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Evaluations of Physiologic and Behavioral Responses to Noxious Procedures
in Sedated Critically Ill Adult Patients

by

Denise Tsai-Yun Liu Li

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

the School of Nursing

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

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by

Denise Tsai-Yun Liu Li, RN, MS, PhD

Dedication

This dissertation is dedicated to my children Natalie, Andrew, and Amanda. As I ventured out beyond the confines of motherhood to realize personal dreams, you were always there by my side to cheer me on. I thank you for the unconditional love, patience, and understanding when mommy needs to “work on my papers”. You are my inspirations to dream the impossible dream.

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As Langston Hughes once said “A life without dreams is a broken winged bird that cannot fly.” Because of support from my family, friends, colleagues, and professors, I am able to ascend from the web of life’s obstacles to realize my dream of attaining the highest academic achievement. These special people came along at different phases of this journey and they offered support in many ways. I am grateful to all of them because they believed in me.

My journey through doctoral education was one with many life complications. Yet, my mother, in her very special ways, was always there to help lessen burdens of responsibility from my shoulders. I thank her for the unconditional love that she has for me and my children. This academic achievement fulfills my parents’ dream of providing an excellent education for me when they immigrated to this country over 30 years ago.

During this journey, there were many times when life stresses were looming over me and my strength wavered thin, but my husband, Roger, would always in his casual style, helped me regain perspectives about life priorities and stayed focus on the path to the finish line. I thank him for his unspoken faith and confidence in me, and his efforts to provide our family security and comfort, thus enabling me to enjoy a blissful life as a mother and a student.

Fourteen years ago, I met my mentor Dr. Kathleen Puntillo, who inspired me to envision a life of advance nursing career. Since, she has served as the most important driving force behind this endeavor. Words are simply inadequate to reflect my wholehearted appreciation for Dr. Puntillo’s support and confidence in me. I extend my

deepest gratitude to her for her outstanding mentorship as well as her friendship. I hope I will continue to have the privilege of having her as my advisor for life.

I have admired Dr. Miaskowski for her many exceptional qualities as a nurse scientist and scholar. I am extremely privileged to have her as one of the main faculty advisors during my doctoral education. I sincerely thank her for her words of wisdom and unwavering support when I felt bewildered during the qualifying examination process. Today, I am able to reach the endpoint of this journey with clarity and insight because of her excellent guidance.

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I sincerely thank Dr. Dorrie Fontaine for her support during my qualifying examination. Moreover, she always offered kind words and encouragement whenever we crossed path in school hallways. As a doctoral student under much stress, her kindness was heart warming and most appreciated.

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Evaluations of Physiologic and Behavioral Responses to Noxious Procedures in Sedated,
Ventilated Critically Ill Adult Patients

Denise Tsai-Yun Liu Li, RN, MS, PhD

Abstract

Acute pain is caused by strong noxious stimulation and is associated with unpleasant sensory and emotional signs and symptoms. The significance of acute pain in critically ill patients in the Intensive Care Unit (ICU) is well documented, yet a standardized objective measure of nociception for use in nonverbal ICU patients remains elusive. The purpose of this dissertation was to evaluate clinically useful physiologic and behavioral indicators of nociception for use in deeply sedated, nonverbal ICU patients.

The first study was a prospective description of mechanically ventilated ICU patients' perceptions of pain, dyspnea, thirst, nausea, hunger, tired/fatigue, anxiety, generalized discomfort, depressed feelings. Fifteen medical and surgical patients who were able to self-reported symptom intensity rated their symptoms by was assessed by using numeric rating scales (0=none, 10 worst possible intensity). The study found that over 33% of the patients experienced moderate to severe pain, thirst, tiredness, anxiety, hunger, and generalized discomfort. The study highlighted the need to develop an objective measure for pain and other symptoms since many ICU patients are not able to provide a self-report.

The second study addressed this problem by examining physiologic and behavioral indicators of pain as proxy measures in patients unable to provide a self-report. We compared changes in heart rate (HR), blood pressure (BP), pupil size, and cortical arousal per the Bispectral (BIS) Index, and behaviors between a noxious

procedure [endotracheal suctioning (ETS) or turning] and a non-noxious procedure (gentle touch) in 48 sedated, ventilated ICU patients. Repeated measures of the outcome variables were taken at baseline, during the procedure, and after the procedure. The study found that HR, systolic BP, pupil size, and the BIS Index increased significantly during the noxious condition but not during the non-noxious condition ($p < 0.01$). The effects of the significant changes in these physiologic responses during the noxious condition ranged from 4% (HR) to 16% (pupil size). There were little variations in sedated patients' behaviors during both conditions. The study suggested that certain physiological responses are potentially useful for the assessment of nonverbal patients' pain. Common pain behaviors do not sufficiently reflect sedated patients' response to noxious stimulation.

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CHAPTER 1

INTRODUCTION

Acute pain is a natural human response to a noxious stimulus that is associated with autonomous activity, nocifensive reflexes and reactions, and aversive emotions and avoidance behavior (Merskey, 1991). Acute pain emerged as a leading concern for critically ill patients in published reviews of 35 studies conducted between 1967 and 1997 on critically ill patients' perceptions of care in the Intensive Care Unit (ICU) (Chyun, 1989; Stein-Parbury & McKinley, 2000). Acute pain is one of the major ICU stressor (Fontes Pinto Novaes et al., 1999) and is reportedly one of the most distressing symptoms for many critically ill patients (Desbiens, Mueller-Rizner, Connors, Wenger, & Lynn, 1999; Nelson et al., 2004; Nelson et al., 2001). Based on studies of critically ill patients' pain associated with illnesses, surgery, and therapeutic procedures, it is estimated that 60% of ICU patients experienced an average pain of moderate intensity (Kuperberg & Grubbs, 1997; Nelson et al., 2001; Puntillo, 1990; Puntillo, 1994; Puntillo et al., 2001; Stanik-Hutt, Soeken, Belcher, Fontaine, & Gift, 2001; Stein-Parbury & McKinley, 2000). Unrelieved pain is associated with serious physical, psychological, immunologic, and physiologic consequences for ICU patients (Puntillo, Miaskowski, & Summer, 2003).

One of the main causes of pain in the ICU is related to mechanical ventilation (MV) (Gries & Fernsler, 1988; Morrison et al., 1998). It provides an artificial airway, oxygenation, and ventilation. Because of the placement of an endotracheal (ET) tube, ventilated patients are unable to speak or eat. Limited research have shown that, in addition to pain, many mechanically ventilated patients experience a number of

discomforting symptoms, including difficulties sleeping (Johnson & Sexton, 1990), anxiety and frustration (Bergbom-Engberg & Haljamae, 1989), and feelings of helplessness and fear of death (Jablonski, 1994). Only two known ICU studies were done in recent years that documented moderate or severe pain, anxiety, sleep disturbance, hunger, and thirst experienced by a substantial number of mechanically ventilated cancer patients (Nelson et al., 2001) and chronically critically ill patients receiving long-term respiratory support (Nelson et al., 2004).

Critically ill patients who are receiving aggressive life-saving therapies may suffer a greater number and severity of symptoms due to disease acuity, invasive procedures and the stressful ICU environment. In Chapter 2, we reported findings from a pilot study that evaluated ventilated medical, surgical, and trauma ICU patients' self-reported intensity of eight symptoms (i.e., pain, dyspnea, thirst, nausea, hunger, tiredness, anxiety, generalized discomfort, and depressed feelings) and the relationships between all symptoms. The study showed that pain and several symptoms existed at moderate levels and there was evidence of associations among them. More importantly, this study highlighted the potential issue of underassessment and undermanagement of pain for many mechanically ventilated ICU patients who are unable to communicate. A number of factors in the ICU hinder a patient's ability to reliably self-report pain, including the use of drugs with sedative effects and pathological processes. When these patients are unable to give pain reports using subjective pain measures (e.g., Numeric Rating Scale), the use of objective pain measures is an essential alternative approach for pain assessment.

In Chapter 3, we presented a critical review of the psychometric properties of six objective pain measures that were developed to assess pain in nonverbal adult patients in

the ICU (i.e., Behavioral Pain Rating Scale (Mateo & Krenzischek, 1992); Behavioral Pain Scale (BPS) (Payen et al., 2001); Pain Behaviors Assessment Tool (Puntillo et al., 2004); Critical-Care Pain Observation Tool (CPOT) (Gelinas, Fillion, Puntillo, Viens, & Fortier, 2006); Pain Assessment and Intervention Notation Algorithm (PAIN-Algorithm) (Puntillo et al., 1997); and Nonverbal Pain Scale (NVPS) (Odhner, Wegman, Freeland, Steinmetz, & Ingersoll, 2003)). The review demonstrated that only two of the six objective pain measures (i.e., BPS, CPOT) showed good evidence of validity and reliability, but none has undergone vigorous validation or been accepted as a standardized measure.

Common objective indicators of pain include behaviors (e.g., facial expressions, body movement) and physiologic responses (e.g., heart rate (HR), blood pressure (BP)). Deeply sedated ICU patients' behaviors and hemodynamic changes to noxious stimulation have not been adequately characterized in the literature. A few studies suggested that changes in pupil size (Larson, Berry, May, Bjorksten, & Sessler, 2007; Larson et al., 1997) and cortical arousal using Bispectral Index (BIS) (Guignard, Menigaux, Dupont, Fletcher, & Chauvin, 2000; Takamatsu, Ozaki, & Kazama, 2006) could be used to reflect a balanced analgesia-nociception state in anesthetized patients. However, these measures have not been used to evaluate physiologic responses to nociception in nonverbal ICU patients.

Given the paucity of research related to clinically useful indicators of nociception for use in sedated, critically ill patients, we conducted a prospective study aimed to determine if certain physiologic responses are associated with nociception. We evaluated 48 sedated ICU patients' HR, BP, pupil size, and cortical arousal changes per BIS to a

noxious (e.g., endotracheal suctioning, turning) and a non-noxious (gentle touch) procedure. We examined the effects of change in physiologic responses occurring during the noxious procedure. Additionally, we described patients' behaviors (i.e., facial expression, body movement and posture, and ventilator response). The study found that the most commonly reported pain-related behaviors (Puntillo et al., 2004) were not evident in this sample of deeply sedated patients. However, HR, pupil size, and BIS responses had significant changes during a noxious stimulation but not during a non-noxious stimulation.

Despite advancing science in the field of pain management, pain assessment in nonverbal patients remains an immense challenge for critical care clinicians. Recognizing patients' responses associated with noxious stimuli is critical to achieving the timely management of the adverse effects of nociception and to evaluate the effectiveness of interventions in these high-risk patients.

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CHAPTER 2
A PILOT STUDY ON COEXISTING SYMPTOMS IN INTENSIVE CARE
PATIENTS

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Abstract

Little is known about the nature of coexisting symptoms in critically ill patients. This study prospectively evaluated ventilated ICU patients' perceptions of 8 symptoms and examined their relationships. Patients' symptoms were assessed by subjective report using a numeric rating scale. The results showed that many symptoms existed at substantial levels and evidence of associations among them. Further research is needed to evaluate and validate the relationship among these symptoms and the impact of symptom burden on ICU patients. In order to improve ICU patient comfort, there needs to be increased attention to the multiple symptoms that these patients experience.

The issue of pain in critically ill patients is well documented for over two decades. Yet, there is a limited description of a constellation of symptoms that are experienced by these patients while in the Intensive Care Unit (ICU). Pain was identified as a major ICU stressor (Rotondi et al., 2002; Stein-Parbury & McKinley, 2000). Surgery (Puntillo, 1990; Yorke, Dip, Wallis, & McLean, 2004) and procedures (Puntillo et al., 2001) inflicted substantial degree of pain and distress on ICU patients. Earlier studies of ventilated patients suggested that additional symptoms existed, including anxiety and frustration (Bergbom-Engberg & Haljamae, 1989), feelings of helplessness and fear of death (Jablonski, 1994), difficulties sleeping and being immobilized (Johnson & Sexton, 1990), and discomfort from positive pressure ventilation (Gries & Fernsler, 1988). To date, only two studies have focused on symptoms in cancer ICU patients (Nelson et al., 2001) and chronically critically ill patients receiving long-term respiratory support (Nelson et al., 2004).

