



# STIMULATION OF CRITICALLY ILL PATIENTS: RELATIONSHIP TO SEDATION

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**Objectives** To describe the number and type of stimulation events and the relationship of stimulation to sedation level in patients receiving mechanical ventilation.

**Methods** A 4-hour direct observation was conducted in 103 patients receiving mechanical ventilation. Stimulation events and sedation level before and after the stimulation were documented. Eight categories of stimulation events were developed in a previous pilot study of 36 patients receiving mechanical ventilation. Sedation was measured continuously by using a processed electroencephalographic score (patient state index [PSI]) and intermittently by using the Richmond Agitation-Sedation Scale.

**Results** Patients were mostly alert/mildly sedated (54.4%) at study enrollment. During the 349 hours of observation, 58.8% of the time included stimulation events. General auditory types of stimulation were most common (41.2% of observed time), followed by respiratory management and tactile family stimulation. For all events, auditory-talking, tactile-general, tactile-noxious, and tactile-highly noxious stimuli were associated with higher PSIs (all  $P < .001$ ) after stimulation; other stimuli were not. Level of consciousness influenced response to stimuli, with almost all types of stimuli increasing PSI for patients more deeply sedated (PSI < 60) just before the stimuli. However, the effect of stimulation on PSI for more alert patients (PSI > 60) was small and variable.

**Discussion** Critically ill patients receiving mechanical ventilation are subjected to various forms of auditory and tactile stimulation frequently throughout the day. All types of stimuli increased arousal in patients who were more deeply sedated. The effect of stimulation in patients who were not deeply sedated was minimal and inconsistent. (*American Journal of Critical Care*. 2016;25:e48-e55)

Critically ill patients receiving mechanical ventilation are treated with sedatives to promote their comfort by attenuating the anxiety, pain, and agitation associated with mechanical ventilation and the critical care environment.<sup>1-5</sup> Although sedatives are among the most frequently prescribed drugs in intensive care units (ICUs),<sup>6</sup> the achievement and evaluation of optimal sedation remains a clinical challenge. The overall goals of sedation in the critical care setting are to provide physiological stability, ventilator synchrony, and comfort for the patient.<sup>1,4,7,8</sup> Sedative agents should facilitate patients' comfort without inducing prolonged and/or deep sedation, which has been linked to prolonged mechanical ventilation and long stays in the ICU.<sup>1,9</sup> Identifying the appropriate level of sedation enables clinicians to adjust sedative dosing to the desired clinical effect while minimizing the risk of excessive or inadequate sedation.

In the absence of objective data about whether use of sedation is, in fact, achieving desired sedation goals, including during times when patients are stimulated, development of strategies to improve sedation evaluation and management is difficult. Therefore, a first step in improving patients' outcomes is to systematically determine whether optimal sedation is being achieved, even during times of stimulation. These data will provide empirical evidence to understand the relationship of patients' stimulation to levels of sedation. Therefore, the aim of this study was to describe the number and type of stimulation events experienced and the relationship of stimulation to sedation level in patients receiving mechanical ventilation.

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## Methods

### Setting and Participants

This study was a planned subset of a larger, prospective, 24-hour, observational study conducted in a 779-bed tertiary care university medical center in 3 critical care units: the surgical trauma ICU (STICU), the cardiac surgery ICU (CSICU), and the medical respiratory ICU (MRICU).<sup>10</sup> The specific aim of the larger prospective study was to describe the relationship among sedation, stability of physiological status, and comfort during a 24-hour period in patients receiving mechanical ventilation. The larger study sample (N = 176) was drawn from all patients admitted to these ICUs who were intubated, receiving mechanical ventilation, 18 years of age or older, and expected to receive at least 24 hours of mechanical ventilation. Patients who had a tracheostomy were excluded because the discomfort associated with a tracheostomy tube may be different from the discomfort associated with an endotracheal tube.<sup>11</sup> Also excluded were patients who received paralytic agents, had chronic persistent neuromuscular disorders (such as cerebral palsy and Parkinson disease), or had suffered head trauma or stroke, as all of these would affect patients' movement and the study measurements. Study participants were recruited during a 2-year data collection period (August 2007-July 2009). The planned subset of 103 participants for the study reported here was a convenience sample based on availability of research personnel to conduct the observations.

