to completely. My consequent challenge was to design a trial to establish whether morning light therapy can reduce postoperative sleep-wake cycle and circadian disruption with a less complex data collection profile.
To my knowledge, this is the first randomised placebo controlled trial assessing the effects of morning bright light therapy on sleep-wake cycles and the circadian clock in postoperative cardiac patients. The results indicate an improvement in the postoperative circadian rhythms of 6-sulphatoxymelatonin and a change in sleep-wake cycle timing. These findings merit further investigation.

5.5.6. Conclusion

Morning bright light therapy appears to consolidate the mean 6-sulphatoxymelatonin excretion rates of postoperative cardiac patients. There is no identifiable effect of morning light therapy on patients’ sleep, patients’ lengths of hospital stay and on patients’ postoperative mood scores.
Chapter 6. General discussion

Most people will, at least once in their lives, require hospitalisation or surgery with anaesthesia. These have been associated with the disruption of sleep-wake cycles and circadian rhythms. Sleep-wake cycles and circadian rhythms have also been shown to play roles in a number of important functions, and it is possible that sleep and circadian disruption following hospitalisation, surgery and anaesthesia may negatively affect postoperative patients’ recoveries.

In New Zealand, where public healthcare is funded, a solution to facilitate the decrease of time in hospital may benefit both the patient and the healthcare system.

Thus, the primary objectives of this thesis were three-fold:

1. to explore our hospital lighting environment and assess the ambient light levels that postoperative cardiac patients are exposed to in this clinical setting,
2. to determine the effects of the hospital lighting environment on the length of hospital stay of postoperative patients, and
3. to establish whether the acknowledged adverse effects of surgery, anaesthesia and hospitalisation on the sleep-wake cycles and circadian rhythms of postoperative cardiac patients can be ameliorated with postoperative morning bright light therapy.

6.1. A summary of the main findings

6.1.1. Validating wrist-level measurement for the estimation of eye-level light exposure

The first study in this series was an investigation into the validity of ambulatory wrist-level light monitoring devices for estimating eye-level light exposure in this clinical setting. Patients were asked to wear an eye-level light monitoring device, which was considered to be the gold standard, and a wrist-level light monitoring device, at the same time.
There was adequate agreement at eye-level light intensities of less than 5000 lux; the differences between the two devices remained less than 10 lux. At eye-level light intensities of 5000 lux or more, the differences between the devices were greater than 100 lux. Agreement between the eye- and wrist-level light measurements was influenced by time of day. During the day wrist-level measurements were on average 50 lux lower than eye-level measurements. At night wrist-level measurements were on average 50 lux higher than eye-level measurements. The results confirm the validity of wrist-level light measurement devices for assessing eye-level light exposure in the low level lighting environment of the clinical setting.

The main limitation of these data was the small number of participants. However, the collection of continuous data in one-minute epochs ensured a large dataset. This study is, to my knowledge, the first to validate wrist-level light measurements within the clinical setting. The findings are positive and they support the use of wrist-level light-monitoring for research purposes, with some confidence in the results.

6.1.2. The hospital lighting environment

Light intensity measurements were taken in one-minute epochs continuously over 72 h at the head of the bed. Median daytime (7:00 a.m. – 7:00 p.m.) bedspace light levels ranged from 8 lux to 406.7 lux. Eighty-one percent of all data collected were less than 100 lux, classified as “dim to moderate indoor light” and sixty-four percent of the daytime data collected were less than 100 lux. All the bedspaces were categorised as low or moderately lit. None of the bedspaces could be classified as “brightly lit”. Street-facing bedspaces were significantly brighter (median = 145 lux, IQR = 50.2-211.5) than internal bedspaces (median = 31.3 lux, IQR = 16.3-65.7, \( p = .015 \)). Bedspaces with windows (median = 68.3 lux, IQR = 43.3-164) were significantly brighter than bedspaces without (median = 29.7 lux, IQR = 17.5-37.4, \( p = .001 \)).

The results of this descriptive study confirmed that the ambient light levels are low in this hospital environment. There were not great differences between the brighter and the darker bedspaces. Interestingly, this problem was considered in the design of this hospital building.
All the rooms were designed to have access to natural light, but at the bedspaces the light levels measured remain within the “very-dim-to-moderate-to-bright” categories (Scheuermaier, Laffan et al. 2010).

This description of the lighting environment played a significant role in subsequent investigations into the effects of ambient light levels on postoperative cardiac patients. The results set the scene for me to determine whether this lighting environment influenced postoperative patients’ lengths of stay in hospital.

6.1.3. The effect of hospital ambient lighting environment on patients' length of hospital stay

In the study described in Chapter 4, I aimed to use the ambient hospital light levels (described in Chapter 3) to determine if there was a relationship between the ambient lighting environment in the cardiothoracic ward and the postoperative cardiac patients’ postoperative length of ward stay.

