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Does Music Influence Stress in Mechanically Ventilated Patients?

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Abstract

Objectives—Mechanically ventilated patients experience profound stress. Interventions are needed to ameliorate stress that does not cause adverse effects. The purpose of this study was to explore the influence of music on stress in a sample of patients over the duration of ventilatory support.

Research Methodology/Design—Randomized controlled trial randomized patients (56.8 ± 16.9 years, 61% male, APACHE III 57.2 ± 18.3) receiving ventilatory support to: 1) patient-directed music (PDM) where patients self-initiated music listening whenever desired from a preferred collection, 2) Headphones only to block ICU noise, or 3) usual ICU care. Twenty-four hour urinary cortisol samples were collected from a sub-set of subjects with intact renal function and not receiving medications known to influence cortisol levels ($n = 65$).

Setting—12 ICUs in the Midwestern United States.

Main Outcome Measures—Urinary free cortisol (UFC), an integrative biomarker of stress.

Results—Controlling for illness severity, gender, and baseline UFC (29-45 mg/day), mixed models analysis revealed no significant differences among groups in UFC over the course of ventilatory support.

Conclusion—While music did not significantly reduce cortisol, less profound spikes in UFC levels were observed but that, given the limitations of the research, this observation could have occurred merely by chance.

INTRODUCTION

Receiving mechanical ventilatory support is stressful for critically ill patients. Stress is any disturbance that perturbs homeostasis and leads to activation of stereotypical stress-adaptation mechanisms referred to collectively as a stress response (Crofford, 1996). A stressor can be metabolic, physiologic, traumatic, inflammatory/infectious, or psychoemotional (Crofford, 1996). Physiological stressors (such as anoxia, heat/cold, hypoglycemia, noxious stimuli like noise) disturb the internal environment, while

psychological stressors such as fear are among the most potent activators of the hypothalamic-pituitary-adrenal (HPA) axis (Johnson, et al., 1992). Prolonged activation of the stress response can cause myopathy, fatigue, hypertension and immunosuppression (Johnson, et al., 1992). Activation of the HPA axis is usually modulated by intrinsic rhythmic elements that follow a normal circadian pattern with negative feedback loops regulating the endocrine system (Lovallo, 1997). However, during critical illness, the usual diurnal pattern of cortisol secretion does not exist; instead there is relatively constant secretion of cortisol and adrenocorticotrophic hormone (ACTH), with persistent glucocorticoid secretion (Sikes, 1992), resulting in large amounts of plasma cortisol (up to six-fold) (Stanford, 1994). However, this is not the usual response in all critically ill patients as some studies show continuously elevated levels of cortisol during critical illness whereas other studies do not (Beishuizen, et al., 2001; Marik et al., 2008).

The usual treatment for managing the stress response in critically ill mechanically ventilated patients is the administration of intravenous sedative agents (Conti, et al., 2002) to reduce central nervous system (CNS) activity and sympathetic nervous system (SNS) outflow (Plunkett et al., 1997). However, these medications have many adverse effects such as bradycardia, hypotension, gut dysmotility, immobility, weakness, and delirium (Arroliga et al., 2008; Mehta et al., 2006; Mehta et al., 2009; Mehta et al., 2007; Pandharipande et al., 2008; Pandharipande et al., 2006). Further, it is recommended that non-pharmacologic interventions be tried first prior to the routine administration of sedative agents (Kress, et al., 2002), to reduce stress and elicit a relaxation response (White, 1999) by desensitizing and reducing over-all activity within the limbic system through the reduction of SNS arousal, neuromuscular arousal, and cognitive excitation (Antoni et al., 2000; Everly & Benson, 1989). Music is one such intervention that has been shown to modulate stress and promote relaxation (White, 1999). The ability of music to ameliorate the stress response in mechanically ventilated patients over time is not known as previous investigations have been limited to cross-sectional designs (Chlan et al., 2007). The purpose of this study was to explore the influence of music on urinary free cortisol (UFC), a biochemical marker of stress, as compared to two control conditions in patients receiving mechanical ventilatory support. We hypothesized that mechanically ventilated patients who self-initiated music listening would experience less stress than patients who did not listen to music.