### Key Variables and Their Measurement

**Sedation.** Two measures of sedation were used, an intermittent sedation scale, the Richmond Agitation-Sedation Scale (RASS) and a continuous electroencephalography-based system, the patient state

Achievement and evaluation of optimal sedation remains a clinical challenge.

**Table 1**  
Stimulation event categories<sup>a</sup>

Stimulation event category	Examples of stimulation events
Auditory-general	Environmental noise, including routine alarms
Auditory-talking	Health care providers, family, visitors talking to the patient, to each other
Auditory-highly noxious	Sudden or loud noises including loud alarms, dropped items, moving equipment
Tactile-general	Tactile stimulus from health care providers, in general, or during care
Tactile-family	Tactile stimulus from family members
Tactile-noxious	Bathing, turning, uncomfortable procedures, mouth care, eyedrops
Tactile-highly noxious	Endotracheal tube suctioning, wound care, invasive procedures, sternal rub
Respiratory management	Breathing treatments, ventilator setting changes (not changes in fraction of inspired oxygen), tubing changes

<sup>a</sup> Stimulation event categories were developed on the basis of data collected through a pilot study of 36 critically ill patients receiving mechanical ventilation. During direct observations, 1304 separate events were recorded and collapsed into 65 categories and eventually to the 8 general categories listed here. All types of events in each category are not included here.

Stimulation events included any stimulation of patients (auditory or tactile) by any person.

index (PSI). The RASS is a 10-point scale, ranging from -5 (unarousable) to 0 (calm and alert) to +4 (combative), based on observations of specific patient behaviors.<sup>12</sup> This scale is used widely in critical care and demonstrates excellent interrater reliability and criterion, construct, and face validity.<sup>1,12,13</sup> We have further summarized the 10 levels of sedation as

moderate/deeply sedated (RASS of -5, -4, or -3), alert/mildly sedated (RASS score of -2, -1, or 0), or restless/agitated (RASS score of +1, +2, +3, or +4).<sup>12,14</sup> The PSI is a continuous, objective measure of sedation (SEDLine, Masimo Corp) that is based on quantitative electroencephalographic features that differ markedly between states of sedation.<sup>15</sup>

The PSI has a range of 0 to 100, with decreasing values indicating increasing depth of sedation. Significant differences have been documented between mean PSI values obtained during different sedation states.<sup>15,16</sup> Researchers in several studies<sup>17-20</sup> have compared PSI with subjective sedation tools and reported significant relationships between the PSI and these tools as well.

**Stimulation Events.** A pilot study was conducted to identify and categorize typical stimulation events in patients receiving mechanical ventilation and included any type of stimulation of patients (auditory or tactile) by any person (health care provider, family, other visitors, etc). In the pilot study (unpublished data), patients were observed for up to 4 hours in a convenience sample of patients receiving mechanical ventilation. Spectator GO! Software (Biobserve), an observation-recording program based on a personal digital assistant, was used to allow real-time event acquisition for a variety of stimulation events. Each event was defined as a single event or continuous activity. After the institutional review board

approved the study, 36 patients were observed continuously for up to 4 hours. During these pilot study observations, 1304 separate events were recorded. The events were then collapsed into 65 categories and, through a continuing iterative process, ultimately grouped into 8 general categories (Table 1). Although each event was identified separately, multiple events did occur simultaneously.

