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Acute Physiologic Stress and Subsequent Anxiety Among Family Members of ICU Patients

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Objectives: The ICU is a complex and stressful environment and is associated with significant psychologic morbidity for patients and their families. We sought to determine whether salivary cortisol, a physiologic measure of acute stress, was associated with subsequent psychologic distress among family members of ICU patients.
Design: This is a prospective, observational study of family members of adult ICU patients.
Setting: Adult medical and surgical ICU in a tertiary care center.
Subjects: Family members of ICU patients.
Interventions: Participants provided five salivary cortisol samples over 24 hours at the time of the patient ICU admission. The primary measure of cortisol was the area under the curve from ground; the secondary measure was the cortisol awakening response. Outcomes were obtained during a 3-month follow-up telephone call. The primary outcome was anxiety, measured by the Hospital Anxiety and Depression Scale-Anxiety. Secondary outcomes included depression and posttraumatic stress disorder.
Measurements and Main Results: Among 100 participants, 92 completed follow-up. Twenty-nine participants (32%) reported symptoms of anxiety at 3 months, 15 participants (16%) reported depression symptoms, and 14 participants (15%) reported posttraumatic stress symptoms. In our primary analysis, cortisol level as measured by area under the curve from ground was not significantly associated with anxiety (odds ratio, 0.94; $p = 0.70$). In our secondary analysis, however, cortisol awakening response was significantly associated with anxiety (odds ratio, 1.08; $p = 0.02$).
Conclusions: Roughly one third of family members experience anxiety after an ICU admission for their loved one, and many family members also experience depression and posttraumatic stress. Cortisol awakening response is associated with anxiety in family members of ICU patients 3 months following the ICU admission. Physiologic measurements of stress among ICU family members may help identify individuals at particular risk of adverse psychologic outcomes. (*Crit Care Med* 2018; 46:229–235)
Key Words: family members; intensive care; postintensive care syndrome; psychologic distress; salivary cortisol

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The ICU is a complex and stressful environment with significant, unfavorable physical, cognitive, psychologic, and functional consequences for both patients and families (1–3). Patients who survive critical illness experience high rates of anxiety, depression, and posttraumatic stress disorder (PTSD) that persist months to years after hospital discharge (1). This constellation of psychologic morbidities is an important component of postintensive care syndrome (PICS) (4). Studies also demonstrate that

family members of ICU patients commonly suffer from psychologic disorders including persistent anxiety, depression, and PTSD (2, 5–7) and may experience a decrease in quality of life that may persist for 2 years or more (7). Such psychologic disorders among ICU family members are characteristics of PICS-family (PICS-F) (8) and are often associated with significant financial and emotional burden (9).

Multiple recent studies have begun to elucidate risk factors for PICS-F, including female sex, age of family member or patient, history of anxiety, and amount of social support (6, 7, 10). Family members also appear to be at higher risk for persistent psychologic distress if they were involved in medical decision-making or perceived that communication with clinicians was inadequate (2). Previous studies have not evaluated whether physiologic markers of acute stress in the family members of adult patients are associated with subsequent PICS-F.

Evidence from other types of traumatic events (e.g., automobile collisions, combat exposure, psychosocial or workplace stress, myocardial infarction) suggests that acute physiologic stress may manifest in aberrations in the hypothalamus-pituitary axis (HPA) and may predispose an individual to persistent psychologic distress (11, 12). The HPA regulates the stress response by modulating cortisol secretion (12), and physical, emotional, and intellectual stresses are individually associated with alterations in the normal pattern of serum cortisol secretion (13). Previous studies in non-ICU populations have shown that cortisol secretion is elevated in patients with acute and chronic anxiety (14, 15).

We sought to determine whether salivary cortisol measured early in an ICU admission is associated with subsequent anxiety among ICU family members. We hypothesized that elevation in salivary cortisol would be associated with anxiety 3 months later among ICU family members.

METHODS

Study Participants

In a prospective cohort study, we enrolled adult family members of patients newly admitted to a multidisciplinary medical/surgical ICU with an admission Acute Physiology and Chronic Health Evaluation (APACHE) II (16) score greater than 15 (a score associated with at least a 10–20% hospital mortality in contemporary environments). Study inclusion criteria were ability to speak and read English. Participants were enrolled within the first 24 hours of the patient's ICU admission. Study eligibility criteria excluded pregnant or breastfeeding females, prisoners, and children (age < 18 yr) or a known history of PTSD, dementia, or schizophrenia (17). Study participants who used steroid-containing medications, which interfere with cortisol secretion, were also excluded (18). To ensure enrollment within the acute phase of ICU exposure, family members of patients who had been transferred from another ICU after an inpatient stay longer than 24 hours or had a previous ICU or long-term acute care hospital admission within the 90 days prior to the index admission were also excluded. One study participant per patient was eligible for study enrollment. If more than one family member was available, participants were prioritized based on their relationship with the patient according to the algorithm depicted in **Figure E1** (Supplemental Digital Content 1, http://links.lww.com/CCM/D18), with preference for a spouse or family member living with the patient.