The median length of stay was the same in dim to moderately lit rooms (0-99 lux, median = 5 d, IQR = 4-7) and in moderate to brightly lit rooms (100-1000 lux, median = 5 d, IQR = 4-7); there was no significant difference. The median lengths of stay of patients in bedspaces with windows and in bedspaces without windows (5 d, IQR = 4-7 and 5 d, IQR = 4-7, respectively) were the same. The median lengths of stay of patients in internal bedspaces (5 d, IQR = 4-7) and in street-facing bedspaces (5 d, IQR = 4-7) were also the same.

This was the first prospective audit of the effects of ambient light levels on postoperative cardiac patients’ lengths of hospital stay. It was also the first audit conducted using continuously monitored light levels. The results of this audit raise an important question. Why was there no relationship between environmental light levels and length of hospital stay in this clinical setting? We saw significant differences in the light levels at bedspaces with varying positions and structures, but the differences were insufficient to affect the clock enough to influence patients’ lengths of hospital stay.
It may be that these moderate light levels are insufficient for entrainment and that they may not counteract the disruptive effects of surgery and anaesthesia on the circadian clock and sleep-wake cycles. The mean age in this patient population is 63.2 y and it may be that because of an age-related decrease in sensitivity to entraining light signals, we would require brighter light levels to see an effect on patients’ lengths of hospital stay (Duffy, Zeitzer et al. 2007). Alternatively, it may be that environmental lighting just does not affect postoperative cardiac patients. A list of quantifiable contributing factors were considered, but there are a number of additional factors, such as surgeon policy or staffing issues, which could affect the length of stay and which could not be addressed in this audit. However, the results and the subsequent questions supported the concept of a randomised controlled trial to investigate the effects of light therapy on the circadian clock and the sleep-wake cycles in this same patient population.

6.1.4. Assessing the effects of morning light therapy for the amelioration of sleep-wake cycle and circadian disruption in postoperative cardiac patients

In this single blind randomised placebo controlled trial, I aimed to establish whether morning bright light therapy can ameliorate postoperative sleep and circadian disruption because of hospitalisation, surgery and anaesthesia. Patients were asked to wear an actigraph and provide urine samples, for one preoperative night and for 72 h postoperatively.

There was no identifiable circadian rhythm in the placebo group 6-sulphatoxymelatonin excretion rates. In the light therapy group there was an identifiable circadian rhythm in the 6-sulphatoxymelatonin group means on postoperative day two (acrophase of 5:35 a.m.), with an advance in the acrophase on day three (3:59 a.m.). Postoperatively placebo patients excreted significantly less 6-sulphatoxymelatonin overnight than they did preoperatively (mean difference 261.1 ng/h, 95 % CI = 18.4-503.9, \( p = .03 \)). There were no statistically significant or clinically relevant differences in measures of sleep quality, quantity, sleep and wake times, mood scores or lengths of hospital stay.

The results of this randomised controlled trial indicate that a significant increase in morning light therapy may entrain patient circadian rhythms. While we do not see an effect of light on
patients’ lengths of hospital stay, these results show that light does affect the circadian rhythms of the patients and the quantity of 6-sulphatoxymelatonin they are excreting postoperatively. The results warrant further investigation. However, there were a number of limitations to these data. Missing datapoints, the homogeneity of the population and the short follow up time (72 h), for example, may have affected the results.

6.2. Challenges in the research presented in this thesis

6.2.1. Designing a randomised controlled trial

I began this program with a more ambitious randomised placebo controlled trial of the effects of morning light therapy on postoperative sleep-wake cycles and circadian rhythms. I recruited preoperative elective cardiac patients to participate and collected data assessing sleep-wake cycles, circadian rhythms, mood and chronotype. Collections took place preoperatively (baseline data of one week), postoperatively for the duration of their hospital stay, postoperatively at home in the week after patients were discharged from hospital and for one week three months after their surgery. After 12 months, 93 patients had been approached, 15 had been recruited and only five patients had made it through to surgery enrolled as study patients. I made the decision to start again with a different trial design more likely to be acceptable to patients. There were some useful lessons from this experience regarding data collection, time frames and study populations.

Patient compliance is an important consideration. Patients are enthusiastic when signing up, but their enthusiasm can wane, understandably, when they are tired and in pain. When data collection is extensive, it can be frustrating for the patients and the researcher. The willingness of hospital staff to comply with the requirements of a researcher must also be considered. Research is important, but it can represent additional work and difficulties for the staff. For example, in this study, staff who forgot about or were unaware of the study and were quick to clean their patients’ bedspaces sometimes discarded urine samples. The
relationships between hospital staff and researchers are important for ensuring that data collection proceeds smoothly and for encouraging further research.

6.3. Implications for theory and research

6.3.1. Validating the use of wrist-level light monitors in the clinical environment
The agreement between the wrist-level and eye-level light monitoring devices was acceptable and supports the use of wrist-level light monitoring devices in the clinical setting.

6.3.2. The effects of light therapy on 6-sulphatoxymelatonin excretion
The effects of the bright light therapy on increasing the 6-sulphatoxymelatonin excretion rates of the postoperative patients support the potential use of bright light therapy to phase-shift the clock and maintain postoperative 6-sulphatoxymelatonin excretion. More work is required to understand the clinical value of this finding.