**Demographic Characteristics.** Characteristics of the study participants were documented and included age, ICU (reflecting type of critical illness and population; ie, surgical, medical, cardiac surgery), duration of endotracheal intubation (in hours), ICU length of stay (in hours), as well as type and amount of sedative and analgesic agents administered. To describe patients' severity of illness at study initiation, data for the Acute Physiology and Chronic Health Evaluation (APACHE) III were documented on study enrollment by using data from the preceding 24 hours.<sup>21</sup>

### Procedures

The study was approved by the institutional review board, and informed consent was obtained from each study participant's legally authorized representative. Patients were enrolled during any period of mechanical ventilation as long as they met the inclusion criteria and did not meet the exclusion criteria. This subset of data was collected during the 24-hour period of the larger study and occurred on any day of mechanical ventilation.

To provide a period of monitored activity that included a variety of stimulation (eg, endotracheal suctioning, turning, routine nursing care) and non-stimulation conditions, a 4-hour direct observation was chosen and was contained within the 24-hour data collection period for the larger study. The timing of the observation period was flexible to accommodate patient care needs and family preferences

for individual patients. All stimulation events based on the final 8 event categories as identified through the pilot study were documented. After extensive training, research assistants visually observed each patient within the ICU room. Individual start/stop toggle switches corresponding to each of the 8 categories were interfaced to a computer that recorded the beginning and end times of each directly observed event. Although the goal was a continuous 4-hour observation period, because of the critical condition of the patients, changes in patients' condition and transport of patients to areas outside the ICU, two 2-hour observations were also used. At the end of the observation period, all data were downloaded and time synchronized and the event duration for each category was calculated.

Data for the RASS were obtained by the nursing staff per unit protocol and retrieved from the medical record obtained every 4 hours. If the patient's clinical condition warranted more frequent RASS determinations, those data also were retrieved for the study. The PSI data were collected only for this study and were continuously documented during the observation period and downloaded for analysis.

### Data Analysis

The aim of this study was to describe the number and type of stimulation events and the relationship of stimulation to level of sedation in patients receiving mechanical ventilation. Patients' characteristics and stimulation events were described in total and by category using standard descriptive measures (means, standard deviations, median, interquartile range, counts, and proportions). Means are reported for variables that were normally distributed, and medians are reported for skewed distributions. Because multiple events occurred simultaneously, we identified a subset of singular events with no other stimulation event(s) for 20 seconds before, during, and 20 seconds after the singular event and used those events to compare the relationship of the stimulus type to PSI. A correlation analysis was used to compare the linear relationship of the mean PSI before and after stimuli across all stimulation types. A linear mixed-effects model was used to construct an *F* test to test for a change in the mean and rate of change of PSI between 20 seconds before the start of the event and for 20 seconds directly after the event.

The relationship of type of stimulation to changes in sedation level was evaluated. Patients are sedated to various levels, which may alter their response to stimulation; therefore, patients were dichotomized into those with a mean PSI less than 60 before the event and those with a mean PSI of 60 or greater before the event. A PSI less than 60 is considered deeply sedated, whereas a PSI of 60 or greater includes moderately to mildly sedated or

alert/wake states.<sup>17,19,22</sup> The models contained fixed effects of before or after the event, time, and the interaction of the 2 and random effects of patient, time, and the interaction of time and before or after event by using an estimated spatial power covariance pattern for the within-subject variance and unstructured covariance pattern for between-subject variance. The spatial power covariance pattern takes into account the autocorrelation of the repeated measures of the individual event occurrences. All statistical tests used a significance level ( $\alpha$ ) of .05. SAS Software (SAS Institute Inc) was used for all statistical analyses.

### Results

The characteristics of the 103 patients in the sample are summarized in Table 2. Patients had a median age of 55 years, were 61.2% male, were primarily African American or white, and most were from the MRICU. Median APACHE III scores along with median duration of intubation and length of ICU stay are also shown.