METHODS

Design

This paper reports on the exploratory aim from a parent study of a three group, randomized controlled trial whose primary aim was to determine the effects of patient-initiated music listening on anxiety during mechanical ventilatory support (Chlan, 2011). Subjects were randomly allocated to one of three groups: 1) experimental patient-directed music intervention (PDM), 2) active control condition of noise-canceling headphones only, or 3) control group of usual ICU care. Anxiety was measured daily in all subjects using a 100-mm vertical visual analog scale. Subjects remained on protocol as long as they were receiving ventilatory support (30 day maximum), withdrew, were extubated, transferred from ICU, or died. For the PDM protocol, subjects listened to preferred music whenever desired for as long as desired. Details on the PDM protocol (Chlan & Heiderscheid, 2009) and associated findings are reported elsewhere (Chlan, 2011).

Setting

Participants were enrolled from 12 ICUs contained in 5 hospitals in the urban area of Minneapolis and St. Paul from September 2006-March 2011. Human subjects' approval was

obtained from the PI's parent Institutional Review Board as well as those of the participating medical centers.

Sample

Critically ill patients were invited to participate in the study if they were: receiving acute ventilatory support for a pulmonary problem, alert, appropriately following commands, had adequate/corrected vision and hearing, and were cognitively intact to participate in the consent process. Patients were not invited if they were receiving aggressive ventilatory support, were unstable hemodynamically, unresponsive, receiving chronic ventilator support prior to hospitalization, or had a documented mental incompetence (e.g., Alzheimer's disease). Only those subjects who had intact renal function and were not receiving medications known to affect cortisol were eligible for urine collections.

Variables and Their Measurement

Demographic and Study Entry Data—Data were collected on gender, race, ethnicity, age, length of time mechanically ventilated and ICU stay prior to study enrollment, medical diagnoses, ventilator settings, and all medications. Data from ICU admission day were abstracted from the medical record to complete the Acute Physiology, Age & Chronic Health Evaluation (APACHE) III illness severity scoring (Knaus et al., 1991). APACHE III scores are used to stratify patients based on their illness severity on ICU admission day. We calculated APACHE III scores on all participants one time at study entry.

Urinary Cortisol as an Integrative Measure of Stress—Mechanical ventilation is conceptualized as a source of chronic stress for critically ill patients (Schmidt & Kraft, 1996). Urinary measures of stress hormones have been used as biomarkers of chronic stress (Dimsdale & Ziegler, 1991) so daily 24-hour urine collections were done to test our hypothesis that PDM reduces patients' stress. Urinary free cortisol (UFC) is a marker of HPA axis activity and has been used as an integrative non-invasive measure of stress by other investigators to assess overall hormonal output of cortisol over a standardized time period (Yehuda, et al., 1993). In addition, cortisol is the primary glucocorticoid released during a stress response and has been shown to be elevated in critically ill patients (Stanford, 1994). UFC was measured instead of serum cortisol, since sampling urine was less invasive and collection over 24 hours removes cortisol transients produced by ultradian rhythms in adrenal secretion (Kong, et al., 1999).

Specimen collection time was from 0700h-0700h each day. Urine collection bottles were kept on ice in a convenient location at each subject's bedside to ensure that no urine was accidentally discarded into the toilet. Urine collections less than 400 ml were discarded as this was the minimum amount needed for analysis (Vgontzas et al., 1998).

Aliquots and Assay techniques—Total volume of urine was processed in a central laboratory; an aliquot of the 24-hour specimen was couriered to Associated Regional & University Pathologists, Inc. (ARUP). UFC was assayed by liquid chromatography/tandem mass spectrometry (LC-MS/MS), a highly specific method that separates cortisol from endogenous metabolites including cortisone with a sensitivity of 0.25 ug/dl (Taylor, et al., 2002). Intra- and inter-assay variability is < 5.1% and < 6.5%, respectively (ARUP's Guide to Clinical Laboratory Testing, 2004). Results were posted to the electronic medical record from the laboratory as total mg/day of UFC as the standard reporting value; a reference value of 20 mg/day was provided by the laboratory as normal.

Analysis

Descriptive statistics, graphing and appropriate analyses were performed on all data to assess the shape of the variables' distributions and to determine if there were important covariates to be controlled for such as illness severity and gender.

Subjects with at least 3 UFC values were used in the change over time analysis. Three time points or more give a more accurate estimate of change. Changes over time by study group were first assessed using scatterplots and line graphs of the UFC values over time. Mixed effects models were used for analysis as they accommodate correlated and non-homogeneous residuals, which would be expected in repeated measures. Mixed models are an ideal analysis for dealing with disparate assessment time points and/or missing data points.