6.4. Future directions for research

6.4.1. Timing of light therapy
The work presented in this thesis forms part of a wider body of research in our department exploring the interactions between hospitalisation, surgery and anaesthesia, and sleep-wake cycle and the circadian clock in humans. Additional work exploring the effects of general anaesthesia on the circadian clock in animal models is also on-going. Specifically, work has been completed looking at the effects of general anaesthesia on the circadian clock in the honey bee (*Apis mellifera*). In so doing, Ludin *et al.* found that the phase shifting effects of Isoflurane anaesthesia on the circadian rhythms of the honey bee ran counter to the phase shifting effects of light (Ludin, Rescan *et al.* 2012). The next logical step in this research, given the effects of light on the 6-sulphatoxymelatonin excretion rates of postoperative cardiac patients, is to determine whether light therapy administered at the same time as general anaesthesia can counteract the sleep-wake cycle and circadian disrupting effects of surgery and anaesthesia.
It is also possible that light therapy could be tailored to individual patients. The timing of the light therapy could be set by chronotype or according to the timing of the surgery. In this clinical setting that was not practical, but with patients in private rooms, perhaps even a dawn simulator could be used, with an overall increase in the light levels in the room as shown by Giménez et al. (2011) (Giménez, Geerdinck et al. 2011).

6.4.2. Other therapies

The finding that the circadian rhythms and sleep-wake cycle timing of these postoperative patients respond to light stimuli is promising. Other circadian interventions, such as timed administration of melatonin, may improve postoperative patient outcomes.

6.4.3. Timing of surgery

Cheeseman et al. found that there was no phase-shifting effect of nighttime general anaesthesia on the circadian clock of the honey bee (Cheeseman, Winnebeck et al. 2012). It would be interesting to establish whether nighttime operations have the same effects on the circadian clock and sleep-wake cycles as daytime operations.

6.5. General conclusions

In this thesis, I have described a comprehensive investigation into the effects of the hospital lighting environment, and into the efficacy of a simple, non-invasive intervention for the amelioration of postoperative sleep and circadian disruption in cardiac patients.

The major findings of this work were that:

1. commonly used wrist-level light monitors estimated eye-level light exposure at light intensities below 5000 lux reliably enough for the purposes of research, particularly if many datapoints are collected,

2. there was no relationship between median daytime hospital bedspace light intensities and the lengths of hospital stay of postoperative cardiac patient, possibly because the differences between the median light levels in the bedspaces were small,
3. in postoperative cardiac patients we saw an identifiable circadian rhythm in the group mean 6-sulphatoxymelatonin excretion rates after one day of morning bright light therapy,

4. in postoperative cardiac patients we saw the postoperative excretion levels of 6-sulphatoxymelatonin maintained after morning bright light therapy.

Overall, these results provide encouragement for more research to refine our understanding of the clinical disrupted circadian physiology in hospital after surgery. It remains to be seen whether light therapy could be used to better effect, and whether worthwhile clinical gains can be achieved this way.
List of Appendices

Appendix A  Ethics approval for the validation of wrist-level light monitoring devices.

Appendix B  Light intensity measurements over 72 hours at each of the thirty-five bedspaces in the cardiothoracic ward.

Appendix C  Ethics approval for the audit of length of hospital stay.

Appendix D  Audit results: The parameter estimates of the generalised linear models for the response variable “length of stay”.

Appendix E  Ethics approval for the randomised placebo controlled trial of morning light therapy in postoperative cardiac patients.

Appendix F  Munich Chronotype Questionnaire.

Appendix G  Beck Depression Inventory.

Appendix H  Actograms presented for sixty participants in the randomised placebo controlled trial.
Appendix A: Ethics approval for the validation of wrist-level light monitoring devices.

Northern Y Regional Ethics Committee
Ministry of Health
3rd Floor SNZ Building
254 Victoria Street
PO Box 1931
Hamilton
Phone (07) 858 7021
Fax (07) 858 7070

26 November 2008

Dr Guy Warman
Dept of Anaesthesiology
University of Auckland
PB 92 019/Auckland

Dear Dr Warman

A pilot study to monitor light exposure and sleep wake cycles in post-operative cardiac patients and its implications for hospital stay and depression.

Investigators: Dr Guy Warman, Ms Anoscara Jardim, Ms Mirjam Guesgen, Prof. Alan Merry, Dr Matthew Pawley, Prof. Christopher Steele

Ethics ref: NYT/08/08/086
Locations: Auckland City Hospital

The above study has been given ethical approval by the Northern Y Regional Ethics Committee.

Approved Documents
- Participant Information sheet, Version 1: 20/08/08.
- Consent Form, Version 1: 20/08/08.
- Sleep Diary.
- Profile of Mood States.

Certification
The Committee is satisfied that this study is not being conducted principally for the benefit of the manufacturer or distributor of the medicine or item in respect of which the trial is being carried out.

Accreditation
The Committee involved in the approval of this study is accredited by the Health Research Council and is constituted and operates in accordance with the Operational Standard for Ethics Committees, April 2006.