The distribution of baseline RASS scores indicated that patients had a range of sedation states but were primarily alert/mildly sedated (54.4%, RASS = 0, -1 -2); 42.7% were moderately/deeply sedated (RASS = -3, -4, -5) and 2.9% (RASS = +1, +2) were restless/agitated. Patients received both analgesics (78% received fentanyl, 17% morphine, 3% hydromorphone) and sedatives (57% received midazolam, 20% propofol, 14% lorazepam) as well as haloperidol (5%) via continuous infusion and/or bolus administration depending on the patient's requirements.

**A subset of singular events with no other stimulation for 20 seconds before, during, and after the event was identified.**

### Observations and Stimulation Events

Direct patient observations occurred for almost 349 hours throughout the entire project, during which more than 205 hours of stimulation events were documented, comprising 58.8% (SD, 25.7%) of the total observation time (Table 3). A mean of 3.39 hours per patient were observed, with 1.99 hours of those hours including stimulation events. Observations were initiated throughout the day and night but occurred primarily during late afternoon and evening hours (16.4% 7 AM to 3 PM; 82.6% 3 PM to 11 PM; 0.9% 11 PM to 7 AM). General auditory types of stimulation (environmental noise) were the most common (41.2% of observed time), followed by respiratory management and tactile-general stimulation (Table 3). The correlation between all mean PSIs before and after the stimulation event showed a strong positive linear relationship ( $r=0.92$ ,  $P<.001$ ), which indicated that a linear model was appropriate.

**Table 2**  
Characteristics of 103 patients included in the study

Characteristic	No. of patients	%
Sex		
Female	40	38.8
Male	63	61.2
Race		
Black/African American	49	47.6
White	48	46.6
Other	2	1.9
Unknown or not reported	4	3.9
Ethnicity		
Hispanic	3	2.9
Non-Hispanic	100	97.1
Critical care unit		
Cardiac surgery	13	12.6
Medical respiratory	62	60.2
Surgical trauma	28	27.2
Score on Richmond Agitation-Sedation Scale		
-5 Unarousable	3	2.9
-4 Deep sedation	12	11.7
-3 Moderate sedation	29	28.2
-2 Light sedation	24	23.3
-1 Drowsy	14	13.6
0 Alert and calm	18	17.5
1 Restless	2	1.9
2 Agitated	1	1.0

Characteristic	No. of patients	Mean	SD	Median	IQR
Age, y	102	53.8	14.52	55.0	45-64
APACHE III score	100	73.2	25.69	68.0	57-85
Days of intubation	103	8.9	6.29	7.1	4.1-12.3
Days in intensive care unit	103	17.9	15.13	13.0	8.8-20.8
Days of Intubation at study enrollment	103	4.2	4.67	2.4	1.3-5.6

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; IQR, interquartile range.

**Table 3**  
Patients, observation time, and percentage of time in each category over the entire observation time (348 hours, 57 minutes)

Category	No. of patients	Total time in category, <sup>a</sup> (hours:minutes:seconds)	Time in category, <sup>b</sup> %	Duration, mean (SD), hours:minutes
All stimuli	103	205:18:00	58.83	
Auditory-general	102	143:46:18	41.20	02:52 (12:07)
Auditory-talking	91	21:06:38	6.05	00:47 (03:09)
Auditory-highly noxious	90	10:54:05	3.12	00:34 (03:09)
Tactile-general	100	33:07:06	9.49	01:04 (02:51)
Tactile-family	61	29:44:10	8.52	04:21 (15:02)
Tactile-noxious	85	22:40:04	6.50	03:01 (13:36)
Tactile-highly noxious	66	17:19:00	4.96	04:05 (17:50)
Respiratory management	73	39:51:57	11.42	01:30 (08:15)

<sup>a</sup> Totals are less than the sum of the categories because multiple stimulation events can occur simultaneously.

<sup>b</sup> Percentage in category totals more than 100% because multiple stimulation events can occur simultaneously.

