Sleep and Disease Issues in the Hospitalized Patient

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Disclosures

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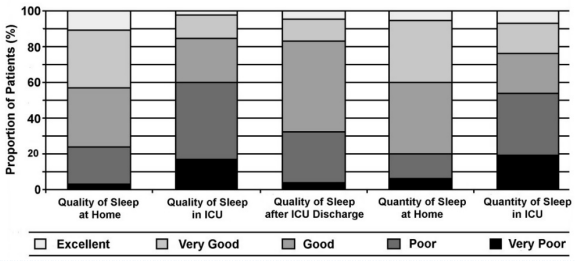
Considerations

- Effects of hospitalization and illness on sleep
  - Inpatient stay
    - Environmental disturbance - noise, light, observations
    - Psychological disturbance - anxiety
    - Physiological disturbance - pain, fever, infirmity
  - Post discharge
    - Insomnia
- Effects of disturbed sleep on health status, post-op. recovery
  - Cardiovascular, metabolic, cognitive, psychomotor, psychological, immune, inflammatory, catabolic
- Hospitalization risks associated with pre-existing sleep disorders
  - Sleep-related breathing disorders
  - Other sleep disorders

Effects of Hospitalization and Illness on Sleep

Little et al, 2012



n = 116

Factors Affecting Sleep Quality in ICU after Thoracic Surgery

Zhang et al, 2013

CATEGORY			PSQI >7 (n (%))	PSQI ≤7 (n (%))	n	X^2	P
ENVIRONMENTAL	Unfamiliar environment	Y	39 (55.7)	25 (30.5)	64	9.858	0.002*
		N	31 (44.3)	57 (69.5)			
	Nursing attention at night	Y	32 (45.7)	23 (28.0)	55	5.104	0.024*
		N	38 (54.3)	59 (72.0)			
	Nurses' footsteps	Y	14 (20.0)	6 (7.3)	20	5.316	0.021*
		N	56 (80.0)	76 (92.7)			
	Other patient voices	Y	36 (51.4)	26 (31.7)	62	6.081	0.014*
		N	34 (48.6)	56 (70.7)			
PATHO-PHYSIOLOGICAL	Dyspnea	Y	35 (50.0)	24 (29.3)	59	6.834	0.009*
		N	35 (50.0)	58 (70.7)			
	Pain	Y	51 (72.9)	45 (54.9)	96	5.246	0.022*
		N	19 (27.1)	37 (45.1)			
	Presence of tracheal tube	Y	44 (62.9)	38 (46.3)	82	4.146	0.042*
		N	26 (37.1)	44 (53.7)			
PSYCHOLOGICAL	Anxiety	Y	40 (57.1)	33 (40.2)	83	4.320	0.038*
		N	30 (42.9)	49 (59.8)			

*PSQI = Pittsburgh Sleep Quality Index, * p<0.05*

Effectiveness of Noise Reduction Strategies in ICU

Xie et al, 2009

Effectiveness of noise reduction strategies in intensive care units

Author and year published	Method	Participants	Setting	Intervention	Outcome
Zahr and Traversay, 1995 [50]	Controlled clinical trial	30 premature infants	NICU in USA	Earmuffs	Improve sleep by 39.0%
Wallace *et al.*, 1999 [51]	Controlled clinical trial; polysomnography	6 healthy adult subjects	Sleep Lab in USA	Earplugs	Improve sleep by 33.7%
Richardson *et al.*, 2007 [27]	Controlled clinical trial; patient self-report	64 adult patients	CCU in UK	Earplugs + eye masks	Improve sleep by 10%
Mann *et al.*, 1986 [53]	Controlled clinical trial; nurse observation	41 premature infants	Newborn nursery in UK	Behaviour modification	Improve sleep by 13.8%
Olson *et al.*, 2001 [56]	Controlled clinical trial; nurse observation for sleep; noise monitoring	843 adult ICU patients	Neurocritical care unit in USA	Behaviour modification	Improve sleep by 18.3%
Gragert, 1990 [58]	Controlled clinical trial; RCSQ; researcher observation	40 old ICU patients	Coronary care unit in USA	Sound masking	Improve sleep by 22.9%
Williamson, 1992 [59]	Controlled clinical trial; RCSQ	60 CABG patients	A public hoepital in USA	Sound masking (ocean sound)	Improve sleep by 37.5%
Stanchina *et al.*, 2005 [60]	Polysomnography	4 healthy adult subjects	Sleep lab in USA	Sound masking (white noise)	Improve sleep by 67.6%