The National Institute of Nursing Research has identified symptom management as a research priority, underscoring the need to further understand patient perceptions of common symptoms associated with critical illness and nature of their coexistence. Such knowledge will assist clinicians to determine appropriate interventions in order to improve the overall comfort of ICU patients. The purpose of this pilot study was to evaluate ventilated ICU patients' self-reported symptoms. The specific study aims were to: 1) document the prevalence and intensity of 8 symptoms (*pain dyspnea, thirst, nausea, hunger, tiredness, anxiety, generalized discomfort, and depressed feelings*), and 2) examine relationships between all symptoms.

Method

Sample and Setting

This study was conducted in adult ICUs in two western U.S. hospitals. The study received approval from the Human Research Committee at the researchers' academic institution and at both participating hospitals. The study included patients who were between 21 and 80 years of age; had been on mechanical ventilation (MV) for ≥ 12 hours duration; understood English; and had a Ramsay score of 2 (i.e., oriented and follows command) (Ramsay, Savege, & Simpson, 1974) assessed by the patient's primary care nurse. Patients who did not meet all of the above inclusion criteria, exhibited signs of severely impaired cognition, or had underlying neurological disease or a head injury diagnosis were excluded from the study. Informed written consent was obtained from the patient.

Instruments

The intensity of symptoms was assessed by using a multiple 0-10 Numeric Rating Scales (NRS) that were anchored with the sensation of the symptom (e.g., 0=no pain, 10=worst pain). The approach was modified based on the Edmonton Symptom Assessment Scale (Bruera, Kuehn, Miller, Selmsler, & Macmillan, 1991), which is a standardized instrument used to assess similar symptoms in cancer patients. Reliability of a verbally administered NRS has been shown in acutely ill patients (Paice & Cohen, 1997; Singer, Kowalska, & Thode, 2001).

Study Procedures

After obtaining consent from the patient, separate NRS with anchors for each symptom was shown and read to the patient. He/she was asked to nod or point to a number corresponding to his/her ratings of symptom intensity. Data analysis was

performed using Statistical Package for Social Science for Windows version 11.0 (SPSS, Inc., Chicago, Ill.). For aim#1, symptom prevalence was presented in frequency of patients reporting each category of intensity (NRS score 0= none, 1-3= mild, 4-6= moderate, 7-10= severe) (Collins, Moore, & McQuay, 1997). Symptom intensity was presented using descriptive statistics. For aim #2, Pearson's correlation coefficients were computed to examine the relationship between symptoms. A level of significance of $p < 0.05$ was established a priori.

Results

Sample Characteristics

The study included 15 conveniently sampled medical, surgical, and trauma ICU patients. The patients' ages ranged from 31 to 80 years old (mean 63 ± 16 years) and were Caucasian men ($n=7$) and women ($n=8$). At the time of study, patients had been in the ICU for an average of 12 days and the mean duration of ventilator support was 6 ± 4 days. Analgesics and anxiolytic agents given in the previous 24 hours included opioids (i.e., morphine sulfate), benzodiazepines (i.e., midazolam, lorazepam) (Table 1).

Symptom Prevalence and Intensity

The most prevalent symptom was dyspnea, reported by all patients. About 40% of patients reported severe *thirst* and moderate to severe *pain*. One third of patients also had moderate *thirst*, *tiredness*, *hunger*, *generalized discomfort*, and *depressed feelings*. A greater severity of *tiredness*, *anxiety*, *hunger*, and *generalized discomfort* were reported by 20% of patients. Nausea was the least experienced symptom. Only 30% of patients reported having some degree of nausea (Table 2).

Nearly all symptoms were reported at severe intensity (NRS>7/10) by some patients, the exception was *nausea*. When comparing intensity across symptoms, five symptoms were notable for their moderate mean intensity, including *thirst* (mean NRS score=5.7), *tiredness* (5), *generalized discomfort* (4.9), *anxiety* (4.5) and *hunger* (4.3). Mild mean intensity was reported for *pain* (2.8) and *depressed feelings* (2.6) (Table 3).

Correlations Between Symptoms

A number of symptoms were shown to have significant correlations. Specifically, tiredness had strong correlations with *thirst* ($r=0.79$), *anxiety* ($r=0.79$), and with *generalized discomfort* ($r=0.75$). *Thirst* was moderately correlated with *hunger* ($r=0.58$), *anxiety* ($r=0.55$), and with *generalized discomfort* ($r=0.52$). In addition, moderate correlation existed between dyspnea and depressed feelings ($r=0.52$) (Figure 1).

Discussions

Ventilated critically ill patients are at a high risk of undermanagement of symptoms due to their inability to communicate verbally. This pilot study identified a constellation of symptoms reported by patients while they were being ventilated in the ICU. The study included mostly surgical patients who had been on MV for similar duration described in other ICU patients (Esteban et al., 2000; Rotondi et al., 2002). In our study, patients received small doses of parenteral opioids and benzodiazepines for pain and anxiolysis. At this regimen, we found that patients were able to provide symptom report through the use of quantitative questions (i.e., verbal and visual NRS).

Our study showed a lower prevalence (40%) of moderate to severe pain than found in previous studies (e.g., 60% (Carroll et al., 1999); 80% (Kuperberg & Grubbs, 1997)]. However, patients in these two studies were all recently (<48 hours)

postoperative patients. Another possible explanation is that lower pain prevalence in our study reflected advancement in surgical and anesthetic techniques and overall improvement of ICU care in the past decade.

On the other hand, evidence of critically ill patients suffering from additional physical and emotional distress is consistent with previous research. Dyspnea was found to be a frequent complaint of ventilated patients (Bergbom-Engberg & Haljamae, 1989; Gries & Fernsler, 1988; Johnson & Sexton, 1990), but these studies did not evaluate other symptoms. Pain, dyspnea, nausea, anxiety, and depressed mood were suggested to constitute symptom burden of seriously ill patients (N=1582) who had been hospitalized for a median of 8 days (Regueiro et al., 1998). In study of terminally ill cancer ICU patients (n=50) moderate or severe pain, discomfort, anxiety, sleep disturbance, hunger, and thirst were reported by over 55% of patients (Nelson et al., 2001). Same authors identified similar symptoms in another study of ventilated chronically ill patients in the respiratory care unit (Nelson et al., 2004). Critically ill patients who are receiving aggressive life-saving therapies may suffer a greater number and severity of symptoms due to disease acuity, invasive procedures and the stressful ICU environment. Hence, understanding critically ill patients' symptom perceptions is a necessary first step to address symptom management.

Only one known study has examined the coexisting nature of pain, dyspnea, and nausea in seriously ill patients (Lynn et al., 1997). It showed that patients with more severe level of dyspnea were more likely to have more pain compared to patients without dyspnea (odds ratio: 2.73, 95% CI: 1.83, 4.07, $p < 0.05$). Although our analysis found very low correlation between pain and dyspnea, we did find that dyspnea was associated

with depressed feelings. This is not surprising since dependency on a mechanical mode of ventilation and the inability to communicate are likely causes of negative mood states in these patients. In addition, environmental ICU stressors may provoke a heightened sense of anxiety [(i.e., feelings of apprehension, uncertainty, dread and worry (McKinley, Coote, & Stein-Parbury, 2003))] and affect one's sleep or ability to rest. Tiredness or fatigue [(i.e., a sustained sense of exhaustion and a feeling of lack of energy (Piper, 2003))] was shown to have strong and significant correlation with anxiety.

In addition, we found significant correlations between some other symptoms. Specifically, thirst appears to be a central symptom, having the highest prevalence, intensity, and number of significant correlations with other symptoms. The most obvious cause of dry mouth maybe the presence of oral endotracheal tube and their NPO status. Potential fluid deficits and electrolyte imbalances may aggravate the sensation of thirst. The complaint of hunger was associated with thirst. However, since we did not record the mode and amount of nutritional intake in these patients (i.e., tube feeding), we are unclear whether the sensation of hunger was related to the lack of oral stimulation of food/fluid or related to inadequacy of nutritional intake via tube feedings.

Limitations of the Study

We recognize that several limitations exist due to the nature of a pilot study design. Primarily, study findings were limited by the small sample size, a lack of a diverse ethnic group representation, and included mostly surgical patients. Consequently, we are not able to generalize findings to other patient groups. We also did not examine other factors that could influence certain symptoms, for example, medications to improve respiratory mechanics, fluid intake and output, weight changes, or other medications that

may have an adverse effect on the symptom studied. Although the small sample precluded us from finding significant associations between some of the symptoms, it is also possible that significant correlations may not exist in spite of a larger sample. Considerations of these limitations should be included in future studies of patient symptoms.

Conclusions

In spite of advances in the science of critical care management, this pilot study suggested that symptom management remains substandard for many ventilated ICU patients. These pilot data demonstrated that despite of increasing recognition of pain in ICU patient, many mechanically ventilated patients experience a constellation of symptoms at a substantial level of intensity. There may be some relationships among a number of these symptoms that deserve attention. The study highlights the importance of investigation of symptoms in critically ill patients and their impact on patient well-being and comfort.

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Table 1. Demographic & treatment characteristics (N=15)

Age in years (mean \pm SD (range))	63 \pm 17 (31 to 80 years)		
Gender (n (%))	Male	7 (47)	
	Female	8 (53)	
Ethnicity (n (%))	Caucasian	15 (100)	
Diagnoses (n (%))	Medical	3 (20)	
	Surgical	10 (67)	
	Trauma	2 (13)	
Days on MV (mean \pm SD (range))	6 \pm 4 (2 to 17 days)		
Days in ICU prior to interview (mean \pm SD (range))	12 \pm 9 (3 to 31 days)		
Meds ordered in prior 24 hours	Meds given in prior 24 hours		
	N	Min -Max dose (mg)	Mean \pm SD
Morphine sulfate	11	4.0-71.0	14 \pm 19.3
Midazolam	5	1.0-5.0	2.0 \pm 1.7
Lorazepam	3	0.5-1.0	0.7 \pm 0.3
Haloperidol	1	5.0	5.0

Table 2. Symptom Prevalence (N=15)*

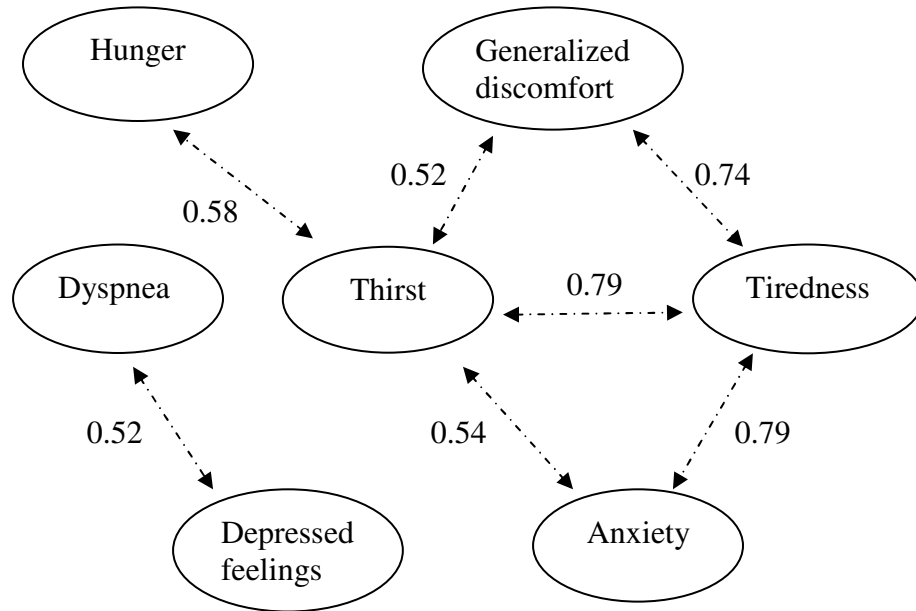
Symptoms	None	NRS 1-3	NRS 4-6	NRS 7-10
Thirst	20	7	33	40
Tiredness	13	20	40	27
Anxiety	13	35	27	27
Hunger	27	13	33	27
Generalized discomfort	7	7	67	20
Pain	40	20	27	13
Dyspnea	0	60	33	7
Depressed feelings	40	20	33	7
Nausea	67	27	7	0