This study was approved by the Intermountain Medical Center Institutional Review Board (number 1040305). Written consent was obtained from all participants. Each participant received a $50 gift card upon return of the cortisol samples, and another $50 gift card on completion of the 3-month telephone interview.

Demographic Data

Demographic characteristics and medical history of study participants were obtained, including self-reported history of anxiety or depression and use of medications or substances known to interfere with salivary cortisol secretion or collection (18). A modified Perceived Stress Scale (PSS) was also collected at study enrollment to record participant's levels of perceived stress (19).

Characteristics of the ICU patient were also collected, including admission APACHE II score, Elixhauser comorbidity score (20), age, sex, ICU and hospital length of stay, in-hospital mortality, and 3-month mortality, as well as the patient's number of prior ICU admissions in the last 5 years, based on participant report.

Salivary Cortisol

We obtained five consecutive saliva samples from participants beginning the morning after study enrollment. Samples were obtained upon awakening and at prespecified time intervals throughout the day (immediately upon awakening, 30 min post awakening and before breakfast, 30 min before lunch, 30 minutes before dinner, and just before bedtime) (21). Saliva samples were collected using a Salivette (Sarstedt AG & Co, Nümbrecht, Germany), a sampling device for measuring salivary cortisol. Participants were instructed to follow standard protocol for salivary cortisol measurements using the salivette (21). Samples were collected the next day from participants by a research coordinator and stored at –20°C until analysis (22). Cortisol levels were evaluated using quantitative commercial enzyme immunoassay with chemiluminescence detection (chemiluminescence immunoassay; IBL-Hamburg, Germany). The assay has a lower detection limit of 0.1 nmol/L with intra- and interassay coefficients of variation less than 8% (21). Cortisol via saliva sampling has been shown to have high correlation ($r = 0.90$) with cortisol from serum and plasma samples (23). The area under the curve with respect to ground (AUC_g) was the prespecified primary measure of salivary cortisol (24). The AUC_g is an established method of reporting cortisol levels and is obtained by calculating the area under the curve and above the baseline (ground) when results are graphed over time (for a sample calculation, see **Fig. E2**, Supplemental Digital Content 1, http://links.lww.com/CCM/D18). We normalized the AUC_g values for total time elapsed between the first and last samples. Cortisol awakening response (CAR) was a prespecified secondary measure of salivary cortisol. CAR

represents the increase in cortisol level from the first (awakening) sample to the following sample 30 minutes later (25).

Cortisol values were excluded from analysis if any value was greater than 3 SDs from the mean of all samples for the entire population or if the elapsed time between the first two samples (used to calculate the CAR) was greater than 90 minutes (i.e., > 1 hr late). Participants' data were excluded entirely from analysis if they did not provide the cortisol samples necessary to calculate either AUC_g or CAR.

Outcome Instruments

The primary outcome was anxiety, assessed during a telephone follow-up 3 months (± 1 mo) after enrollment, as measured by the Hospital Anxiety and Depression Scale-Anxiety (HADS-A) (26). The Hospital Anxiety and Depression Scale (HADS) screens for anxiety and depression using a 14-item scale with scores ranging from 0 to 21 for anxiety and depression; a HADS score greater than or equal to 8 on either section is indicative of possible or probable anxiety or depression, respectively (26). In addition to the primary outcome, we also screened for depression (HADS-depression [HADS-D] [26]) and symptoms of posttraumatic stress (Impact of Event Scale-Revised [IES-R] [27]) during the 3-month follow-up. The IES-R is a 22-item scale measuring intrusion, avoidance, and hyperarousal; a mean score of greater than or equal to 1.6 indicates PTSD symptoms (27).

Statistical Methods

Our prespecified primary analysis was a logistic regression of AUC_g on anxiety at 3 months, controlling for a history of self-reported anxiety. In a prespecified secondary analysis, we repeated the primary analysis, using the CAR instead of AUC_g. We also report secondary outcomes including depression (HADS-D score ≥ 8) and symptoms of PTSD (IES-R score ≥ 1.6).

Sensitivity analyses were performed to determine whether patient severity of illness or participant PSS altered the association between CAR and anxiety after correcting for a history of self-reported anxiety. Sensitivity analyses were also conducted to control for potentially relevant covariates using backward stepwise logistic regression. In addition to our predictors of interest (AUC_g, CAR), candidate covariates included age, sex, tobacco history, alcohol use, obesity, history of depression, history of anxiety, as well as whether the ICU patient had a previous ICU admission within the last 5 years. Covariates were retained in the model using a backward stepwise feature selection strategy that optimized Akaike information criterion.