Final Report
The study is approved until 25 November 2009. A final report is required at the end of the study. The report form is available on http://www.ethicscommittees.health.govt.nz and should be forwarded along with a summary of the results. If the study will not be completed as advised, please forward a progress report and an application for extension of ethical approval one month before the above date.

Requirements for SAE Reporting
The Principal investigator will inform the Committee as soon as possible of the following:
- Any related study in another country that has stopped due to serious or unexpected adverse events
- Withdrawal from the market for any reason
- All serious adverse events occurring during the study in New Zealand which result in the investigator breaking the blind code at the time of the SAE or which result in hospitalisation or death.
- All serious adverse events occurring during the study worldwide which are considered related to the study medicine. Where there is a data safety monitoring board in place, serious adverse events occurring outside New Zealand may be reported quarterly.

All SAE reports must be signed by the Principal Investigator and include a comment on whether he/she considers there are any ethical issues relating to this study continuing due to this adverse event. If it is assumed by signing the report, the Principal Investigator has undertaken to ensure that all New Zealand investigators are made aware of the event.

Administered by the Ministry of Health
Approved by the Health Research Council
http://www.nhsc.govt.nz/ethicscommittees

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Amendments
All amendments to the study must be advised to the Committee prior to their implementation, except in the case where immediate implementation is required for reasons of safety. In such cases the Committee must be notified as soon as possible of the change.

Please quote the above ethics committee reference number in all correspondence.

The Principal Investigator is responsible for advising any other study sites of approvals and all other correspondence with the Ethics Committee.

It should be noted that Ethics Committee approval does not imply any resource commitment or administrative facilitation by any healthcare provider within whose facility the research is to be carried out. Where applicable, authority for this must be obtained separately from the appropriate manager within the organisation.

Yours sincerely

[Signature]

Amrita Kuruvilla
Northern Y Ethics Committee Administrator
Email: amrita_kuruvilla@moh.govt.nz
Appendix B: Light intensity measurements over 72 hours at each of the thirty-five bedspaces in the cardiothoracic ward.
Figure B:1
The raw light intensity data ($y+1$, log$_{10}$lux) expressed as a function of time for bedspaces 1A, 1B, 1C, 1D, 2A, 2B, 2C, 2D, 3 and 4. These data were log transformed, with an addition of 1 lux to each datapoint to account for the 0 lux values, to facilitate visual analysis. The shaded areas indicate nighttime (7:00 p.m. – 7:00 a.m.).
Figure B:2
The raw light intensity data ($y+1, \log_{10}\text{lux}$) expressed as a function of time for bedspaces 6, 7, 8, 9, 10A, 10B, 10C, 10D, 11 and 12. These data were log transformed, with an addition of 1 lux to each datapoint to account for the 0 lux values, to facilitate visual analysis. The shaded areas indicate nighttime (7:00 p.m.-7:00 a.m.).
Figure B:3
The raw light intensity data ($y+1, \log_{10}\text{lux}$) expressed as a function of time for beds 13, 14, 15A, 15B, 15C, 15D, 16, 17, 18 and 19. These data were log transformed, with an addition of 1 lux to each datapoint to account for the 0 lux values, to facilitate visual analysis. The shaded areas indicate nighttime (7:00 p.m. - 7:00 a.m.).
Figure B:4
The raw light intensity data ($y+1, \log_{10}\text{lux}$) expressed as a function of time for bedspaces 20, 21A, 21B, 21C and 21D. These data were log transformed, with an addition of 1 lux to each datapoint to account for the 0 lux values, to facilitate visual analysis. The shaded areas indicate nighttime (7:00 p.m.-7:00 a.m.).
Appendix C: Ethics approval for the audit of length of hospital stay.

Northern X Regional Ethics Committee  
Ministry of Health  
3rd Floor, Union Building  
650 Great South Road, Penrose  
Private Bag 30 552  
Wellesley Street, Auckland  
Phone (09) 359 9705  
Fax (09) 359 9201

Mailing Address:  
Private Bag 30 552  
Wellesley Street  
Auckland 1141

email address:  
northern_ethicscommittee@  
mohe.govt.nz

Ms Anisoara Jardim  
Dept of Anaesthesiology  
University of Auckland  
Private Bag 92 019  
Auckland 1142

Dear Anisoara

Ethics ref: NTX/10/EXP/129 (please quote in all correspondence)
Study title: Audit of duration of hospital stay following cardiac surgery
Investigators: Ms Anisoara Jardim, Professor Alan Merry
Supervisor: Dr Guy Warman

Thank you for your application received 26 July 2010. The above study has been given ethical approval by the Chairperson of the Northern X Regional Ethics Committee under delegated authority.

Approved Documents
— Protocol [updated, received 20/7/2010]
This approval is valid until 23 July 2011.

Amendments and Protocol Deviations
All significant amendments to this proposal must receive prior approval from the Committee. Significant amendments include (but are not limited to) changes to:
— the researcher responsible for the conduct of the study at a study site
— the addition of an extra study site
— the design or duration of the study
— the method of recruitment
— information sheets and informed consent procedures.