*Shown in % of patients reporting at each level of pain intensity

Table 3. Symptom intensity on 0-10 Numeric Rating Scale (shown in descending order)

	Mean	Std. Deviation	Minimum	Maximum
Thirst	5.7	3.7	0	10
Tiredness	5.0	3.0	0	10
Generalized discomfort	4.9	2.3	0	10
Anxiety	4.5	2.9	0	10
Hunger	4.3	3.7	0	10
Dyspnea	3.4	2.0	1	8
Pain	2.8	3.1	0	9
Depressed feelings	2.6	2.7	0	8
Nausea	1.0	1.8	0	6

Figure 1. Illustration of Significant Correlations Between Symptoms ($p < 0.05$)



CHAPTER 3

**A REVIEW OF OBJECTIVE PAIN MEASURES FOR USE WITH
NONVERBAL CRITICALLY ILL ADULT PATIENTS**

Abstract

Critically ill patients experience significant levels of pain and discomfort from multiple intrinsic and extrinsic sources while in the Intensive Care Unit (ICU). The use of objective pain measures in nonverbal patients is an essential alternative approach for pain assessment when self-reports are unavailable. This paper provides a critical review of the psychometric properties of six objective pain measures that were developed to assess pain in nonverbal adult patients in the ICU. The strengths and weaknesses of these objective measures are evaluated, as well as their applicability for use with this patient population. While two of the six objective pain measures showed good evidence of validity and reliability, none have undergone vigorous validation or been accepted as a standardized measure. Findings from the available studies of objective pain measures provide useful information to direct future research in order to develop and validate clinically useful pain measures for use with nonverbal critically ill patients.

Acute pain has emerged as a leading stressor for patients with various diagnoses and conditions in the Intensive Care Unit (ICU) (Stein-Parbury & McKinley, 2000). Unrelieved acute pain gives rise to negative physiologic and psychological events that can be detrimental to critically ill patients' health outcomes (Granja et al., 2005; Puntillo, Miaskowski, & Summer, 2003; Schelling et al., 2003). Common causes of pain in these patients include surgery, trauma, invasive procedures and therapeutic devices, and certain routine nursing interventions (Morrison et al., 1998; Puntillo et al., 2004). While routine pain assessment procedures can be employed with ICU patients who are verbal, a substantial number of ICU patients may not be able to provide a self-report of the presence or intensity of their pain. The (Stevens, 1998)assessment of pain in these nonverbal critically ill patients poses numerous challenges.

Research on the measurement of pain in nonverbal critically ill adults (i.e., nonverbal ICU patients) has emerged only within the past two decades. However, no measure of pain in nonverbal ICU patients is accepted as the "gold standard". The purposes of this review are to: 1) describe six objective pain measures for use with nonverbal ICU patients; 2) provide a critical evaluation of the psychometric properties of these measures; and 3) evaluate the strengths and weaknesses of these measures for use with nonverbal ICU patients.

Overview of Objective Pain Measures

Objective pain measures are observational instruments that can be categorized as either unidimensional or multi-dimensional. A unidimensional objective measure (e.g., behavioral scale) may use a single domain (e.g., facial expression) or several domains (e.g., facial expression, body movements, sound) to evaluate a person's responses to pain.

A multi-dimensional objective measure evaluates two or more pain dimensions (e.g., behaviors, physiologic responses) and has several domains within each dimension. In the absence of self-report, unidimensional measures with multiple domains or multi-dimensional measures are the preferred tools to evaluate acute pain in nonverbal ICU patients (Labus, Keefe, & Jensen, 2003; Stevens, 1998). In an excellent review of 27 studies, Labus and colleagues demonstrated that self-reports of pain were more likely to be significantly correlated with multi-domain behavioral ratings of pain compared to a single item behavioral rating. Likewise, in a comprehensive review of neonatal/pediatric objective pain measures (Stevens, 1998), the authors concluded that multi-dimensional measures were more useful clinically and that no one single domain was reliable or valid when used alone.

Methods

The PubMed and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases were searched using three specific strategies. First, the search was limited to papers published in English between 1986 and 2007, and used the key words: pain, assessment, measurement, and validity. This strategy generated 403 citations. Abstracts were reviewed and articles were selected if they addressed: *acute pain* in *adult* patients in an *acute care setting*. Studies or reports that focused on the neonatal/pediatric population, elderly patients with dementia, chronic pain, and outpatient and/or community settings were excluded. The second search strategy explored additional relevant articles by using the “related articles option” on the databases to generate a snowball list of articles. Again, relevant articles were selected if they focused on acute pain in acutely ill adults. The final pool of articles selected for this review was based on

their meeting four criteria: 1) it described a unidimensional measure with multiple domains or a multidimensional objective pain measure; 2) the measure was used in verbal and/or nonverbal critical care adult patients; 3) the measure had undergone psychometric evaluation; and 4) the article was available in full text. Additional articles were identified using the references from these articles.

Together, these search strategies identified five unidimensional objective pain measures (i.e., Behavioral Pain Rating Scale (Mateo & Krenzischek, 1992); Behavioral Pain Scale (BPS) (Payen et al., 2001); Colorado Behavioral Numeric Pain Scale (CBNPS) (Salmore, 2002); Pain Behaviors Assessment Tool (Puntillo et al., 2004); and Critical-Care Pain Observation Tool (CPOT) (Gelin, Fillion, Puntillo, Viens, & Fortier, 2006)) and three multi-dimensional objective pain measures (i.e., Pain Assessment Algorithm (Blenkharn, Siobhan, & Morgan, 2002); Pain Assessment and Intervention Notation Algorithm (PAIN-Algorithm) (Puntillo et al., 1997); and Nonverbal Pain Scale (NVPS) (Odhner, Wegman, Freeland, Steinmetz, & Ingersoll, 2003)). Two instruments (the Pain Assessment Algorithm and CBNPS) were excluded because they did not meet the second and third selection criteria for this review. The validity and reliability of the remaining six instruments were evaluated using criteria set forth in the psychometric literature (Nunnally & Bernstein, 1994; Polit & Hungler, 2004). Table 1 provides a summary of dimension(s) and domains of each of the objective pain measures included in this review.

Unidimensional Objective Pain Measures

The Behavioral Pain Rating Scale (BPRS)

Description

The BPRS is a unidimensional objective measure that assesses four behavioral domains: restlessness, tense muscles, frowning or grimacing, and patient sounds. Each domain contains three descriptors that indicate a progressive increase in pain severity and are scored on a scale that ranges from 0 (normal behaviors) to 3 (extreme pain behaviors). The total BPRS score can range from 0 (no pain) to 12 (most pain) (Mateo & Krenzischek, 1992).

Psychometric properties

Two studies evaluated the psychometric properties of the BPRS in Post-Anesthesia Care Unit (PACU) adult patients (Mateo & Krenzischek, 1992; Webb & Kennedy, 1994). The first study of 30 patients (Mateo & Krenzischek, 1992) evaluated whether behaviors on the BPRS were associated with patients' self-reports of pain intensity measured by a verbal descriptor scale (VDS). The second study examined the relationship between BPRS scores and patients' self-reports of pain intensity using a 0 (no pain) to 10 (worst pain) numeric rating scale (NRS) in 36 women who had gynecologic surgery and who received morphine patient controlled analgesia (PCA) (Webb & Kennedy, 1994).

Face validity of the BPRS was established because it was based on a previously developed scale (Chambers & Price, 1967) and modified by expert clinicians (Mateo & Krenzischek, 1992). Both studies showed that the BPRS possessed criterion validity because significant correlations were found between BPRS scores and patients' self-reports of pain intensity. Behaviors in three domains (i.e., facial expression, muscle tension, patient sound) had moderate correlations with patients' VDS pain scores ($r=0.63$ to 0.69 , $p<0.05$) (Mateo & Krenzischek, 1992). Total BPRS scores were found to have

moderate to strong correlations with patients' NRS scores ($r=0.56$ to 0.80 , $p<0.05$) (Webb & Kennedy, 1994). In addition, BPRS scores decreased after the administration of morphine PCA ($F=12.85$; $p<0.001$), which suggests that the measure is responsive to the effects of analgesia. The BPRS demonstrated high internal consistency (i.e., Cronbach's $\alpha=0.92$) (Mateo & Krenzischek, 1992). The interrater reliability for the BPRS was reported as a Pearson's correlation coefficient. Strong and positive correlation ($r>0.80$, $p<0.01$) was found between pairs of nurses' BPRS ratings.

Strengths and weaknesses

While the BPRS appears to possess satisfactory internal consistency, neither reports (Mateo & Krenzischek, 1992; Webb & Kennedy, 1994) provided data on the inter-item correlations for each item, which is a criterion for using Cronbach's α as a reliability indicator (Ferketich, 1990). The interrater reliability of the BPRS requires additional evaluation since the tests of association between ratings are not estimates of agreement between raters (Polit & Hungler, 2004).

Generalizability of the BPRS findings (Mateo & Krenzischek, 1992; Webb & Kennedy, 1994) to nonverbal ICU patients is limited because it was tested in small homogeneous samples of PACU patients. In fact, patients with major complications and neurological problems were excluded from the studies. Moreover, the BPRS requires a patient to vocalize and to show discernible movements, which is likely to limit its use in a substantial portion of nonverbal ICU patients who may have an altered level of consciousness (LOC) or who have received neuromuscular blocking agents.

The Behavioral Pain Scale (BPS)

Description

The BPS evaluates three behavioral domains (i.e., facial expression, movements of upper limbs, compliance with ventilation). Each domain contains four descriptors that are rated on a 1 to 4 scale and the total BPS score can range from 3 (no pain) to 12 (most pain) (Payen et al., 2001).

Psychometric properties

The validity and reliability of the BPS in sedated, ventilated ICU patients were evaluated in three studies (Aissaoui, Zeggwagh, Zekraoui, Abidi, & Abouqal, 2005; Payen et al., 2001; Young, Siffleet, Nikoletti, & Shaw, 2006). BPS scores of ICU patients undergoing non-painful (i.e., compression stocking applications or central venous catheter dressing changes) and painful (i.e., endotracheal suctioning (ETS) or turning) procedures were compared using independent paired ratings made by nurses before and during the procedure (Payen et al., 2001). A second study of 30 medical ICU patients (Aissaoui et al., 2005) compared BPS scores during a resting state to those obtained during a painful procedure (i.e., ETS or peripheral venous catheter insertion). Almost all of the patients in this study had deep levels of sedation (i.e., responsive only to noxious stimuli). The third BPS validation study (Young et al., 2006) compared BPS scores in 44 medical and surgical ventilated ICU patients undergoing two procedures (i.e., non-painful: saline eye wash; painful: turning). The majority of study patients were in a state of deep sedation and were either responsive to noxious stimuli or unresponsive (Devlin et al., 1999).

The construct validity of BPS as a pain measure was established by contrasting scores between groups that were expected to have different scores (i.e., non-painful

versus painful procedure). Indeed, the BPS scores for the painful procedure were significantly higher than for the non-painful procedure ($p < 0.01$) (Aissaoui et al., 2005; Young et al., 2006). Additionally, based on principal component factor analysis, the three BPS domains converged on a single pain expression factor that explained a large proportion (55% to 65%) of the total variance (Aissaoui et al., 2005; Young et al., 2006).