A series of models were estimated to determine the best model of change for the cortisol data (Fitzmaurice, et al., 2009; Singer & Willett, 2003). An unconditional means model was first estimated to determine if further modeling was appropriate. The unconditional means model assesses two null hypotheses: (a) no change across days, and (b) no variation between subjects. Rejecting these null hypotheses warrants doing further analysis. Next, an unconditional growth model with DAY added as a predictor incorporated estimation of change coefficients. Models with several within-person error covariance structures were explored. The cortisol levels were quite variable, without strong correlations from day to day. Because of this, an unstructured covariance structure was chosen for the mixed models.

Analysis was performed using SPSS v.17 and Proc Mixed in SAS v.9.2. Final parameter estimates were considered significant at $p < .05$. Aikake's information criterion (AIC) and the Bayesian information criterion (BIC) were used to select the best model for this sample.

RESULTS

Characteristics of cortisol eligible sample

A total of 70 enrolled subjects were initially eligible for 24-hour urine collections out of a sample of $n = 363$. The majority of subjects were not eligible for urine collection due to the receipt of steroid medications (68%) or other medications known to influence cortisol, and to renal insufficiency or renal failure (32%). Of the enrolled and urine-eligible subjects, a resulting sample of 65 subjects were provided 24-hour urine collections and are reported in this sub-sample. The 5 patients originally eligible for 24-hour urine collection did not provide the 3 samples necessary for analysis due to being extubated or transferred from the ICU. This sub-sample of patients 56.8 (SD 16.9) years of age, had been in the ICU for a median of 9 days (.22-55), and receiving mechanical ventilation for a median of 6 days (.27-55) prior to study enrollment. Mean APACHE III scores for this sub-sample was 57 (SD 18.3) (Table 1).

Study entry median 24-hour UFC was 45.5 mg/day, ranging from 1-264.8, which demonstrates extremely high variability on this measure. Likewise, there was wide variability in baseline UFC for subjects randomized to each of the three groups (Table 1). These baseline UFC values are all slightly higher than the lab reference normal of 20 mg/day. There were no PDM-urine eligible subjects on protocol after day 20 (Table 1, Figure 1 & 2) as these subjects were either extubated, withdrew, transferred from the ICU or died. Both control conditions had eligible subjects for urine collection for the duration of the protocol.

Influence of patient-directed music on urinary free cortisol

The large standard error (*SE*) for the effect of the treatment groups in the mixed models indicates the large variability in UFC levels among study subjects. The baseline values for each of the groups were controlled for in the mixed models analysis (Table 2).

Based on the results from the final models (Table 2), there was no significant difference in UFC over time by study group. The research hypothesis was rejected; PDM did not result in decreased cortisol over time, suggesting that these subjects did not experience significantly less stress than those subjects in the control groups. There were no significant effects for time or treatment, nor were there any significant interaction effects of PDM or either control condition on UFC (Table 2). Further, neither illness severity nor gender significantly contributed to the UFC levels over time. Non-significant results are believed to be due in part to the small number of subjects eligible for urine collection, and the extreme variability among subjects in their cortisol levels.

DISCUSSION

The purpose of this study was to explore the influence of a patient-directed music intervention on the stress response in ICU patients receiving mechanical ventilatory support. We had hypothesized that those mechanically ventilated patients who self-initiated music listening whenever desired would experience less stress than those patients in either control group. While results were not significant and our hypothesis was not supported, there is a pattern for the PDM group that demonstrates somewhat less extreme values over time as compared to the headphones (HPs) group (Figure 1 & 2). The median UFC levels for the PDM group demonstrate a slight upward and downward pattern over time. The pattern of median UFC levels in the two control conditions demonstrate a more extreme and varying pattern of increases and decreases over the study period, particularly for the HPs group (Figure 1 & 2). We cannot state with certainty why the median UFC in the HPs group demonstrated an extreme peak around study day #11-12. We did not query subjects as to their perceived level of stress, thus it is unknown if other stressful occurrences were experienced by subjects randomized to the HPs group. Overall, the pattern of these data suggest that PDM may serve as a stress buffer; this warrants additional research.

UFC was used as a biomarker of stress induced by mechanical ventilation since it is the least invasive approach to collect samples to assess HPA activity. Blood and saliva sampling are optimal in assessing rapid changes in cortisol secretion in human subjects (Kirschbaum & Hellhammer, 1994). Previous studies that have reported success in using music therapy have assessed indices of anxiety and stress during the intervention application. For example, physiological indices of stress including heart rate, arterial blood pressure and respiratory rate have been shown to be reduced by acute treatment (Bradt, et al., 2010). However, the experimental design of the parent study allowed patients to use music freely whenever desired, making it unfeasible to collect samples temporally related to each music exposure. Extensive blood sampling was too invasive for critically ill patients, and saliva sampling was not viable for patients who were intubated. Studies have shown that 24-hour UFC is correlated with salivary and blood cortisol in chronically ill patients (Kos-Kudla, et al., 1996) and in individuals during physiological stress (Neary, et al., 2002).