**Table 4**  
Change in patient state index (PSI) before and after individual stimuli by sedation level before stimulation

Stimulus	Singular events <sup>a</sup>	No. of patients	PSI, mean (SD)		Change estimate	95% CI	P
			Before event	After event			
Auditory-highly noxious	451	62	63.2 (22.1)	63.8 (22.3)	-0.004	-0.10 to 0.10	.99
Mean PSI before event <60	180	42	40.4 (13.5)	42.2 (16.4)	0.87	0.66 to 1.08	<.001 <sup>b</sup>
Mean PSI before event ≥60	266	46	78.8 (9.7)	78.6 (10.8)	-0.62	-0.75 to -0.50	<.001 <sup>b</sup>
Auditory-talking	169	45	69.1 (18.4)	69.9 (17.4)	1.06	0.87 to 1.24	<.001 <sup>b</sup>
Mean PSI before event <60	44	22	43.8 (12.0)	49.5 (17.1)	3.88	3.33 to 4.44	<.001 <sup>b</sup>
Mean PSI before event ≥60	120	34	78.7 (8.9)	77.6 (9.4)	-0.04	-0.24 to 0.15	.76
Respiratory management	456	49	60.7 (21.8)	60.4 (21.6)	-0.07	-0.16 to 0.17	.23
Mean PSI before event <60	195	30	39.4 (13.4)	39.8 (13.8)	0.45	0.28 to 0.63	<.001 <sup>b</sup>
Mean PSI before event ≥60	257	44	77.0 (9.6)	76.0 (10.6)	-0.47	-0.58 to -0.37	<.001 <sup>b</sup>
Tactile-family	120	23	53.5 (20.9)	54.0 (22.1)	0.23	-0.08 to 0.52	.35
Mean PSI before event <60	69	16	37.6 (10.2)	38.2 (13.4)	0.64	0.29 to 0.98	.001 <sup>b</sup>
Mean PSI before event ≥60	50	15	75.5 (8.0)	75.5 (10.2)	-0.35	-0.77 to 0.07	.15
Tactile-general	500	74	63.4 (21.0)	64.8 (20.5)	1.25	1.09 to 1.40	<.001 <sup>b</sup>
Mean PSI before event <60	181	50	40.1 (13.5)	45.6 (17.7)	4.43	4.11 to 4.75	<.001 <sup>b</sup>
Mean PSI before event ≥60	311	62	77.2 (9.1)	76.2 (11.4)	-0.67	-0.83 to -0.51	<.001 <sup>b</sup>
Tactile-highly noxious	33	18	75.0 (13.3)	75.3 (14.2)	1.45	1.39 to 1.49	<.001 <sup>b</sup>
Mean PSI before event <60	3	3	42.8 (10.8)	39.3 (6.1)	Model was nonestimable		
Mean PSI before event ≥60	26	15	78.7 (7.0)	79.4 (7.2)	3.29	3.20 to 3.38	<.001 <sup>b</sup>
Tactile-noxious	45	23	66.3 (18.4)	70.7 (14.2)	3.74	2.89 to 4.59	<.001 <sup>b</sup>
Mean PSI before event <60	15	11	43.1 (8.2)	57.8 (17.7)	13.58	12.55 to 14.61	<.001 <sup>b</sup>
Mean PSI before event ≥60	30	18	77.8 (8.6)	77.8 (13.1)	-1.63	-2.43 to -0.83	<.001 <sup>b</sup>

<sup>a</sup> Because multiple events occurred simultaneously, a subset of singular events with no other stimulation event(s) for 20 seconds before, during, and 20 seconds after the singular event was used for comparisons. Patients could have events in both <60 and ≥60 categories; <60 and ≥60 categories may not equal the total for singular events because of missing values.

<sup>b</sup> Statistically significant at the  $\alpha = .05$  level.