The reliability of BPS was evaluated in these three studies. The BPS domains were shown to possess homogeneity and that the internal consistency estimates for the BPS (i.e., Cronbach's $\alpha = 0.64$; $\alpha = 0.721$) were acceptable for a newly developed instrument (Nunnally & Bernstein, 1994). However, the interrater reliability estimates for the BPS were not consistent across the three studies. In one study (Payen et al., 2001), paired nurses' ratings on the BPS showed satisfactory interrater reliability (i.e., weighted kappa coefficient = 0.74) and Intraclass Correlation Coefficients (ICC) for the BPS total score (ICC = 0.95, 95% CI, 0.94-0.97) were high (Aissaoui et al., 2005). However, in one study (Young et al., 2006), only 40% of BPS ratings had good agreement after a painful procedure while about 70% of BPS ratings were in good agreement after a non-painful procedure. The differences in inter-rater reliabilities across these studies may relate to how nurses were trained to use the BPS. However, details of the training procedures were not described.

Strengths and weaknesses

Findings from three studies (Aissaoui et al., 2005; Payen et al., 2001; Young et al., 2006) suggest that the BPS is a valid and reliable measure for use in nonverbal ICU patients. However, attention to a number of factors would improve its clinical utility. First, the range of scores on the BPS (i.e., 3=no pain to 12=most pain) should be revised

so that a score of 0 reflects no pain behavior. Second, on the BPS, the lack of body movement equates with a pain free state. Research has shown that nurses reported observing slow, decreased, or no movement as a pain behavior in nonverbal ICU patients (Puntillo et al., 1997). In addition, many factors (e.g., weakness, use of sedatives) may influence a nonverbal ICU patient's ability to move their extremities. Moreover, wrist restraints and physical devices are sometimes used to protect ventilated ICU patients from self-harm, to stabilize joints, or to ensure the security of therapeutic devices (Minnick, Leipzig, & Johnson, 2001; Reigle, 1997).³ These devices would interfere with a patient's ability to move their upper extremities to the extent described in the BPS.

The inconsistent findings for interrater reliability of the BPS are likely due to the ambiguity of some of the items and their lack of specificity for pain. For example, under the domain of compliance with ventilation, descriptors such as "tolerating movement", "coughing but tolerating ventilation for most of the time", and "fighting ventilator" lack clear operational definitions. Moreover, clinicians might associate lack of ventilator compliance with other clinical states such as agitation or hypoxia. In sum, while the BPS appears to be a promising tool to assess pain in nonverbal ICU patients, it requires additional testing in order to confirm its validity and reliability and to improve its clinical utility.

Pain Behavior Assessment Tool

Description

This unidimensional assessment tool was developed for a large-scale descriptive study of patients' pain perceptions and behaviors associated with common hospital procedures in acute and critical care settings (Puntillo et al., 2004; Puntillo et al., 2001).

The Pain Behavior Assessment Tool consists of three behavioral domains with several descriptors within each domain (i.e., facial expressions=10 descriptors; body movement=15 descriptors; verbal responses=7 descriptors). The tool is scored based on the presence or absence of each of these descriptors.

Psychometric properties

In a study of 5957 adult medical, surgical, and trauma patients in 169 national and international hospitals (Puntillo et al., 2004), nurses assessed patients' behaviors using the Pain Behavior Assessment Tool during any one of the following six procedures (i.e., femoral sheath removal, central venous catheter placement, tracheal suctioning, wound care, wound drain removal, turning). The face validity of this tool was established through review by an expert advisory group. The construct validity of this tool is supported by an increase in the frequency of patient behaviors (e.g., grimace, wincing, moaning) during the various painful procedures ($p < 0.001$). Criterion validity for the Pain Behavior Assessment Tool was confirmed through a moderate and significant positive correlation between the total number of pain behaviors and the "gold standard" of self-report of pain intensity on a NRS ($r = 0.54$, $p < 0.001$).

Although no statistical data were provided for the Pain Behavior Assessment Tool's interrater reliability, the authors indicated that extensive trainings was provided to the study nurses to standardize the assessment procedures.

Strengths and weaknesses

The Pain Behavior Assessment Tool contains a number of features that enhances its clinical utility. All of the tool's domains and descriptors have operational definitions

that help to standardize the scoring of the behavioral observations. The scoring procedure is simple (i.e., mark the presence or absence of a behavior) and not subject to interpretation. This approach contrasts with conventional objective pain measures that assign scores at the item level and use a sum score to indicate a patient's level of pain. The significant increase in the number of observed behaviors in patients with self-reported pain (Puntillo et al., 2004) lends support to the use of a presence versus absence of behaviors as a pain measurement unit.

The fact that data were collected on a large number of acutely ill patients and ICU patients in a variety of clinical settings suggests that the measure is feasible for the evaluation of procedural pain in nonverbal ICU patients. In order to increase its applicability for use in nonverbal ICU patients, the tool requires modifications to the verbal response domain and the body movement domain because certain descriptors (e.g., moaning, guarding, massaging) are not applicable in nonverbal patients with a decreased LOC. Additional evaluation is needed to confirm responsiveness of the Pain Behavior Assessment Tool to other sources of acute pain, as well as to the administration of analgesics.

Critical-Care Pain Observation Tool (CPOT)

Description

The CPOT is a unidimensional measure designed for use with intubated and non-intubated ICU patients. It evaluates four behavioral domains (i.e., facial expressions, movements, muscle tension, ventilator compliance). Each CPOT domain is scored from 0 to 2 and the total score can range from 0 (no pain) to 8 (most pain) (Gelinas et al., 2006).

Psychometric properties

The CPOT was developed based on retrospective chart reviews (N=52) of common pain notations and through focus groups with ICU clinicians (Gelinas, Fortier, Viens, Fillion, & Puntillo, 2004). A subsequent study (Gelinas et al., 2006) used the CPOT to evaluate 105 ICU patients during a resting state and during a painful procedure (i.e., turning). Pain assessments were done three times when the patients had different levels of sedation and intubation status (between the 2nd and 8th hours after cardiac surgery). Patient's self-reported pain intensity was obtained using a verbal descriptive scale (VDS) (0=no pain to 4=unbearable pain) once patients were alert and extubated.

Although the face validity of the CPOT was suggested by including nurses' and physicians' interviews and common pain notations in patients' charts, the level of pain management expertise of these clinicians was not described. Construct validity of the CPOT was determined by a significant increase in CPOT scores associated with the turning procedure ($p < 0.001$) (Gelinas et al., 2006). While a moderate correlation was found between CPOT scores and patients' VDS scores ($p < 0.001$), an increased CPOT score (mean 2.1) was seen in patients who did not report pain. This finding suggests that additional evaluation is needed in order to confirm criterion validity of the CPOT.

No data were reported on the CPOT's internal consistency or homogeneity. As for interrater reliability, an overall evaluation of all nine assessments indicated that the CPOT showed substantial to good agreement ($k = 0.62$ to 0.88). The exception was at time four when patients were conscious and intubated at rest, where the agreement between CPOT ratings and nurses ratings was only moderate ($k = 0.52$). The reason for varying degrees of agreement between raters at different assessment periods is unclear.

Strengths and weaknesses of the CPOT

The CPOT contains operationally defined descriptors and utilizes an intuitive and easy to use scoring system. Clinical utility of the CPOT is enhanced by having unique descriptors for patients who can verbalize and for those who are intubated. However, the responsiveness of CPOT behaviors to painful stimuli in deeply sedated patients remains to be determined. The main concern relates to the fact that generally low mean CPOT scores were reported in all patients across all assessments during painful procedures (i.e., mean score range 2.7 to 3.4; total possible score 0 to 8). One possible explanation for the low score is that procedural pain intensity is generally at a low level. However, it is possible that since unresponsive patients would not display behaviors (therefore a CPOT score of 0), the low mean CPOT scores resulted from averaging scores from those who were able to respond to noxious stimuli and not from those who were unresponsive.

In sum, the CPOT appears to be a well-designed behavioral pain measure for use with verbal and nonverbal ICU patients. While its initial testing demonstrated adequate validity and reliability, further research is needed to address areas of concerns discussed above in order to confirm satisfactory psychometric support for this measure.

Multi-Dimensional Objective Pain Measures

Pain Assessment and Intervention Notation (PAIN) Algorithm

Description

The PAIN Algorithm is a systematic pain assessment and management tool developed for critical care nurses (Puntillo et al., 1997). It consists of three parts: pain assessment; assessment of a patient's ability to tolerate opioids; and guidelines for analgesic treatment decisions and documentation. The pain assessment part of the PAIN

Algorithm prompts nurses to observe the patient for the presence or absence of six behavioral domains (i.e., facial expression, movement, posture, vocal sounds, pallor, perspiration) and three physiologic indicators (i.e., heart rate (HR), blood pressure (BP), respiration). Then, the tool prompts nurses, based on their appraisal of these dimensions of pain, to rate the severity of the patient's pain on a 0 (no pain) to 10 (most pain) NRS. Subsequent pain management decisions are based on the nurse's NRS ratings.

Psychometric properties

The PAIN Algorithm was used in a study that examined the accuracy of nurses' inferences about ICU patients' pain based on physiologic and behavioral indicators, and assessed the relationship between nurses' and patients' pain scores and doses of opioid administered (Puntillo et al., 1997). Nurses performed five hourly assessments using the PAIN Algorithm in a sample of 31 postoperative ICU and PACU patients who were on mechanical ventilation (MV) or who had been extubated in the previous four hours. The content validity of this instrument is supported by consistent findings of common pain behaviors observed by nurses (i.e., no movement (38%); grimacing, frowning, or wincing (34%); and vocalization (24%)). Increased HR (30%) and BP (26%) were the most frequently documented physiologic pain indicators. Other indicators of pain such as changes in respiration, decreased HR, BP, perspiration, or pallor were less evident (< 15% of observations). Significant correlations between the number of behavioral and physiologic pain indicators and the nurses' ratings of pain intensity ($p < 0.05$) suggest that the PAIN Algorithm possess convergent validity. The interrater reliability of the tool was not reported.

Strengths and weaknesses

The PAIN Algorithm may be a useful tool to standardize pain assessment and management in the ICU. However, the length of the tool limits its clinical utility (Puntillo, Stannard, Miaskowski, Kehrle, & Gleeson, 2002). Another limitation of this tool is that it does not standardize the measurements of behavioral and physiologic responses. Accordingly, nurses made clinical judgments or interpretations of behavioral and physiologic responses based on their experiences. A measure that contains predefined criteria and parameters for various responses is necessary to ensure reliability of pain measurement.

Nonverbal Pain Scale (NVPS)

Description

The NVPS (Odhner et al., 2003) was modified from an infant pain measure (i.e., Face, Legs, Activity, Cry, Consolability (FLACC)) (Merkel, Shayevitz, Voepel-Lewis, & Maylviya, 1997). A number of behavioral domains on the FLACC (e.g., cry, consolability) were eliminated because they were not applicable to nonverbal adult patients. The NVPS includes three behavioral domains (i.e., facial expression, body movement, guarding). Additionally, four physiologic domains were added based on a review of literature and grouped into two categories: changes in vital sign over four hours and changes in skin color, warmth, and pupil dilation. Each NVPS domain is scored from 0 to 2 and the total score can range from 0 (no pain) to 10 (most pain).

Psychometric properties

The NVPS was evaluated in a single study of 59 nonverbal ICU patients with various diagnoses (Odhner et al., 2003). Nurses made a total of 100 independent paired

ratings of pain using the NVPS and the FLACC while patients were at rest and during a painful procedure (i.e., turning or ETS).