There remains much controversy regarding the optimal method for assessing HPA activity during chronic illness (Arafah, 2006). Previous studies have been criticized for overestimating adrenal secretory responses by using assays that lack specificity for measuring unbound or free cortisol, considered the biologically active form of the hormone (Murphy, 2000). Measurement of total cortisol includes free and cortisol bound to proteins including transcortin and albumin. Since plasma proteins can be abnormal in critically ill

patients, changes in total cortisol can differ from free cortisol during the course of chronic illness (Vogesser, et al., 2003). By using the highly specific assay method of LC-MS/MS, we could ensure that the values obtained represented UFC.

There are a number of important variables that likely influenced the impact of PDM on UFC in this sample. Patients were enrolled after being in the ICU for a median of almost 8 days and receiving mechanical ventilation for 6 days (Table 1). Previous studies showing that music therapy was efficacious in reducing anxiety and physiological indices of stress (Han et al., 2010; Lee, et al., 2005) initiated the treatment when patients had been in the ICU for only a few days. It is possible that the effectiveness of PDM in this sample would have been enhanced if patients could have been enrolled earlier during the ICU stay. The delay in enrolling patients also meant that cortisol responses to the initial stress induced by mechanical ventilation could not be measured. Although some studies have reported that cortisol remains elevated during chronic illness (Hamrahan, et al., 2004) others report that cortisol decreases over time in the ICU (Beishuizen, et al., 2001); decreased cortisol could result from a reduction in stimulation of the HPA axis and/or from reduced adrenal function induced by chronic illness (Marik, et al., 2008). Likewise, subjects may have experienced adrenal fatigue as evidenced by their normal levels of UFC despite experiencing a significant source of prolonged stress in mechanical ventilation, critical illness and the ICU environment. Thus, the absence of a response to PDM may have resulted in part from a floor effect; that is, adrenal cortisol secretion could not be reduced from its low initial value. Further, there was wide variability in baseline UFC, which may have contributed to the non-significant study findings. This wide variability may be attributed to our eligibility criteria and enrollment protocol where subjects entered the study any ICU day from first ICU day upwards to 55 days. Given the physiological complexity and individual responses of ICU patients, there typically is wide variability in most physiological measures, including those biomarkers of the stress response. These heterogeneous responses of ICU patients can make clinical research extremely challenging.

As with any clinical research study, there are limitations with this study. Given the limited number of subjects eligible for urine collection and the extreme variability among UFC within and among study groups, this study was severely under-powered to detect any significant differences. A couple issues came together to affect power; the PDM group had a significantly shorter time in the study, limiting the number of repeated measures of cortisol for comparisons and it was only possible to collect an average of 1.5 cortisol levels per week per patient. Sample sizes needed for adequate power in mixed models depends on differences in the rate of change between groups, the time span and the number of repeated measures over the time span. There was an approximate 52% change in cortisol levels from the first to last measure between PDM and the control. Even with a measure each of the 18 days, a sample size of 93 would be needed to detect this as significant. Ten measures over 30 days would require a sample size of 54. There was a much smaller percent change between the PDM and HP groups of 23%. Eighteen measures in 18 days would require a sample size of 475 to detect this as significant, 10 measures over 30 days would require a sample size of 274 for significance. However, the findings from this study provide a picture of the stress response in a sample of critically ill patients experiencing prolonged ventilatory support, which can be used for planning future studies.

We did not assay the collected urine for cortisone, an important component to consider when interpreting UFC levels. Likewise, we did not freeze any aliquots of urine for future testing or for verification of any discrepancies among values. Further, our UFC results were posted to the electronic medical record in total mg/day, not micrograms/day which makes direct comparison of our findings to those reported by other investigators impossible. Lastly, we did not specifically examine adrenal function in study subjects, which may have provided

some insight into the UFC values. The question remains as to whether this sample of mechanically ventilated patients had attenuated to stress and/or experienced adrenal fatigue from prolonged ICU stays and periods of ventilatory support.

Implications for practice

Music may be a comforting, familiar intervention for patients experiencing a stressful ICU treatment modality in the form of mechanical ventilatory support. While PDM did not significantly reduce UFC, patterns of UFC in those who self-initiated music listening suggest a potential buffering effect over the course of ventilatory support with less extreme values over time, as compared to increased UFC levels in the HPs group, suggesting increased stress (Figure 1 and Figure 2). There are resources available to ICU clinicians desiring to implement music intervention into their patient care practices (Chlan & Heiderscheidt, 2009).