RCSQ = Richards Campbell sleep questionnaire

Sleep During Early Recovery From Critical Illness

McKinley et al, 2013

		N	%
PreHospital	No insomnia (ISI <15)	181	82
	Insomnia (ISI ≥15)	41	18
ICU	Poor (RCSQ <70)	162	73
	Good (RCSQ ≥70)	60	27
Ward	Poor (RCSQ <70)	136	68
	Good (RCSQ ≥70)	63	32
ICU & Ward	RCSQ poor in ICU & ward	104	52
	RCSQ poor in ICU or ward	77	39
	RCSQ good in ICU & ward	18	9
2 months	Poor (PSQI >5)	109	62
	Good (PSQI ≤5)	66	38
6 months	Poor (PSQI >5)	101	57
	Good (PSQI ≤5)	75	43
2 & 6 months	PSQI poor at 2 and 6 months	73	40
	PSQI poor at 2 or 6 months	64	32
	PSQI good at 2 and 6 months	45	25

ISI = Insomnia Severity Index; RCSQ = Richards Campbell Sleep Questionnaire; PSQI = Pittsburgh Sleep Quality Index

Effects of Disturbed Sleep (Duration, Timing, Quality) on Health Status, Postoperative Recovery

- Cardiovascular dysfunction
  - Hypertension, cerebrovascular d, cardiovascular d
- Metabolic impairment
  - Insulin resistance
- Cognitive impairment
  - Delirium, pain perception
- Psychomotor disturbance
  - Impaired coordination, falls risk
- Psychological disturbance
  - Anxiety, depression
- Immune dysfunction, pro-inflammatory
  - Infection and other risks, pain
- Catabolic propensity
  - Negative nitrogen balance

Metabolic & Inflammatory Consequences of Sleep Loss

Sleep Loss, Circadian Misalignment, Diabetes & Inflammation

Leproult R et al, 2014

- 26 healthy adults studied in hospital
- Parallel group design:
  - 3 baseline days of 10hr nocturnal sleeps, followed by 8 days of sleep restriction:
    - 8 x 5 hr nocturnal sleeps ("circadian alignment")
    - 4 x 5 hr nocturnal sleeps + 4 x 5hr daytime sleeps ("circadian misalignment")

	Circadian Alignment (n = 12)		Circadian Misalignment (n = 13)	
	Baseline	Sleep Restriction	Baseline	Sleep Restriction
Insulin Sensitivity Index ($mU^{-1}.L^{-1}.min^{-1}$)	6.6 (4.2, 9.7)	4.0 (3.1, 5.5)**	6.2 (5.8,8.1)	2.9 (2.2,4.7)**
High Sensitivity C-Reactive Protein ($mg.dL^{-1}$)	0.05 (0.03,0.16)	0.08 (0.04,0.16)	0.03 (0.02,0.05)	0.06 (0.03,0.11)*

Median (25^{th}, 75^{th} percentile) * p<0.01 ** p<0.001

- Implications
  - Sleep loss increases insulin resistance and inflammatory markers acutely
  - Changes greater when circadian misalignment added to restriction