A mean NVPS score of 0.66 (\pm 0.53) was reported. However, it is not clear what the mean score represents because no NVPS scores were reported at rest or during the painful procedure. The NVPS showed strong positive correlations with the FLACC and has good internal consistency for a newly developed instrument (coefficient α = 0.78) (Odhner et al., 2003). The authors reported that “no significant differences” were found between pairs of nurses’ assessments, but interrater reliability estimates were not reported.

Strengths and weaknesses of the NVPS

The NVPS has limited content validity and reliability as a pain measure for nonverbal ICU patients. Several limitations are worth noting. First, certain NVPS behavioral descriptors such as smile or lying in normal position cannot be equated with a non-painful state. Moreover, measurement of the physiologic indicators (e.g., pupil dilation, perspiration) was not defined or standardized. In addition, the authors did not describe the rationale for their selection of vital sign parameters for pain (e.g., respiratory rate increased by >10 breaths/min over 4 hours, SBP increased by >20mm Hg over 4 hours). The literature suggests a more common form of report for physiologic changes associated with pain is by percent of change from baseline values (Aissaoui et al., 2005; Ambuel, Hamlett, Marx, & Blumer, 1992; Krechel & Bildner, 1995; Suominen et al., 2004). In addition, a gradual increase in a vital sign parameter over a period of time contradicts previous findings that showed that acute pain induces an almost immediate increase in HR and BP (Payen et al., 2001; Puntillo et al., 1997).

Construct validity of the NVPS cannot be inferred because differences in NVPS scores during a painful and non-painful procedure were not provided in the report. The one study of the NVPS (Odhner et al., 2003) does not offer adequate evidence to support its validity and reliability as an objective measure of pain in non-verbal ICU patients.

Summary and Discussion

Psychometric Properties of the Objective Pain Measures

Table 2 presents a summary of the evidence on the validity and reliability of the six objective pain measures reviewed in this paper. All but the NVPS measure have some evidence to support content (face) validity. Four measures have good evidence of construct validity by demonstrating their responsiveness to change following a noxious stimulus (i.e., BPS, Pain Behavior Assessment Tool, CPOT) or administration of an analgesic (i.e., BPRS). Three measures (i.e., BPRS, Pain Behavior Assessment Tool, CPOT) provided evidence of good criterion validity by demonstrating significant correlations between scores on the measure and patient's self-report of pain intensity. One measure (i.e., PAIN Algorithm) showed convergent validity by demonstrating significant correlation with nurses' pain ratings.

In terms of reliability, three measures (i.e., BPRS, BPS, NVPS) reported internal consistency estimates for their various domains, but only the BPS met the homogeneity criterion for this reliability indicator. Interrater reliability was evident in three measures (i.e., BPRS, BPS, CPOT), while others did not evaluate this psychometric property. Therefore, based on a careful analysis of their psychometric properties, only two objective pain measures (i.e., BPS, CPOT) have shown evidence of at least three forms of validity and interrater reliability. Yet, neither of these measures has undergone vigorous

psychometric validation.

Evaluation of Various Dimensions and Domains in the Objective Pain Measures

Unlike self-report measures that commonly focus on the sensory (e.g., pain intensity) and/or affective (e.g., distress) dimensions of pain, the objective measures evaluated in this review focused on behavioral and physiologic dimensions. For the behavioral dimension (see Table 1), all six measures included the domains of facial expression and body movement. Four of the six instruments evaluated body posture (i.e., BPRS, PAIN Algorithm, NVPS, CPOT), four evaluated some aspect of verbal responses (i.e., BPRS, PAIN Algorithm, Pain Behavior Assessment Tool, CPOT), but only two included measures of ventilator compliance (i.e., BPS, CPOT). Of note, only two measures included some physiologic dimension (i.e., PAIN Algorithm, NVPS).

In terms of the specific descriptors within the facial expression domain, some of the measures included a range of facial expressions (e.g., smile/relaxed to grimacing) while others focused on more negative facial expressions (e.g., clenched teeth, wincing). Facial descriptors such as grimace or frown are associated with reflexive pain responses and have been shown to possess validity (Hadjistavropoulos, LaChapelle, Hadjistavropoulos, Green, & Asmundson, 2002). Yet, none of the measures included indices of the affective response (e.g., fear, anxiety). Negative emotions such as anxiety or fear are known to be consequences of acute pain (Szokol & Vender, 2001). Research is needed to develop facial indicators that reflect pain-related affective distress. In terms of using the descriptors of relaxed facial appearance or smile to infer a pain free state, one would be concerned with whether patients can indeed feel at ease or contentment in the context of critical illness. In addition, studies need to determine if facial pain descriptors

change as part of natural aging appearance as well as to determine what effects sedatives and the presence of an endotracheal tube and/or its securing device have on facial expressions of pain.

Within the body movement domain, the common descriptor across five of the measures was restlessness. In addition, all six instruments provided a range of descriptors from none/quiet to restless. For the four measures that included a body posture domain in addition to a body movement domain (i.e., BPRS, PAIN Algorithm, NVPS, CPOT), it is difficult to distinguish between these two domains based on the descriptors provided. In the majority of the measures, a non-painful state is described as a lack of movement or having a relaxed body position. Additionally, a range of behavioral descriptors are used to describe conscious responses (e.g., splinting, guarding, slow cautious movement) and/or reflexive muscle activities (e.g., restless, withdrawal from stimulus, rigid, tense). The validity of these descriptors can be affected by external factors that hinder a patient's ability to exhibit body movement (e.g., physical restraints, CNS depressants, muscle relaxants). Clinical utility of these behavioral descriptors would be enhanced by categorizing these responses according to those that are driven by conscious processes and those that are reflexive in nature. This approach would result in valid descriptors of body movement that could be used to evaluate pain in patients who are alert and in those who are not alert and/or unable to communicate.

Only four of the measures (i.e., BPRS, PAIN Algorithm, Pain Behavior Assessment Tool, CPOT) evaluate patients' verbal responses to pain. The most common descriptors across the four measures are cry and moaning. Vocalization of sound is a valid and reliable pain response that is used to evaluate pain of cognitively impaired

geriatric patients (Decker & Perry, 2003; Hurley, Volicer, Hanrahan, Houde, & Volicer, 1992) and pediatric patients (Bildner & Krechel, 1996; Merkel et al., 1997; Stevens, Johnston, & Petryshen, 1996). However, this domain would not be applicable for use in ICU patients with endotracheal intubation. Two measures (i.e., BPS, CPOT) designed for use with intubated patients added ventilator compliance as an indicator of pain. Several studies have associated pain with mechanical ventilation and its interventions (e.g., endotracheal suctioning) (Morrison et al., 1998; Puntillo, 1994; Puntillo et al., 2001). Since a number of factors unrelated to pain can affect patients' breathing patterns with the ventilator, studies are needed to develop well defined descriptors in order to increase the responsiveness and construct validity of this domain as a pain behavior and to improve its interrater reliability.

Only two instruments evaluated the physiologic dimension of pain (i.e., PAIN Algorithm, NVPS). The common descriptors in these two measures were increased HR and BP. Sensitivity of these autonomic responses to pain is demonstrated in experimental pain studies using healthy volunteers (Stancak, Yamamoto, Kulls, & Sekyra, 1996; Tassorelli, Micieli, Osipova, Rossi, & Nappi, 1995). Clinical studies have also established that physiologic responses are valid indicators of nociception in critically ill neonates (Stevens et al., 1996; Suominen et al., 2004) and anesthetized adult volunteers (Larson et al., 1997; Larson et al., 1993). In addition, stability of these autonomic responses were shown to reflect balanced anesthesia and adequacy of analgesia during intubation procedures (Guignard, Menigaux, Dupont, Fletcher, & Chauvin, 2000). Of the two objective pain measures that evaluated HR and BP responses, the PAIN Algorithm did not describe the criterion for an increase in HR or BP while the NVPS parameters for a HR

and BP increase did not demonstrate validity. Given that the validity of these responses are evidenced in other patient populations and that these data are readily available (i.e., routinely monitored in all ICU patients), further research is warranted in order to establish parameters for an increase in these responses and their specificity as a pain response in ICU patients.

CONCLUSIONS

Despite advances in pain research and management, the measurement of pain in nonverbal ICU patients remains an immense challenge for critical care clinicians. The dilemma of adequate versus inadequate pain management in these high-risk patients is largely attributed to the lack of vigorously tested valid and reliable pain measures. This critical review demonstrated that although two objective pain measures (i.e., BPS, CPOT) showed validity and reliability, they have not received rigorous evaluation to consider them as a robust pain measure for use in nonverbal ICU patients. Still, findings from studies of objective pain measures provide useful information to direct future research in order to develop and validate clinically useful pain measures for use with nonverbal critically ill patient.

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Table 1. Dimensions and Domains (end anchors) for Six Objective Pain Measures for Use with Nonverbal ICU Patients

Scoring Method (Scale in each domain & total score)	Behavioral Dimension					Physiologic Dimension
	Facial Expression Domain	Body Movement Domain	Body Posture Domain	Verbal Response Domain	Ventilator Compliance Domain	
Scale: 0 to 3 Total score: 0 (no pain) to 12 (most pain)	None to constant frowning	Quiet to very restless	Relaxed to extreme tenseness	Normal speech to crying out	-----	-----
Presence or absence of each pain behavior	Frown, grimace, wince	None or slow movement to restless	Rigid, splinting, tenseness	Cry, moaning	-----	Changes in heart rate, blood pressure, respiration, pallor
Scale: 1 to 4 Total: 3 (no pain) to 12 (most pain)	Relaxed to grimacing	No movement to limbs retracted	-----	-----	Tolerating movement to unable to control ventilation	-----
Score: 0 to 2 Total: 0 (no pain) to 10 (most pain)	No expression or smile to frequent grimace, frown	Lying quietly to restless, excess activity/withdraw from stimulus	Lying quietly to rigid, stiff	-----	-----	Vital sign changes in past 4 hours. Changes in skin moisture/ color or pupil size
Present or absent	10 descriptors (e.g., grimace, clenched teeth)	15 descriptors (e.g., , rigid, restless)	-----	7 descriptors (e.g., moan, cry screaming, verbal complaints)	-----	-----
Score: 0 to 2 Total: 0 (no pain) to 8 (most pain)	Relaxed to grimacing	No movement to restless	Relaxed to very tense/rigid	For non-intubated patients: Normal speech or no vocalization to crying out	For intubated patients: tolerate ventilator or movement to fighting ventilator	-----

Table 2. Summary of Psychometric Properties of Objective Pain Measures for Use with Nonverbal ICU Patients

Measures	ICU Evaluation Studies		Psychometric Properties			
	Study Reference#	Sample * Setting	Validity	Evidence Rating**	Reliability	Evidence Rating**
Behavioral Pain Rating Scale	Mateo (1992)	N=30 General surgery	Content (Face) validity	+	Interrater reliability	---
		N=36 GYN surgery	Criterion validity	+		
		*Post-Anesthesia Care Unit	Construct validity	+		
PAIN Algorithm	Puntillo et al (1997)	N=31 Cardiothoracic/general surgery *ICU and PACU	Content (Face) validity	+	Interrater reliability	---
Behavioral Pain Scale	Payen et al (2001)	N=30 Medical patients	Content (Face) validity	+	Interrater reliability	+
	Aissaoui et al (2005)	N=34 General diagnoses	Content validity	+	Homogeneity	+
	Young et al (2006)	N=44 Medical/Surgery	Construct validity	+	Internal consistency	+
Non Verbal Pain Scale	Odhner et al (2003)	N=59 Burn/ Trauma/Surgery	Content (Face) validity	---	Interrater reliability	---
		*ICU	Construct validity	---	Internal consistency	+
Pain Behavior Assessment Tool	Puntillo et al (2004)	N=5957 Medical/Surgical patients	Content (Face) validity	++	Interrater reliability	---
		*Acute care & ICU	Construct validity (Response to pain)	+		
Critical Care Pain Observation Tool	Gelinas et al (2006)	N=105 Cardiothoracic surgery	Content (Face) validity	+	Interrater reliability	+
		*ICU	Construct validity	+		
			Criterion validity	+/-		