Significant deviations from the approved protocol must be reported to the Committee as soon as possible.

Annual Progress Reports and Final Reports
A Final Report is required at the conclusion of the study. The Final Report Form is available at www.ethicscommittees.health.govt.nz.

If the study is ongoing, the first Progress Report for this study is due to the Committee by 23 July 2011. The Annual Report Form that should be used is available at www.ethicscommittees.health.govt.nz. Please note that if you do not provide a progress report by this date, ethical approval may be withdrawn.

Administered by the Ministry of Health  
Approved by the Health Research Council  
www.health.govt.nz/health/research
We wish you all the best with your study.

Yours sincerely

[Signature]

Chinh Chua-Ethics Committee
Administrator
Northern X Regional Ethics Committee

Cc: ADHB Research Office
Appendix D: Audit results - The parameter estimates of the generalised linear models for the response variable “length of stay”.

The effects of bedspace lighting on length of hospital stay:

Light levels were not found to significantly affect patient length of stay (Wald Chi-square = 0.00, df = 1, p = .99).

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Table D:1

The parameter estimates of the generalised linear model of the relationship between light levels and surgery type, and the response variable “length of stay”. CABG (coronary artery bypass grafting) operations differed significantly in their effects on postoperative patients’ lengths of stay in the ward from the predictor variable reference category, but the light levels in the bedspaces did not contribute to the model.

Note: B indicates estimated coefficient, SE indicates standard error, an asterisk indicates significance at an adjusted α of .006, df indicates degrees of freedom and ref. indicates the predictor variable reference category.
Light levels were not found to significantly affect patients’ length of stay if patients had spent only one night in the CVICU (Wald Chi-square = 0.02, df = 1, p = .89).

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Table D:2
The parameter estimates of the generalised linear model of the relationship between the light levels and surgery type, and the response variable “length of stay” in patients who stayed in the CVICU for one night only. Coronary artery bypass grafting operations, valve operations and “other” operations differed significantly in their effects on postoperative patients’ lengths of ward stay from the predictor variable reference category (redone operations), but the light levels in the bedspaces did not contribute to the model.

Note: B indicates estimated coefficient, SE indicates standard error, an asterisk indicates significance at an adjusted α of .006, df indicates degrees of freedom and ref. indicates the predictor variable reference category.
The effect of ward light levels on total postoperative stay was also tested using a GLM. It was not found to be statistically significant (Wald Chi-square = 0.53, df = 1, p = .47).

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Table D:3
The parameter estimates of the generalised linear model of the relationship between the light levels and surgery type, and the response variable “total postoperative stay”. Coronary artery bypass grafting operations and valve operations differed significantly in their effects on patients’ lengths of total postoperative stay from the predictor variable reference category (redo operations), but the light levels in the bedspaces did not contribute to the model.

*Note:* B indicates estimated coefficient, SE indicates standard error, an asterisk indicates significance at an adjusted $\alpha$ of .006, df indicates degrees of freedom and ref. indicates the predictor variable reference category.
The effect of bedspace structure and position on length of stay

The presence of a window in the bedspaces did not significantly affect patients’ lengths of stay in the ward (Wald Chi-square = 0.15, df = 1, \( p = .7 \)).

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<td>Redo – ref.</td>
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</table>

| Window presence  |        |        |                          |                |
| Window           | 0.04   | 0.1    | -0.15 0.22               | 0.15, 1, .7    |
| No window – ref. |        |        |                          |                |

Table D:4
The parameter estimates of the generalised linear model of the relationship between the presence of a window in the bedspace and surgery type, and the response variable “length of stay”. Coronary artery bypass grafting operations differed significantly in their effects on postoperative patients’ lengths stay in the ward from the predictor variable reference category (redone operations), but the presence of a window in the bedspace did not contribute to the model.

Note: \( B \) indicates estimated coefficient, \( SE \) indicates standard error, an asterisk indicates significance at an adjusted \( \alpha \) of .006, df indicates degrees of freedom and \( \text{ref.} \) indicates the predictor variable reference category.
Whether the bedspaces were street-facing or internal did not significantly affect patients’ length of stay (Wald Chi-square = 0.003, df = 1, p = .9) (Table 4:9).

<table>
<thead>
<tr>
<th>Variables</th>
<th>95% Confidence Intervals</th>
<th>Hypothesis Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>SE</td>
</tr>
<tr>
<td>CABG</td>
<td>-0.6</td>
<td>0.16</td>
</tr>
<tr>
<td>Valve</td>
<td>-0.45</td>
<td>0.18</td>
</tr>
<tr>
<td>Combination</td>
<td>-0.34</td>
<td>0.21</td>
</tr>
<tr>
<td>Other</td>
<td>-0.47</td>
<td>0.2</td>
</tr>
<tr>
<td>Redo – ref.</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Bedspace orientation</td>
<td>B</td>
<td>SE</td>
</tr>
<tr>
<td>Street</td>
<td>0.02</td>
<td>0.09</td>
</tr>
<tr>
<td>Internal – ref.</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Table D:5
The parameter estimates for the generalised linear model of the relationship between bedspace orientation and surgery type and the response variable “length of stay”. Coronary artery bypass grafting operations differed significantly in their effects on postoperative patients’ lengths of ward stay from the predictor variable reference category (redone operations), but bedspace orientation did not contribute to the model.