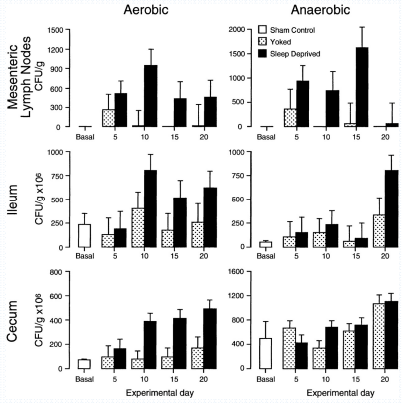
Immune & Inflammatory Changes with Sleep Restriction

Faraut et al, 2012

Sleep restriction (SR)	Immune changes	Inflammatory changes
Vgontzas, 2004; 7 nights of 6 h-sleep (22:30–04:30 h), n = 25 ♀♂		↑ IL-6, TNF-α only in ♂
Irwin, 2006, 2010; 1 night of 4 h-sleep (03:00–07:00 h), n = 30 ♀♂		↑ IL-6, TNF-α gene expression and protein by *in vitro*-stimulated monocytes
Haack, 2007; 10 nights of 4 h-sleep (23:00–03:00 h), n = 18 ♀♂		↑ IL-6, unchanged CRP
Kerkhofs, 2007; 3 nights of 4 h-sleep (01:00–05:00 h), n = 10 ♀	↑ Leukocyte and monocyte counts	
Meier-Ewert; 2007; 10 nights of 4,2 h-sleep (01:00–05:00 h), n = 10 ♂		↑ CRP
Boudjeltia, 2008; 3 nights of 4 h-sleep (01:00–05:00 h), n = 8 ♂	↑ Leukocyte and neutrophil counts	
van Leeuwen, 2009; 5 nights of 4 h-sleep (03:00–07:00 h), n = 13 ♂		↑ CRP, ↑ IL-6, IL-17 and IL-1β gene expression by *in vitro*-stimulated PBMC
Irwin, 2010; 1 night of 4 h-sleep (03:00–07:00 h), n = 26 ♀♂		Greater ↑ IL-6, TNF-α by *in vitro*-stimulated monocytes in ♀ than in ♂
Faraut, 2011; 1 night of 2 h-sleep (02:00–04:00 h), n = 12 ♂	↑ Leukocyte and neutrophil counts	↑ Myeloperoxidase

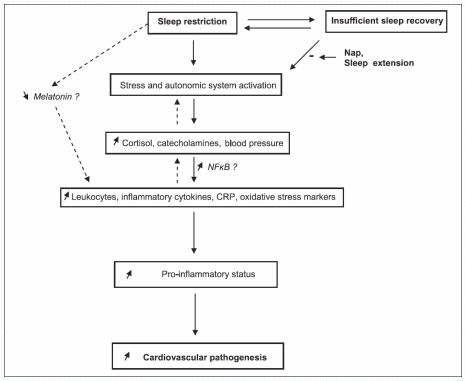
Systematic Bacterial Invasion in Rats Induced by Sleep Deprivation

Everson & Toth, 2000



Pathways by which Sleep Restriction may lead to Cardiovascular Pathologies

Faraut et al, 2012



Acute Sleep Restriction, Hypertension, Sympathetic Activation

Tochikubo et al, 1996

Parameter	Routine Workday	Sleep-Insufficient Day	P
Sleep period, h	7.98±0.85	3.61±0.67	<.05
Waking hours,[1] h	14.3±0.2	14.2±0.3	NS
BP and HR			
Sleep period			
Systolic BP, mm Hg	112±6	114±7	NS
Diastolic BP, mm Hg	65±6	66±5	NS
HR, bpm	60±7	59 ±5	NS
Waking hours			
Systolic BP, mm Hg	123±8	129±8	<.01
Diastolic BP, mm Hg	76±7	79±6	<.05
HR, bpm	79±9	81±10	NS
24 Hours			
Systolic BP, mm Hg	121±7	128±8	<.01
Diastolic BP, mm Hg	74±7	77±6	<.01
HR, bpm	74±8	76±8	NS
Urinary excretion of norepinephrine nmol/g			
Sleep period	124±39	168±78	<.05
Waking hours	230±49	270 ±68	<.05
24 Hours	194±46	223±58	<.05