In the analysis of the relationship of stimulation type to change in sedation level (Table 4), auditory-talking ( $P < .001$ ), tactile-general ( $P < .001$ ), tactile-highly noxious ( $P < .001$ ) and tactile-noxious ( $P < .001$ ) stimuli showed increases in PSI (increased arousal) ranging from 1.06 to 3.74. The remaining event types (auditory-general, auditory-highly noxious, respiratory management, and tactile-family) did not exhibit a difference in PSI before and after the stimulus event. Because of the high occurrence of auditory-general stimulus events, that category was excluded as being a possible concurrent event for the remaining stimulus types.

Further analysis then compared PSI before and after the stimulus separately for patients who were deeply sedated (PSI < 60) and patients who were not (Table 4). For patients with a mean PSI less than 60 before the stimulus event, 6 of the 7 event types demonstrated significant increases in PSI, that is, to a lighter sedation level. For instance, in the 42 patients who were deeply sedated before an auditory-highly noxious event, their PSI increased by 0.87 subsequent to the stimulus ( $P < .001$ ); this change was in contrast to the -0.62 decrease in PSI due to an auditory-highly noxious event in the 46 patients who were not deeply sedated ( $P < .001$ ).

Auditory-talking ( $P < .001$ ), tactile-general ( $P < .001$ ), and tactile-noxious ( $P < .001$ ) stimuli were associated with increases of 3 points or greater in PSI for deeply sedated patients. Auditory-highly noxious ( $P < .001$ ), respiratory management ( $P < .001$ ), and tactile-family ( $P = .001$ ) stimuli resulted in increases of less than 1 point in PSI for deeply sedated patients. The model for the tactile-highly noxious events was not estimable because of the small sample size for deeply sedated patients.

For patients who were not deeply sedated (mean PSI before stimulus event ≥ 60), tactile-highly noxious stimuli were associated with a significant ( $P < .001$ ) increase in PSI of 3.29 (greater arousal). Auditory-highly noxious ( $P < .001$ ), respiratory management ( $P < .001$ ), tactile-general ( $P < .001$ ), and tactile-noxious ( $P < .001$ ) stimuli showed small decreases in PSI after the stimulation event ranging from 0.47 to 1.63. Auditory-talking ( $P = .76$ ) and tactile-family ( $P = .15$ ) stimulation was not associated with a significant change in PSI from before to after the stimulation event for patients with a mean PSI of 60 or greater before the event.

Patients who were deeply sedated showed increased arousal following stimulation.

## Discussion

The aim of this study was to describe the number and type of stimulation events and the relationship of stimulation to sedation level in patients receiving mechanical ventilation. We found that stimulation occurs frequently, more than half of the time, and consists of auditory-general types of stimulation most frequently, followed by respiratory management, tactile-general, and tactile-family types of stimulation. Auditory-highly noxious types of stimulation occurred the least often, followed by tactile-highly noxious, auditory-talking, and tactile-noxious types. Although patients are most frequently stimulated by sounds, it is interesting to note that of all the types of stimulation, talking to or even around the patient occurs infrequently, only 6% of the observed time. Similarly tactile stimulation that is not noxious, either from health care providers or family, is also relatively infrequent (8.5%-9.5% of observed time). As a result,

**Sedated patients may not be able to respond to indicate discomfort.**

the patient's auditory and tactile environment may consist of a barrage of unfamiliar sounds and stimulation that may be frightening and disorienting and may have ramifications

for the development of adverse outcomes such as disorientation and/or delirium.<sup>23-25</sup> Critically ill patients report sleep deprivation as the second worst experience during their stay, superseded only by pain.<sup>26</sup> Sedation, care interventions, noise, disease, and mechanical ventilation are important contributing factors to sleep deprivation.<sup>26</sup> Addressing modifiable risk factors, including excessive or prolonged stimulation, can help to prevent and reduce sleep deprivation and potentially delirium.<sup>25,27,28</sup>

Overall, we found that the patient's level of sedation is affected by some types of stimulation (auditory-talking, tactile-general, tactile-highly noxious, tactile-noxious) and not by others (auditory-highly noxious, respiratory management, tactile-family). All stimulation that might be expected to increase arousal, namely, stimuli of a noxious nature (auditory), did not necessarily do so.