Implications for future research

Stress management is an important area for intervention in critically ill patients as unmitigated stress can be detrimental. Interventions are needed that can ameliorate stress that are effective and do not cause adverse effects; non-pharmacologic interventions such as patient-directed music hold great promise. However, direct measures in serum or urine biomarkers of the stress response are influenced by medications and co-morbidities that complicate and confound their measurement. The investigator is advised to be cognizant of the many confounding factors when measuring biomarkers in response to stress management interventions.

Given the complicated pathways of the stress response, it is important to examine comprehensive biomarkers. The researcher is advised to develop a conceptual model to guide variable selection. Likewise it is essential to have the necessary expertise for planning the collection of biomarkers, including timing of sample attainment and proper handling of specimens. Further, appropriate expertise is needed for the interpretation of results as is the knowledge of medications and consideration of patient co-morbidities when interpreting results.

We recommend recruitment of as homogeneous a patient sample as possible for future investigations in this area. While it was not feasible for this study, the researcher planning to obtain biomarkers of stress needs to carefully consider and plan for potential adrenal fatigue as well as the influence of time on the stress response in mechanically ventilated ill patients.

CONCLUSIONS

Patient-directed music intervention did not significantly reduce UFC in this sample of ICU patients. PDM may have the potential to serve as a stress buffer. Careful consideration of clinical conditions and confounding factors that influence the stress response are necessary for future stress management intervention studies.

Abbreviations List

UFC	urinary free cortisol
PDM	patient-directed music
HP	headphones
UC	usual care

APACHE III	Acute physiology, age and chronic health evaluation III
ICU	intensive care unit
HPA	hypothalamic-pituitary-adrenal axis

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Figure 1.
Median Urinary Free Cortisol Levels over Time with Number of Subjects Providing Daily Samples

Legend:

Grey bar = Median UFC (mg/day)

Black bar = number of subjects providing UFC samples each study day

Figure 2.
Median Urinary Cortisol Levels over Study Period by Group
Legend:
PDM = patient-directed music
HP = Headphones only
UC = usual care

Table 1

Characteristics of Cortisol Eligible Subjects at Study Entry (n = 65)

Variable	+PDM (n =19) Mean (SD) Range	#HPs (n = 27) Mean (SD) Range	Usual Care (n =19) Mean (SD) Range	Total sample Mean (SD) Range	p-value
Age	56.6(18.6)	54.3(15.3)	60.4(17.3)	56.8 (16.9) Range 25-93	.48
^APACHE III	58.2(15.8) Range 27-82	57.3(20.6) Range 15-96	55.7(17.6) Range 26-95	57.2 (18.3) Range 15-96	.92
	N(%)	N(%)	N(%)	N(%)	
Male Gender	11(58%)	15(56%)	13(68%)	39(61%)	.66
Extubated at end of study	10(53%)	6(22%)	9(47%)	25(39%)	.07
	Median(range)	Median(range)	Median(range)	Median(range)	
ICU days prior to study entry	5.9(.35-41)	16.3(.22-55)	4.8(1.6-20.4)	7.9(.22-55)	.30
Ventilator days prior to study entry	3.5(.35-35.5)	12.5(.27-55)	7.0(1.2-16.7)	6(1-55)	.60
Total Days Enrolled in Study	2.8(1-19)	4.3(1-30)	5.0(1-30)	4.2(1-30)	.62
Baseline Urinary Free Cortisol (mg/day)	29.3(1-181.4)	54.0(8.8-241)	33.0(5.9-264.8)	45.5(1-264.8)	.08
Total Study Days with Urine samples	19	30	30		

Note: +PDM = patient-directed music; #HPs = headphones; ^APACHE = acute physiology, age, and chronic health evaluation

Table 2

Summary of Mixed Models Analysis of Cortisol and Covariates

Parameter	β (se(β))	<i>p</i> -value
Day	.79(1.3)	.54
Baseline cortisol	.69(.11)	<.001
+PDM	-1.9(18.9)	.92
#HP	-5.3(16.4)	.75
PDM*day	-3.6(2.6)	.17
HP*day	-1.2(1.8)	.51
Female	-5.0(12.0)	.68
^APACHE III	-.32(.34)	.35

Note: +PDM = patient-directed music; #HPs = headphones; ^APACHE = acute physiology, age, and chronic health evaluation