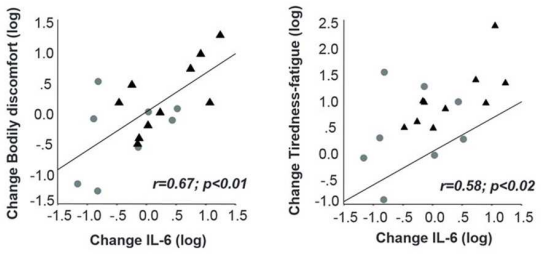
Values are mean±SD.

- 18 healthy males, aged 23-48 yrs
- extensive overtime
- ambulatory BP, activity monitor

Sleep Restriction and Exacerbation of Pain

Correlations Between Change in IL-6 & Bodily Discomfort, Tiredness in Healthy Volunteers

Haack et al, 2007



Baseline to day 11 --- 4 hrs/night (▲) and 8 hrs/night (●)

Sleep Restriction and Energy Expenditure

Sleep Deprivation Promotes Negative Nitrogen Balance

Kant et al, 2007

TABLE 1. *Effect of sleep deprivation on urine constituents*

	Control (Monday)	Sleep deprivation 0–24 h (Tuesday)	Sleep deprivation 24–48 h (Wednesday)	Sleep deprivation 48–72 h (Thursday)	Recovery (Friday)
Glucose	6.6 ± 0.7	6.8 ± 1.2	5.4 ± 0.4	4.5 ± 0.4	3.5 ± 0.9
Urea	1.3 ± 0.2	2.0 ± 0.6	3.4 ± 0.4	3.3 ± 0.6	1.6 ± 0.3
Creatinine	197 ± 22	154 ± 28	121 ± 15	96 ± 18	142 ± 14
Bilirubin	0.43 ± 0.05	0.46 ± 0.12	0.30 ± 0.04	0.37 ± 0.11	0.34 ± 0.11
Cholesterol	1.4 ± 0.4	1.8 ± 0.4	1.6 ± 0.3	1.7 ± 0.1	2.1 ± 0.3
Cortisol	87 ± 27	71 ± 12	65 ± 9	54 ± 5	68 ± 11

Values represent the mean ± SEM; n = 5 for Monday and n = 6 for all other days. Units for cortisol are μg/L; units for urea are g/dl. All other compounds are expressed as mg/dl.

N = 6, healthy male volunteers, ages 18 -21, total sleep deprivation in supervised (laboratory) environment

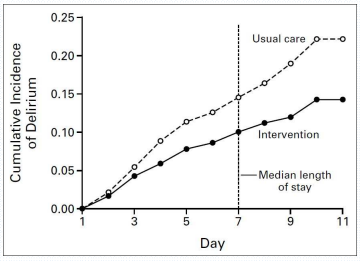
Normal 24 hr balance of degradation and renewal: Wakeful activities favor catabolism, sleep enhances anabolism *(Adam & Oswald, 1984)*

Sleep Loss and Delirium

- **Sleep is a restorative process**
- **OSA-related sleep disruption reduces cognitive reserve** (Alchanatis et al, 2005)
- **Postoperative sleep disruption or restriction may precipitate delirium, particularly where cognitive reserves are low.**
  - **preoperative OSA predisposes to postoperative delirium (OR 4.3, p=0.012)** (Fink BJ et al, 2012)
- **Sleep is the antidote**
  - **how adequate a substitute for sleep is sedation in environments such as ICU?**
  - **how effective are non-pharmacological interventions designed (inter alia) to promote sleep?**