The level of consciousness, or depth of sedation, appears to be an important determinant of the patients' response to stimulation. Although one might assume that some patients are so deeply sedated that noxious stimulation does not elicit a response, we did not find that to be the case. We found that the level of sedation at onset of stimulation (ie, deeply sedated or not) affected whether stimulation events resulted in a change in the patient's level of arousal (higher PSI). In general, patients who were deeply sedated showed increased arousal following stimulation for all 6 stimulation events

with sufficient data to be analyzed. Although some of those PSI increases were small ( $< 1$ ), and most likely not clinically relevant, several increases were greater than 3 (auditory-talking, tactile-general). It is noteworthy that tactile-noxious stimulation resulted in marked arousal with a mean PSI increase of more than 13 in deeply sedated patients. In patients who were more awake at the onset of stimulation (ie,  $PSI \geq 60$ ), inconsistent changes in PSI were found. In this group, most changes were less than 1 and not clinically significant, except for tactile-highly noxious stimuli, which increased arousal (increase in  $PSI > 3$ ). It may be that patients who are more deeply sedated have a greater "startle" response, when stimulated from a deeply sedated state, similar to being startled from a deep sleep. However, patients who are already more awake/less sedated are not as "alarmed" when stimulated and therefore may exhibit less change in PSI. The most recent guidelines for management of pain, agitation, and delirium in the ICU<sup>1</sup> recommend that sedative doses be titrated to maintain a light rather than a deep level of sedation in adult ICU patients, unless clinically contraindicated. The data presented here, obtained several years ago, may not reflect most recent clinical practice that focuses more on lighter sedation management.

Sedated, critically ill patients endure frequent stimulation that is both auditory and tactile, and includes some stimuli that are highly noxious. Sedated patients may not be able to respond to indicate discomfort; therefore, it is important for all care providers to consider patients' responses with this knowledge in mind. Identifying the effects of a variety of stimulating events on level of sedation and ultimately on sleep and potentially delirium is an important step in understanding the impact of different categories of stimulation on patients' experiences in the ICU. Many ICUs do not have a sleeping protocol, and nurses report only a moderate feeling of autonomy and influence regarding the management of sleeping practices.<sup>29</sup> Protocols to cluster care interventions and reduce stimulation for critically ill patients should be considered.

The results presented here are limited by several factors. In creating categories for stimulation events, we reasoned that some stimuli are more noxious than others. However, stimuli are subject to patients' interpretation. An individual patient may experience different manifestations of the same type of stimulus differently. Family or providers speaking to patients may be comforting or noxious. Stimuli that are generally thought to be comforting to most patients may be highly noxious to some. Therefore, the stimulation categories as we have defined them may not be optimal. This study did not address

nurses' decisions regarding sedation management, or amounts or types of sedatives used, but rather focused on the patient's sedation level as determined by the PSI, regardless of the methods used to reach that level. Further analysis of provider factors may shed light on the response to stimulation events. In addition, the direct observation of stimulation events did not include quantification of stimulation level (eg, decibels of auditory stimulation, complexity of care processes), which may have altered our results. Finally, we report the change in PSI that occurred after the stimulus was complete, it may be that more dramatic arousal occurred at the beginning of the stimulus or during the stimulus, especially in those stimuli with a noxious component.

In summary, different forms of auditory and tactile stimulation occurred frequently throughout the day in our critically ill patients. Nearly all types of stimuli increased arousal as measured by quantitative electroencephalography in patients who were more deeply sedated. In contrast, the effect of stimulation on patients who were not deeply sedated was minimal and inconsistent. To our knowledge, this is the largest study using direct observation of stimulation events and their relationship to level of sedation in critically ill patients receiving mechanical ventilation. The virtual barrage of stimulation events found in this prospective observational study has implications for the development of interventions to reduce interruptions in rest and potentially reduce adverse outcomes such as delirium.

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