Note: B indicates estimated coefficient, SE indicates standard error, an asterisk indicates significance at an adjusted α of .006, df indicates degrees of freedom and ref. indicates the predictor variable reference category.
The effect of daylight saving time on patient length of stay

Daylight saving time was modelled against patients’ length of hospital stay (Table 4:11). The results were not statistically significant (Wald Chi-square = 0.1, df = 1, p = .76).

<table>
<thead>
<tr>
<th>Variables</th>
<th>95% Confidence Intervals</th>
<th>Hypothesis Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery Type</td>
<td>B</td>
<td>SE</td>
</tr>
<tr>
<td>CABG</td>
<td>-0.61</td>
<td>0.16</td>
</tr>
<tr>
<td>Valve</td>
<td>-0.45</td>
<td>0.18</td>
</tr>
<tr>
<td>Combination</td>
<td>-0.34</td>
<td>0.21</td>
</tr>
<tr>
<td>Other</td>
<td>-0.47</td>
<td>0.2</td>
</tr>
<tr>
<td>Redo – ref.</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Daylight Saving Time</th>
<th>B</th>
<th>SE</th>
<th>Lower</th>
<th>Upper</th>
<th>Chi-square</th>
<th>df</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>NZST</td>
<td>-0.03</td>
<td>0.09</td>
<td>-0.19</td>
<td>0.14</td>
<td>0.1</td>
<td>1</td>
<td>.76</td>
</tr>
<tr>
<td>NZDT – ref.</td>
<td>0</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table D:6
The parameter estimates for the generalised linear model determining the relationship between daylight saving time and surgery type, and the response variable “length of stay”. CABG (coronary artery bypass grafting) operations differed significantly in their effects on postoperative patients’ lengths of ward stay from the predictor variable reference category, but daylight saving time did not contribute to the model.

Note: B indicates estimated coefficient, SE indicates standard error, an asterisk indicates significance at an adjusted α of .006, df indicates degrees of freedom, NZST indicates New Zealand standard time, NZDT indicates New Zealand daylight saving time and ref. indicates the predictor variable reference category.
The effect of season on patient length of stay

Patient length of ward stay was also analysed according to season. Season did not significantly affect length of stay (Wald Chi-Square = 0.12, df = 3, p = 1).

<table>
<thead>
<tr>
<th>Variables</th>
<th>B</th>
<th>SE</th>
<th>95% Confidence Interval</th>
<th>Hypothesis Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG</td>
<td>-0.6</td>
<td>0.16</td>
<td>(-0.92, -0.28)</td>
<td>13.48 1 .000*</td>
</tr>
<tr>
<td>Valve</td>
<td>-0.45</td>
<td>0.18</td>
<td>(-0.8, -0.09)</td>
<td>6.08 1 .014</td>
</tr>
<tr>
<td>Combination</td>
<td>-0.33</td>
<td>0.21</td>
<td>(-0.73, 0.08)</td>
<td>2.55 1 .11</td>
</tr>
<tr>
<td>Other</td>
<td>-0.47</td>
<td>0.2</td>
<td>(-0.86, -0.08)</td>
<td>5.54 1 .02</td>
</tr>
<tr>
<td>Redo – ref.</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variables</th>
<th>B</th>
<th>SE</th>
<th>95% Confidence Interval</th>
<th>Hypothesis Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summer</td>
<td>0.01</td>
<td>0.12</td>
<td>(-0.23, 0.24)</td>
<td>0.003 1 .96</td>
</tr>
<tr>
<td>Autumn</td>
<td>-0.03</td>
<td>0.12</td>
<td>(-0.26, 0.21)</td>
<td>0.05 1 .82</td>
</tr>
<tr>
<td>Winter</td>
<td>-0.02</td>
<td>0.11</td>
<td>(-0.25, 0.2)</td>
<td>0.04 1 .83</td>
</tr>
<tr>
<td>Spring – ref.</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table D:7
The parameter estimates for the generalised linear model determining the relationship between season and surgery type, and the response variable “length of stay”. CABG (coronary artery bypass grafting) operations differed significantly in their effects on postoperative patients’ lengths of ward stay from the predictor variable reference category, but season did contribute to the model.

Note: B indicates estimated coefficient, SE indicates standard error, an asterisk indicates significance at an adjusted α of .006, df indicates degrees of freedom and ref. indicates the predictor variable reference category.
Appendix E: Ethics approval for the randomised placebo controlled trial of morning light therapy in postoperative cardiac patients.