A Multicomponent Intervention to Prevent Delirium in Hospitalized Older Patients

Inouye et al, 1999



- **Interventions targeted: cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, dehydration**
- **Sleep intervention was non-pharmacological: relaxation techniques at bedtime, noise reduction, re-scheduling of medications and procedures to allow sleep**
- **N = 852, equal numbers in each group**

Risks Associated with Pre-existing Sleep Disorders: Sleep-related Breathing Disorders (1)

OSA and Postoperative Outcomes

Mutter et al, 2014

- **PSG and Manitoba health data 1987-2008**
- **Matched cohort analysis, 1st 7 days postop.**
  - **"Undiagnosed" OSA - surgery anytime before PSG diagnosis (n=1,571)**
  - **"Diagnosed" OSA - surgery anytime after PSG diagnosis (n=2,640)**
  - **Low risk controls matched for procedure, indication, surgery date (n=16,277)**
- **Findings:**
  - **↑ risk of respiratory complications (ARDS, respiratory failure, pneumonia) in both undiagnosed & diagnosed OSA**
    - **OR 2.08 (1.35 - 3.19), p<0.001**
  - **↑ risk of cardiovascular complications (arrest, acute coronary syndrome, CVA, atrial fibrillation/flutter) in undiagnosed but not diagnosed OSA**
    - **Undiagnosed: OR 2.2 (1.16 - 4.17), p<0.02**
    - **Diagnosed: OR 0.75 (0.42 - 1.28), p=0.29**
  - **Odds increased with severity: significant only in severe OSA (AHI>30 event/h)**

Risks Associated with Pre-existing Sleep Disorders: Sleep-related Breathing Disorders (2)

Postoperative Outcomes in Obesity Hypoventilation vs OSA Alone
Kaw et al, 2015

Variables	Hypercapnic OSA (n=194)	OSA (n=325)	Odds Ratio	95% CI	*P*
Postoperative respiratory failure, n (%)	39 (21)	8 (2)	10.9	(3.7- 32.3)	<0.0001
Postoperative HF, n (%)	15 (8)	0	5.4	(1.9 - 15.7)	0.002
Postoperative prolonged intubation, n (%)	24 (13)	12 (4)	3.1	(0.6 - 15.3)	0.2
Postoperative reintubation, n (%)	12 (6)	5 (2)	1.7	(0.2 - 13.4)	0.6
Postoperative tracheostomy, n (%)	4 (2)	3 (1)	3.8	(1.7 - 8.6)	0.002
Postoperative ICU transfer, n (%)	41 (21)	19 (6)	10.9	(3.7- 32.3)	<0.0001
			Beta-coefficient	**Standard error**	*P*
Hospital length of stay, days (IQR) and mean (SD)	5 (3-9) 7.3 (8.2)	0 (0-4) 2.8 (5.1)	2.94	0.87	0.0008

HF = heart failure; ICU = intensive care unit; IQR = interquartile range; SD = standard deviation ICU = intensive care unit, PAP, positive airway pressure; PH, pulmonary hypertension; PSG, polysomnography; SPO2, oxygen saturation via pulse oximetry. *Adjusted for all patient variables in Table 1.

Risks Associated with Pre-existing Sleep Disorders: Other Sleep Disorders

- Insomnia patients at increased risk of disturbed sleep postoperatively — Redeker et al, 2004
- Increased delirium risk in patients with sleep disorders
  - OSA — Flink et al, 2012
  - Poor sleep quality — Slatore et al, 2012
- Restless legs exacerbated by spinal anesthesia — Hogl et al, 2002
- Patients with parasomnias are at increased risk of injury — Schenk & Mahowald, 1991

Conclusions

- Sleep is disturbed during hospitalization
  - Environmental, pathophysiological, psychological
- Disturbed sleep impairs health and recovery
  - Cardiovascular, metabolic, cognitive, psychomotor, psychological, immune, inflammatory, catabolic
- Patients with pre-existing sleep disorders are at increased risk of these consequences during hospitalization