**Evidence rating based on pre-selected criteria (---- Not reported or did not meet criterion; + Met satisfactory criterion ++ Met excellent criterion; +/- Inconsistent findings)

CHAPTER 4

PHYSIOLOGIC AND BEHAVIORAL RESPONSES TO NOXIOUS PROCEDURES IN SEDATED CRITICALLY ILL ADULT PATIENTS

Abstract

This prospective study compared changes in physiologic (heart rate, blood pressure, pupil size, and cortical arousal per the Bispectral Index) and behavioral (facial expressions, body movement, flexion withdrawal, ventilator synchrony) responses in patients undergoing a noxious versus a non-noxious procedure. Sedated, mechanically ventilated critically ill patients following cardiac surgery were recruited from University and community hospital intensive care units. Measurements of behavioral and physiologic responses were taken during a noxious (endotracheal suctioning or turning) and a non-noxious (gentle touch) procedure at baseline, 1 and 3 minutes during the procedure, and 5 minutes after completion of procedure. The sample of 48 patients with ASA status III and IV was predominately male (67%) Caucasians (58%) with a mean age of 65 ± 14 years. On average, these ICU patients required 15 hours of intubation after surgery and 2 days of ICU care. Heart rate, pupil size, and BIS increased significantly over time with the noxious procedure ($p < 0.01$) but not with the non-noxious procedure. Blood pressures (systolic, diastolic, mean arterial pressure) did not differ significantly between the two procedures. Noxious stimulation did not induce the most commonly reported pain-related behaviors in deeply sedated patients. *Conclusions:* Certain physiological responses are potentially useful for the assessment of nonverbal patients' pain. Further research is needed to examine the effects of opioids and sedatives on these physiologic responses and to evaluate the effects of these responses on patient outcomes.

An estimated 60% of critically ill adult patients in the Intensive Care Unit (ICU) suffer acute pain of moderate intensity. The most common causes of acute pain are surgery (Kuperberg & Grubbs, 1997; Yorke, Dip, Wallis, & McLean, 2004), mechanical ventilation (Bergbom-Engberg & Haljamae, 1989; Grap, Blecha, & Munro, 2002), and therapeutic procedures (Morrison et al., 1998; Puntillo et al., 2001; Stanik-Hutt, Soeken, Belcher, Fontaine, & Gift, 2001). Importantly, acute pain triggers autonomic reactions and activates stress responses. These processes can adversely affect the myocardial and respiratory functions of patients who already have a compromised physiologic status (Puntillo, Miaskowski, & Summer, 2003).

Unrelieved pain induces prolonged stress on biologic systems and may predispose a critically ill patient to adrenal insufficiency (Marik & Zaloga, 2002), suppress immune function (Beilin et al., 1996), and/or affect glucose metabolism by increasing insulin resistance (Greisen et al., 2001). Increased postoperative pain was shown to positively correlate with pulmonary morbidity (Puntillo & Weiss, 1994) and increased length of ICU stay (Carroll et al., 1999). Patients who recalled a greater number of negative ICU experiences (e.g., pain episodes, mechanical ventilation) had poorer mental health status (Schelling et al., 2003) and lower quality of life (Granja et al., 2005) after discharge.

The actual incidence of pain in critically ill patients is unknown because of the inability of some patients to self-report and limitations of existing behavioral pain measures. Commonly used physiologic responses (e.g., heart rate (HR), blood pressure (BP)) and behaviors (e.g., facial expressions, body movement) have not been adequately characterized in sedated, nonverbal ICU patients. Findings from a few studies suggested that changes in pupil size (Larson, Berry, May, Bjorksten, & Sessler, 2007; Larson et al.,

1997; Zmarzty, Wells, & Read, 1997) and cortical arousability using Bispectral Index (BIS) (Guignard, Menigaux, Dupont, Fletcher, & Chauvin, 2000; Takamatsu, Ozaki, & Kazama, 2006) can be used as clinical indicators of analgesia-nociception in anesthesia settings. However, these measures have not been used to evaluate physiologic responses to pain in ICU patients.

Given the paucity of research on the physiologic responses of sedated, critically ill patients to pain as well as the lack of data on the use of pupillary and BIS responses to acute pain, the purposes of this study were to: 1) evaluate patients' physiologic responses (i.e., HR, BP, pupil size, and cortical arousability) to a noxious and non-noxious procedure; 2) examine changes in these physiologic responses during the noxious procedure; and 3) describe patients' behaviors (i.e., facial expression, body movement and posture, flexion withdrawal, and ventilator synchrony) during the noxious procedure.

MATERIALS AND METHODS

Subjects and Settings. The study was conducted at an academic medical center and a community hospital in Northern California. It was approved by the Human Subjects Committee at each site. Patients were recruited and provided written informed consent at the preoperative visit one to five day(s) prior to surgery.

Patients were eligible for this study if they were: 1) English speaking and able to give informed consent; 2) between 21 and 85 years of age; and 3) scheduled for coronary artery bypass graft and/or valve repair via sternotomy and cardiopulmonary bypass with an expected ICU admission. Patients with a documented neurological deficit or a history of chronic opioid use (> 3 months) were excluded.

Following surgery and admission to the ICU, patients were included if they were being mechanically ventilated and sedated (i.e., sedation level < -2 on the Richmond Agitation Sedation Scale (RASS) (Sessler et al., 2002). Patients were excluded if they had received epidural analgesics and/or a neuromuscular blocking agent within one hour of the ICU admission. Patients' participation in the study ended: 1) when all of the study measurements were completed; 2) if they developed significant postoperative complications (e.g., excess bleeding or hemodynamic instability); 3) if patients became alert or were extubated; or 5) if the patient's physician or family members made a request to withdraw the patient's participation.

Physiologic Responses. The institutions' Hewlett Packard monitoring systems were used to record HR (in beats/min) and BP [Systolic (SBP), diastolic (DBP), mean arterial pressure (MAP)]. The BP was obtained via a radial or femoral arterial line which was present in all postoperative patients. Pupil size (diameter in millimeters) was measured using a handheld automated pupillometer (NeuroOptics, Inc., San Clemente, CA). This device performs multiple scanning of pupil diameter for 3.2 seconds and then displays an average value. The automated pupillometer provides a reliable measure of pupil size (Du et al., 2005; Meeker et al., 2005). For each measurement, the sedated patient's eyelid was opened by the investigator and the opposite eye was covered with a washcloth. The lighting in the patient's room was controlled so that no intense lights were directly over the patient's head. Pupil measurements were not performed in patients with visible periorbital or facial edema to avoid causing pain or discomfort with the eye opening maneuver.

Cortical arousability was measured using the Bispectral Index (BIS) (A-2000 XP monitoring system, Aspect Medical Systems, Norwood, MA). It is a commercially available biophysical measure of cerebral electrical activity obtained via a sensor placed on a patient's forehead. BIS Indices are a continuous series of numeric values that range from 0 (denotes complete EEG suppression) to 100 (awake) and were derived based on statistical ranking of unique EEG features that characterized anesthetic-induced changes in over 5000 patients (Johansen & Sebel, 2000). The BIS was able to differentiate among various levels of sedation when subjective scales ceased usefulness in unresponsive patients (DeDeyne et al., 1998; Walder, Suter, & Romand, 2001). This study determined BIS reliability as having a signal quality index (SQI) $\geq 90\%$, EMG index ≤ 50 decibels (dB), and a consistency with clinical state per the RASS. The RASS is a valid and reliable sedation scale (De Jonghe et al., 2000; Ely et al., 2003) that has shown convergent validity with the BIS to measure sedation depth in critically ill patients (Ely et al., 2003).

Behaviors. A behavioral checklist was modified from a previously published Pain Behavior Assessment Tool (Puntillo et al., 2004). The modified checklist included six domains (i.e., facial expressions, body movement, postures, flexion of extremities, withdrawal, and synchrony with MV). The Pain Behavior Assessment Tool has demonstrated construct and criterion validity. Reliability of the observations was ensured by having an operational definition for each of the behavioral domains. Patients' pain report (as yes or no to having pain, or unable to report) was assessed during the procedure in patients who became responsive.

Measurements. In this prospective, descriptive study we performed repeated measurements using within-subjects and crossover techniques. Each patient received a noxious [(i.e., repositioning or endotracheal suctioning (ETS))] and a non-noxious (i.e., gentle touch) procedure. The effect of order of procedure was controlled for by randomizing the patient's non-noxious procedure as occurring before or after the noxious procedure. The patient's nurse determined the necessity for and performed the noxious procedure. The investigator performed the non-noxious procedure by gently messaging both of the patient's shoulders for 30 seconds and then the patient's feet for 30 seconds. With each procedure, physiologic and behavioral responses were measured across three states: Baseline state (T_B), 3 minutes before the procedure; Procedural state [1st (T_1) and 3rd (T_3) minute(s) after onset of the procedure]; and Recovery state (T_R), 5 minutes after completion of the procedure.

Statistics. Data analyses were performed using the Statistical Package for Social Science (SPSS) (version 15, Chicago, IL). Heart rate values of patients with active pacemakers or BIS values that did not meet the SQI and EMG criteria were excluded from data analysis. Differences in physiologic responses between the two study procedures were evaluated using two-way repeated measure analyses of variance (ANOVAs) with 2 within subject factors. For physiologic responses that occurred during the noxious procedure, within-group differences were assessed by one way repeated measure ANOVA followed by post-hoc contrasts. The effects of the changes in physiologic responses were calculated as mean difference and percents. Patients' behaviors, reported as frequencies and percentages, were cross tabulated for T_B and T_1 . Based on a power calculation, a sample size of 48 patients was needed to test for

differences with 80% power and a medium effect size (0.50) based on an overall ANOVA alpha level of 0.05 distributed equally among 3 pairwise contrasts for each procedure.

RESULTS

Sample Characteristics. Fifty-eight patients enrolled in the study. Ten patients were withdrawn from the study due to changes in surgery schedule (n=6); at the request of the patient's nurse due to family anxiety (n=1); because they received a neuromuscular blocking agent during the study period in ICU (n=2); or because they had postoperative complications that required resuscitative interventions (n=1). As noted in Table 1, the final sample of 48 patients was predominately male (67%) and comprised of Caucasians (58%), African-Americans (15%), and Asians (17%). The mean age of patients was 65 ± 14 years. On average, patients required 15 hours of MV postoperatively and received ICU care for 2 days.

All patients received a similar general anesthesia approach with opioids for analgesia. Upon admission to the ICU and before the study, most patients were sedated with propofol infusions. The patient's nurse determined the need for and administered intravenous doses of opioids. During the study, the majority of patients (>70%, n>33 of 48) were deeply sedated and responded only to physical stimulation (RASS score = -4) or were totally unresponsive (RASS score = -5). The remainder of patients were moderately sedated and were able to respond to verbal stimulation (RASS score = -2 or -3). In terms of patients' subjective pain reports, all of the patients (21%, n=10 of 48) who were able to give a pain report during the noxious procedure reported pain. During the non-noxious

procedure, only 10% of the patients were able to report whether they had pain or not (4% had pain, 6% had no pain).

Differences in Physiologic Responses Between Study Procedures. Significant differences in HR [F (3, 32) =3.50, p=0.03], pupil size [F (3, 41) =5.65, p<0.001], and BIS [F (3, 41) =3.18, p=0.03] were found between the noxious and the non-noxious procedures. There was no significant difference in SBP [F (3, 43) =2.63, p=0.06], DBP [F (3, 43) =0.40, p=0.75] and MAP [F (3, 43) =1.44, p=0.24] between the two procedures. Figures 1 to 3 illustrate HR, pupil size, and BIS responses across time during both study procedures.