Northern X Regional Ethics Committee
Ministry of Health
3rd Floor, Union Building
650 Great South Road, Penrose
Private Bag 92 122
Wellington, New Zealand
Phone: (04) 381 4300
Fax: (04) 381 4301

Email: pat_chainey@moh.govt.nz

Please note postal address: Administrator, Northern X Regional Ethics Committee, PB 92-522 Wexford St, Auckland 1141
Phone: 09 680 9408

5 October 2009

Me Aniseora Jardim
Dept of Anaesthology
University of Auckland
PB 92 019
Auckland

Dear Aniseora

NTX/09/09/083
The effects of interventional light exposure on sleep-wake cycles in a post-operative cardiac population: PEB/Cens V92, 28/09/09
Principal Investigator: Me Aniseora Jardim
Co-investigators: Dr Guy Warner (supervisor), Prof. Alan Merry, Dr Matthew Pawley
Auckland DHB

Thank you for your letter 28 September 2009 attaching the Committee’s requirements. The above study has been given ethical approval by the Northern X Regional Ethics Committee.

Approved Documents
- Information Sheet/Consent Form V92 dated 28 September 2009
- Documents sent with application form – received 21 August 2009
- Sleep diary
- Pain assessment
- Morningness/eveningness questionnaire
- Munich chronotype questionnaire
- Beck depression questionnaire
- Saliva collection
- Urine collection procedures
- Study protocol

Certification
The Committee is satisfied that this study is not being conducted principally for the benefit of the manufacturer or distributor of the medicine or item in respect of which the trial is being carried out.

Accreditation
The Committee involved in the approval of this study is accredited by the Health Research Council and is constituted and operates in accordance with the Operational Standard for Ethics Committees, April 2005.

Progress Reports
The study is approved until 5 October 2012. However the Committee will review the approved application annually and notify the Principal Investigator if it withdraws approval. It is the Principal Investigator’s
Appendix E

responsibility to forward a progress report covering all sites prior to ethical review of the project on 5 October 2010. The report form should be forwarded to you at least 1 month prior to this date but if not received it is available on http://www.ethiccommittees.health.govt.nz (forms – progress reports). Please note that failure to provide a progress report may result in the withdrawal of ethical approval.

Final Report A final report is required at the end of the study. The report form is available on http://www.ethiccommittees.health.govt.nz (progress reports) and should be forwarded along with a summary of the results. If the study will not be completed as advised, please forward a progress report and an application for extension of ethical approval one month before the above date.

Requirements for SAE Reporting
The Principal Investigator will inform the Committee as soon as possible of the following:
• Any related study in another country that has stopped due to serious or unexpected adverse events
• all serious adverse events occurring during the study in New Zealand which result in hospitalisation or death.
• all serious adverse events occurring during the study worldwide which are considered related to the study

All SAE reports must be signed by the Principal Investigator and include a comment on whether he/she considers there are any ethical issues relating to this study continuing due to this adverse event. It is assumed by signing the report, the Principal Investigator has undertaken to ensure that all New Zealand investigators are made aware of the event.

Amendments
All amendments to the study must be advised to the Committee prior to their implementation, except in the case where immediate implementation is required for reasons of safety. In such cases the Committee must be notified as soon as possible of the change.

Please quote the above ethics committee reference number in all correspondence.

The Principal Investigator is responsible for advising any other study sites of approvals and all other correspondence with the Ethics Committee.

It should be noted that Ethics Committee approval does not imply any resource commitment or administrative facilitation by any healthcare provider within whose facility the research is to be carried out. Where applicable, authority for this must be obtained separately from the appropriate manager within the organisation.

Yours sincerely

Pat Chaineys
Administrator
Northern X Regional Ethics Committee
Cc: ADHB Research Office A- 4505

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Appendix F: Munich Chronotype Questionnaire (Revised).

Date: ______________________

Information about work days: I work _______ days per week

Even if you have indicated that you don’t work, please fill out this section because we have to know whether your sleep-wake habits either differ or are the same between the work week and free days/weekend.

Before work days I go to bed at ______ o’clock

.... at ______ o’clock, I prepare to sleep (switch off the light)

I need _______ to fall asleep

On work days, I wake up at______________ o’clock (before the alarm ☐, with the alarm ☐)

... after ________________ minutes I get up

________________________________________________________________________

Information about free days:

Please describe days without special circumstances (Parties etc.)

Before free days I go to bed at ______ o’clock

.... at ______ o’clock, I prepare to sleep (switch off the light)

I need _______ to fall asleep

On free days, I wake up at______________ o’clock (before the alarm ☐, with the alarm ☐)

... after ________________ minutes I get up

________________________________________________________________________

On average, how long per day do you spend outside exposed to day light (no roof above)?

On work days: _______ h _________ min

On free days: _______ h _________ min
Appendix G: Beck Depression Questionnaire.

Please read each group of statements carefully and pick out the one statement in each group that best describes the way you’ve been feeling since your surgery, including today. Please choose no more than one statement for each group.

1. Sadness

0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all of the time.
3 I am so sad or unhappy that I can’t stand it.

2. Pessimism

0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3. Past Failure

0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.
4. Loss of Pleasure

0  I get as much pleasure as I ever did from the things I enjoy.
1  I don't enjoy things as much as I used to.
2  I get very little pleasure from the things I used to enjoy.
3  I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings

0  I don't feel particularly guilty.
1  I feel guilty over many things I have done or should have done.
2  I feel quite guilty most of the time.
3  I feel guilty all of the time.

6. Punishment Feelings

0  I don't feel I am being punished.
1  I feel I may be punished
2  I expect to be punished
3  I feel I am being punished
7. Self-Dislike

0 I feel the same about myself as ever
1 I have lost confidence in myself
2 I am disappointed in myself
3 I dislike myself

8. Self-Criticalness

0 I don’t criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9. Suicidal Thoughts and Wishes

0 I don’t have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. Crying

0 I don’t cry anymore than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying but I can’t.
11. Agitation

0  I am no more restless or wound up than usual.

1  I feel more restless or wound up than usual.

2  I am so restless or agitated that it’s hard to stay still.

3  I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0  I have not lost interest in other people or activities.

1  I am less interested in other people or things than before.

2  I have lost most of my interest in other people or things.

3  It’s hard to get interested in anything.

13. Indecisiveness

0  I make decisions about as well as ever.

1  I find it more difficult to make decisions than usual.

2  I have much greater difficulty making decisions than I used to.

3  I have trouble making any decisions.

14. Worthlessness

0  I do not feel I am worthless.

1  I don’t consider myself as worthwhile and useful as I used to.

2  I feel more worthless as compared to other people.

3  I feel utterly worthless.
15. Loss of Energy

0  I have as much energy as ever.
1  I have less energy than I used to have.
2  I don’t have enough energy to do very much.
3  I don’t have enough energy to do anything.

16. Changes of Sleeping Pattern

0  I have not experienced any change in my sleeping pattern.
1a I sleep somewhat more than usual.
1b I sleep somewhat less than usual.
2a I sleep a lot more than usual.
2b I sleep a lot less than usual.
3a I sleep most of the day.
3b I wake up 1-2 hours early and I can’t get back to sleep.

17. Irritability

0  I am no more irritable than usual.
1  I am more irritable than usual.
2  I am much more irritable than usual.
3  I am irritable all the time.
18. Changes in Appetite

0  I have not experienced any change in my appetite.

1a  My appetite is somewhat less than usual

1b  My appetite is somewhat greater than usual

2a  My appetite is much less than before.

2b  My appetite is much greater than usual

3a  I have no appetite at all.

3b  I crave food all the time.

19. Concentration Difficulty

0  I can concentrate as well as ever.

1  I can’t concentrate as well as ever.

2  It’s hard to keep my mind on anything for very long.

3  I find I can’t concentrate on anything.

20. Tiredness or Fatigue

0  I am no more tired or fatigued than usual.

1  I get more tired or fatigued more easily than usual.

2  I am too tired or fatigued to do a lot of things I used to do.

3  I am too tired or fatigued to do most of the things I used to do.
21. Loss of Interest in Sex

0  I have not noticed any recent change in my interest in sex.

1  I am less interested in sex than I used to be.

2  I am much less interested in sex now.

3  I have lost interest in sex completely.
Appendix H: Actograms presented for sixty participants in the randomised placebo controlled trial.
Placebo group actograms

Figure H:1
The preoperative night and postoperative 72 h of actigraphy for patient 32 to patient 37 in the placebo group. The grey line separates preoperative and postoperative recording periods. The yellow shading indicates light.
Figure H:2
The preoperative night and postoperative 72 h of actigraphy for patient 38 to patient 43 in the placebo group.
The grey line separates preoperative and postoperative recording periods. The yellow shading indicates light.
Figure H:3
The preoperative night and postoperative 72 h of actigraphy for patient 44 to patient 49 in the placebo group. The grey line separates preoperative and postoperative recording periods. The yellow shading indicates light.
Figure H:4
The preoperative night and postoperative 72 h of actigraphy for patient 50 to patient 55 in the placebo group. The grey line separates preoperative and postoperative recording periods. The yellow shading indicates light.
Figure H:5
The preoperative night and postoperative 72 h of actigraphy for patient 56 to patient 61 in the placebo group. The grey line separates preoperative and postoperative recording periods. The yellow shading indicates light.
Light therapy group actograms

Figure H:6
The preoperative night and postoperative 72 h of actigraphy for patient 1 to patient 6 in the light therapy group. The grey line separates preoperative and postoperative recording periods. The yellow shading indicates light.
Figure H:7
The preoperative night and postoperative 72 h of actigraphy for patient 7 to patient 12 in the light therapy group. The grey line separates preoperative and postoperative recording periods. The yellow shading indicates light.
Figure H:8
The preoperative night and postoperative 72 h of actigraphy for patient 13 to patient 18 in the light therapy group. The grey line separates preoperative and postoperative recording periods. The yellow shading indicates light.
Figure H:9
The preoperative night and postoperative 72 h of actigraphy for patient 19 to patient 24 in the light therapy group. The grey line separates preoperative and postoperative recording periods. The yellow shading indicates light.
Figure H:10
The preoperative night and postoperative 72 h of actigraphy for patient 25 to patient 31 in the light therapy group. The grey line separates preoperative and postoperative recording periods. The yellow shading indicates light.
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