Changes in Physiologic Responses Over Time During the Noxious Procedure. Table 2 lists the means and SD for HR, pupil size, and BIS values at various times and the degree of change in these values as mean differences and percents. During the noxious procedure, significant changes over time were found in HR [F (3, 35) =4.08, p=0.01], pupil size [F (3, 42) =6.97, p=0.001], and BIS [F (3, 42) =13.51, p<0.01]. Post-hoc contrasts showed that significant changes in HR occurred between baseline and T₃ (F (1, 37) =9.62, p=0.004, *partial eta squared*=0.21) or 4% from its baseline value. For pupil size, significant changes were found between baseline and T₁ (F (1, 44) = 21.78, p=0.00, *partial eta squared*=0.33) and between baseline and T₃ (F= 10.39, p=0.002, *partial eta squared*=0.19). Between these two times, the pupil diameter increased by 16% (at T₁) and 13% (at T₃). The change in BIS was significant between baseline and T₁ during the noxious stimulation (F (1, 44) = 23.42, p<0.00, *partial eta squared*=0.35) and between baseline and T₃ (F= 27.35, p<0.00, *partial eta squared*=0.38). These BIS values

increased from baseline values by about 10% at each noxious procedural state (T₁ and T₃).

After completion of the noxious procedure, significant decreases in HR (-4%, $p=0.02$) and pupils size (-12%, $p<0.01$) occurred. These responses returned to their baseline values ($p<0.05$). However, the stimulated BIS response (T₃) did not decrease after the noxious procedure. In fact, it remained significantly higher than its baseline value ($p<0.001$).

Behaviors Observed During the Noxious Procedure. At baseline state, most patients had a relaxed facial appearance (94%, $n=44$ of 47) and body posture (98%, $n=46$), were lying quietly in bed (89%, $n=42$), and breathing in synchrony with the ventilator (94%, $n=45$). The most common behaviors that were observed in some patients during the first minute of the noxious stimulus included facial grimace/frown (17%, $n=8$) and movement of body or extremities (21%, $n=10$). Few patients displayed flexion of the upper or lower extremities (8%, $n=4$) or tensing/rigidity (6%, $n=3$). In addition, few developed asynchronous breathing with the ventilator (6%, $n=3$) or withdrew from the noxious stimulus (2%, $n=1$). Table 3 lists behaviors observed at baseline and T₁.

DISCUSSION

This study is the first to evaluate changes in several physiologic and behavioral indicators during noxious and non-noxious procedures in the same sample of sedated, critically ill patients. Of note, noxious stimulation did not induce the most commonly reported pain-related behaviors (Puntillo et al., 2004) in deeply sedated patients. However, HR, pupil size, and BIS responses were sensitive to change during a noxious stimulation. Importantly, these physiologic responses occurred in a sample of patients

that, for the most part, had received opioids and sedatives. The positive physiologic responses that occurred during the noxious stimulation were congruent with the self-report of pain from those patients who were able to provide a verbal report.

Our finding of a positive HR and pupil size responses associated with nociception is consistent with previous studies that evaluated changes in ICU patients' HR during noxious procedures (Aissaoui, Zeggwagh, Zekraoui, Abidi, & Abouqal, 2005; Payen et al., 2001; Young, Siffleet, Nikoletti, & Shaw, 2006) and pupil size changes in anesthetized healthy subjects during tetanic stimulation (Larson et al., 1997; Larson et al., 1993; Larson, Tayefeh, & Sessler, 1996). As with two previous studies of ICU patients' HR responses to noxious procedures (Aissaoui et al., 2005; Payen et al., 2001), the changes seen in our study, although statistically significant, were not clinically significant. The use of HR response as a specific indicator of nociception in ICU patients may be confounded by many drugs and interventions which affect ICU patients' HR. Hence, clinicians would have difficulty recognizing the small changes in HR as a pain response.

We did confirm that pupil size response is highly reactive to nociception, having the greatest effect compared to the other physiologic responses evaluated in this study. Pupil dilation is a noted autonomic response to pain (Hamill-Ruth & Marohn, 1999) caused by sympathetic reflex in awake patients (Yang, Niemann, & Larson, 2003). In anesthetized patients, pupil response to noxious stimulation is thought to be caused by inhibition of the pupilloconstrictor nucleus in the central pathways or by an unknown synaptic pathway within the iris (Larson & Talke, 2001; Larson et al., 1996). In healthy, anesthetized adults prior to receiving opioids, striking observations of pupil size changes

(pupil size +200%) during noxious tetanic stimulation have been reported (Larson et al., 1997; Larson et al., 1993). However, obvious differences exist between study patient characteristics and types of noxious stimulation (i.e., mechanical vs. tetanic) that limit generalizability of their findings to critically ill patients.

Opioids analgesics may contribute to the smaller changes in HR and pupil size observed in this study. Previous studies have shown that opioids attenuated HR response in anesthetized patients undergoing tracheal intubation (Albertin et al., 2005; Guignard et al., 2000; Wang, McLoughlin, Paech, Kurowski, & Brandon, 2007) and tetanic stimulation (Larson et al., 2007). Thus, use of opioids may help reduce HR variability. Furthermore, increasing plasma concentration of opioids have been shown to attenuate pupil dilation during noxious tetanic stimulation of anesthetized individuals (Barvais et al., 2003; Larson et al., 2007; Larson et al., 1997). Thus, pre-procedural pupil size may be used to determine a patient's underlying analgesic state and to predict the patient's response to noxious procedure.

The BIS is suggested as a measure of cortical arousability (Ely et al., 2004). Cortical arousal reaction is an accepted measure of nociception in anesthesia settings (Takamatsu et al., 2006; Wilder-Smith, Hagon, & Tasonyi, 1995; Zmarzty et al., 1997). Our finding of a positive BIS response during the noxious procedure is consistent with previous reports. Guignard and colleagues (2000) showed that the BIS increased significantly during laryngoscopy and tracheal intubation procedures in anesthetized patients (Guignard et al., 2000). Similarly, significant BIS changes were found during an endotracheal suctioning procedure in ICU patients sedated with propofol (Brocas et al., 2002).

As with HR and pupil size, opioids may have influenced the finding of a small effect on the BIS. Opioids are known to attenuate arousability and content processing (Young-McCaughan & Miaskowski, 2001). Opioids are suggested to produce analgesia at the subcortical level (Smith, McEwan, Jhaveri, & al, 1994) and have synergistic effects with propofol to produce a hypnotic state (Wang et al., 2007). A few studies have shown that the BIS response during nociception was modulated by the use of opioids (e.g., alfentanil, remifentanil) (Brocas et al., 2002; Guignard et al., 2000). Indeed, Albertin and colleagues (2005) did not find significant BIS changes during skin incisions or tracheal intubation in patients sedated by remifentanil and propofol (Albertin et al., 2005). There may be a dose-response effect which we did not address in our study.

Our study findings do not substantiate the validity of common pain behaviors to assess nociception in deeply sedated patient. Few patients in our study displayed behavioral responses (e.g., facial expressions, body movement) during the noxious procedure. These reflexive behaviors were found to be associated with pain in a large descriptive study of patient behaviors associated with painful procedures in acute and critical care settings (Puntillo et al., 2004). The patients in that study differed from ours in that they were alert and all of them were able to give pain reports. Unlike Gelinas and colleagues (2006) who observed asynchronous breathing with the ventilator in sedated ICU patients during noxious stimulation (Gelinas, Fillion, Puntillo, Viens, & Fortier, 2006), ventilator response was not evident in our patients. Thus, the validity of this behavioral domain as a nociceptive indicator in deeply sedated ICU patients remains to be determined.

Limitations. Several limitations of this study are worth noting. Generalizability of study findings are limited by the use of a small sample size and the inclusion of only cardiac surgery patients. Yet, this homogeneous sample helped reduce respondent variability and enhanced the study's internal validity. Although a prospective study approach enabled us to describe the effect of a noxious procedure on physiologic and behavioural outcomes across time, our study design did not allow control over certain factors that could influence patient responses: timing of noxious procedures as well as the use of opioids, sedatives, or vasoactive drugs. In addition, we cannot rule out other influences on the physiologic response such as hypothermia, the residual effects of anesthesia, or various ICU therapies. However, we generated important data, particularly about pupil responses to a nociceptive procedure that deserve further exploration. Opioid and sedative dose-response analyses would be important additions to future studies. In addition, the relationship between sedation and nociceptive responses is an important covariate in these types of studies.

Conclusion. This study confirmed that certain physiologic responses are unique to a noxious procedure when compared to a non-noxious procedure. The baseline analgesic status of the patient may predict these physiologic responses during nociception. The results of this study require confirmation using a larger, heterogeneous sample with different noxious stimuli. Future research should examine a dose response of opioids and sedatives on these physiologic responses and evaluate the effects of these responses on patient outcomes.

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Table 1. Patient Demographic and Treatment Characteristics

CHARACTERISTIC	VALUES	
Age (years)*	65± 14 (range 39 to 88)	
Gender (n (%))		
• Male	32 (67)	
• Female	16 (33)	
Ethnicity (n (%))		
• Caucasian/White	28 (58)	
• African-American/Black	7 (15)	
• Asian/Pacific Islander	8 (17)	
• Hispanic/Latino	3 (6)	
• Other	2 (4)	
ASA Classification** (n (%))		
• III	20 (42)	
• IV	28 (58)	
Mechanical ventilation (hours)*	16 ± 6 (range 4 to 35)	
Length of ICU Stay (days)*	2 ± 1 (range 1 to 6)	
Sedatives/Opioids <60 Minutes Before the Study (n (%))		
• Propofol	26 (54)	
• Propofol and Opioids	19 (40)	
• Opioids	2 (4)	
• Versed	1 (2)	
Sedatives/Opioids During Each Study Procedure (n (%))		
	<u>Noxious</u>	<u>Non-Noxious</u>
• Propofol	4 (9)	7 (15)
• Propofol and Opioids	3 (6)	0
• Opioids	10 (21)	3 (6)
• Versed	1 (2)	0
• None	29 (62)	37 (79)

*Values shown as mean ± SD (range)

**American Society of Anesthesiologist Physical Status

Table 2. Changes in Physiologic Responses During the Noxious Procedure

RESPONSES (N)	TIME	MEAN± SD (RANGE)	Pairwise Contrasts Between Times	ANOVA			DIFFERENCE OF MEANS	% CHANGE BETWEEN TIMES
				F VALUE	P VALUE	PARTIAL ETA SQUARED		
HR (bpm)	T _B	86 ± 13 (59 to 113)	T _B vs. T ₃	9.60	0.004	0.21	3	4%
	T ₁	88 ± 13 (61 to 114)	---	---	---	---	---	---
	T ₃	89 ± 12 (61 to 108)	T ₃ vs. T _R	6.03	0.02	0.14	-3	-4%
	T _R	85 ± 14 (49 to 106)	---	---	---	---	---	---
Pupil size (mm) (n=46)	T _B	2.2 ± 0.5 (1.5 to 5.0)	T _B vs. T ₁	21.72	<0.001	0.33	0.4	16%
	T ₁	2.6 ± 0.7 (1.5 to 4.9)	T ₁ vs. T _R	17.01	<0.001	0.28	0.3	-12%
	T ₃	2.6 ± 0.8 (1.5 to 5.3)	T _B vs. T ₃	10.37	0.002	0.19	0.4	13%
	T _R	2.3 ± 0.5 (1.6 to 5.0)	T ₃ vs. T _R	8.93	0.005	0.17	0.3	-12%
BIS value (n=46)	T _B	56 ± 14 (25 to 83)	T _B vs. T ₁	23.42	<0.001	0.35	6	10%
	T ₁	62 ± 18 (28 to 98)	---	---	---	---	---	---
	T ₃	62 ± 16 (28 to 98)	T _B vs. T ₃	27.35	<0.001	0.38	6	10%
	T _R	61 ± 16 (34 to 100)	T _R vs. T _B	18.21	<0.001	0.29	5	9%

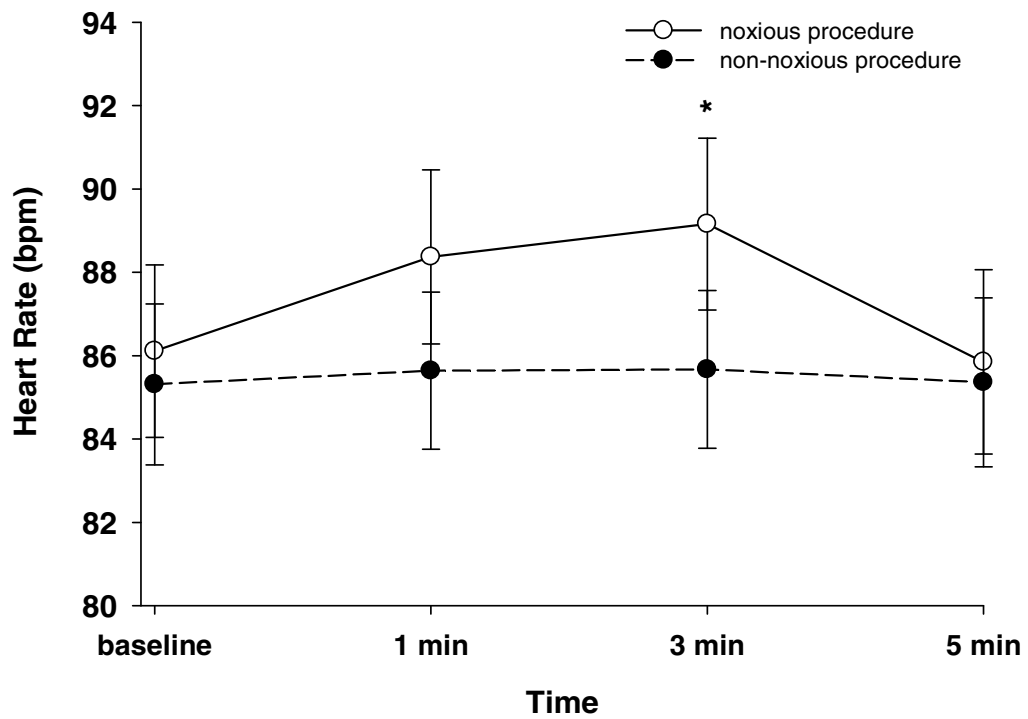
*Reported values with statistical significance (p<0.05)

T_B= Baseline state; T₁ & T₃ = 1st & 3rd minutes after onset of procedure; T_R= Recovery state, 5 minutes after procedure

Table 3. Frequency of Patient Behaviors Observed During the Noxious Procedure (N=47)

BEHAVIORS	NOXIOUS PROCEDURE	
	Baseline [n (%)]	First minute of procedure [n (%)]
Facial pain expressions		
• No	44 (94)	39 (83)
• Yes	3 (6)	8 (17)
Body movement		
• No	42 (89)	37 (79)
• Movement < 5sec	5 (11)	9 (19)
• Movement > 5sec	0	1 (2)
Posture		
• Relaxed	46 (98)	44 (94)
• Tense/rigid	1 (2)	3 (6)
Flexion of arms and/or legs		
• No	45 (96)	43 (92)
• Yes	2 (4)	4 (8)
Withdrawal from stimulus		
• No	----	46 (98)
• Yes	----	1 (2)
Ventilator synchrony		
• Synchronous	45 (96)	44 (94)
• Asynchronous	2 (4)	3 (6)

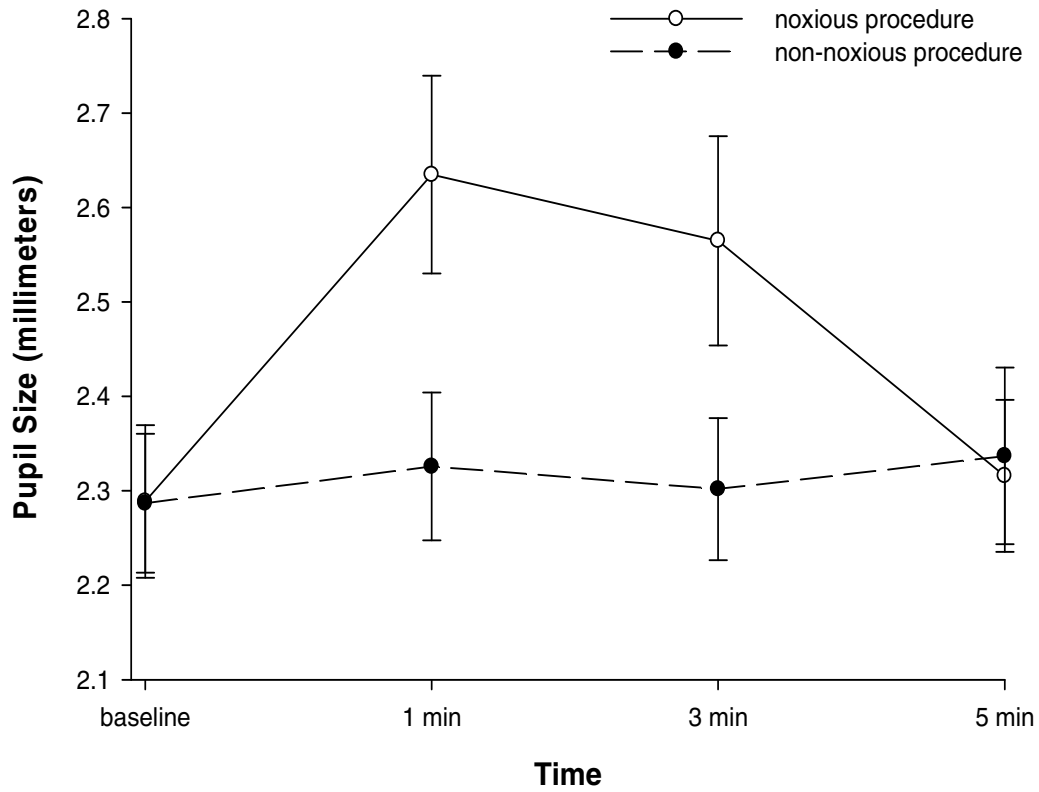
Figure 1. Comparisons of Heart Rate Changes Between the Noxious and the Non-Noxious Procedure



{ Baseline=baseline state; 1 min=1st after onset of procedure; 3 min=3rd minutes after onset of procedure; 5min= recovery state, 5 minutes after completion of procedure.
bpm=beats per minute; mm=millimeter}

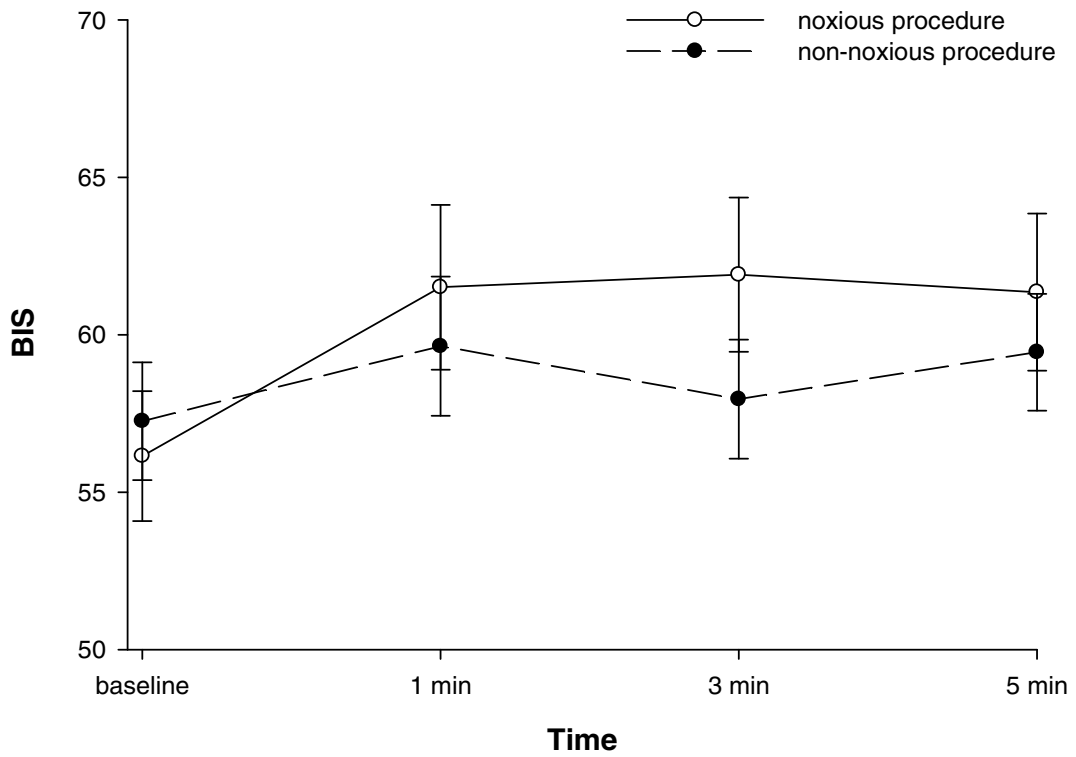
*shown significant changes from the baseline value

Figure 2. Comparisons of Pupil Size Changes Between the Noxious and the Non-Noxious Procedure



{Baseline=baseline state; 1 min=1st after onset of procedure; 3 min=3rd minutes after onset of procedure; 5min= recovery state, 5 minutes after completion of procedure.
bpm=beats per minute; mm=millimeter}

Figure 3. Comparisons of Bispectral Index Changes Between the Noxious and the Non-Noxious Procedure



{ Baseline=baseline state; 1 min=1st after onset of procedure; 3 min=3rd minutes after onset of procedure; 5min= recovery state, 5 minutes after completion of procedure.
bpm=beats per minute; mm=millimeter }

CHAPTER 5

SUMMARY AND CONCLUSION

The significance of pain in ICU patients is well documented in over two decades of critical care research. A substantial number of ICU patients are unable to provide a self-report due to intubation or sedative effects of drugs. In these nonverbal patients, assessment and management of the adverse effects of nociception and the effectiveness of analgesic interventions require the use of valid clinical indicators of nociception.

This dissertation presented the findings from two studies that evaluated pain of mechanically ventilated ICU patients. The first study confirmed that pain is a prevalent symptom for ventilated ICU patients. It showed that almost one half of patients reported having pain at moderate to severe levels and that there was evidence of associations among several discomforting symptoms. This study underscored the need to utilize a valid and reliable objective measure of pain in nonverbal patients.

The second study was the first to evaluate multiple physiologic responses and behaviors within a sample of deeply sedated ICU patients. It showed that HR, pupil size, and cortical arousal changes were associated with nociception. However, because the effects of change were modest, clinical utility of these physiologic responses as nociceptive indicators remains to be determined. This study provided documentation that behavioral pain measures are insufficient to measure nociception in deeply sedated patients.

Our results of physiologic indicators of nociception provided groundwork for additional research topics in future studies. Firstly, these findings should be validated with a larger, heterogeneous sample and different noxious conditions. Additional

validation of these physiologic responses should be done by comparing them with patients' self-reports of pain. Research should continue to evaluate the effects of various potential influencing factors on physiologic responses such as gender, age, and drugs. By using a randomized and rigorous study design, a study would have an enhanced ability to establish clinically useful parameters of change in physiologic responses during nociception. In order to improve pain management outcomes directed by clinically useful nociceptive indicators, it would be essential to determine whether baseline status of nociceptive indicators could be used to predict patients' responses during noxious procedures. Future studies should explore the utility of other potential indicators such as hormonal or immunological responses during nociception.

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