Sample Size and Power Calculation

The power calculation was performed assuming that the mean estimated HADS-A score among individuals with minimal anxiety was 5 (± 2), while individuals with significant anxiety had mean 8 (± 3). We therefore estimated, with 90% power (alpha = 0.05), to detect a slightly more conservative but still clinically important difference of 2 (26, 28) on the HADS-A with 100 enrolled participants with a 15% attrition and a ratio of 1.5:1 in abnormal to normal AUC_g (based on studies documenting the distribution of cortisol levels in different populations) (29–31). Sample size calculations were performed in PASS v12 (32).

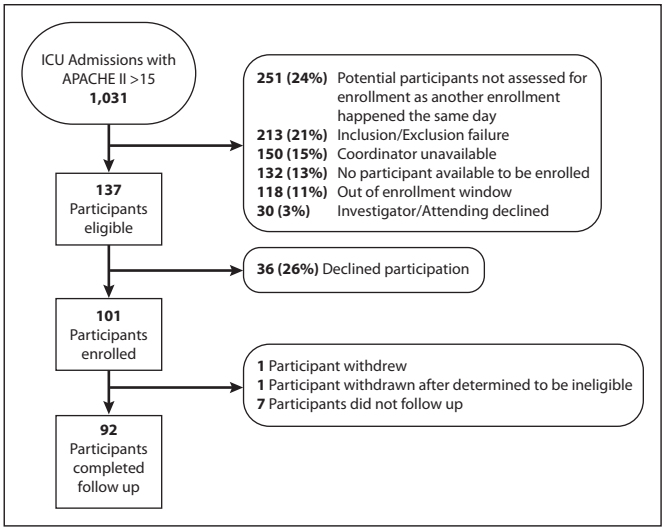

Figure 1. Flow diagram for study cohort. APACHE II = Acute Physiology and Chronic Health Evaluation II.

RESULTS

Of 1,031 admissions to the study ICU, 137 (13%) had a family member eligible for the study and 100 participants were enrolled; one participant withdrew after enrollment and before completing study procedures. Ninety-two participants completed follow-up. See **Figure 1** for consort diagram.

Participant Results

Study participants' mean age was 54 (SD 14) years, and 64% were female. The majority (71%) lived with the patient prior to ICU admission, and 53% were the patient's spouse. A history of anxiety was self-reported by 26 participants (26%). Mean (SD) PSS score at enrollment was 5 (4) and was significantly higher for those with a history of anxiety (4.5 vs 7.0; $p = 0.002$). Demographic information for study participants are found in **Table 1** with additional information available in **Table E1** (Supplemental Digital Content 1, http://links.lww.com/CCM/D18).

Patient Results

The ICU patients had a mean age of 60 (17) years, and 51% were female. Mean APACHE II at admission was 30 (7). Forty-seven of these patients (47%) had been admitted to an ICU within the last 5 years. In-hospital mortality was 21%. Further detailed demographic and medical information for patients are displayed in **Table E2** (Supplemental Digital Content 1, http://links.lww.com/CCM/D18).

Outcomes and Data Analysis

For all participants, median cortisol levels by normalized AUC_g were 3.9 nmol/L (interquartile range [IQR], 2.9–4.7) and by CAR were 1.9 nmol/L (IQR, –2.3 to 8.1). Of the 92 participants

TABLE 1. Study Participant Demographics

Variables	Cohort (*n* = 99)
Age, mean ± SD	54 ± 14
Female sex, *n* (%)	63 (64)
Race, *n* (%)	
American Indian or Alaskan Native	1 (1)
Asian	3 (3)
Black	2 (2)
Native Hawaiian or Pacific Islander	2 (2)
White	89 (90)
Not reported	2 (2)
Ethnicity, *n* (%)	
Hispanic or Latino	8 (8)
Not Hispanic or Latino	90 (91)
Not reported	1 (1)
History of depression, *n* (%)	30 (30)
History of anxiety, *n* (%)	26 (26)
Perceived Stress Scale-4, mean ± SD	5 ± 4
Relationship to patient, *n* (%)	
Spouse	52 (53)
Patient is their parent	26 (26)
Patient is their child	11 (11)
Patient is their sibling	5 (5)
Other family relationship	4 (4)
Close friend	1 (1)
Live with patient, *n* (%)	70 (71)
Hours/wk with patient, *n* (%)	
Full time (> 50 hr weekly or 8 hr daily)	52 (53)
Part time (11–50 hr a week or 3–5 hr daily)	29 (29)
< 10 hr a week (1–2 hr daily)	18 (18)
How much care providing to patient prior to ICU admit, *n* (%)	
None	52 (53)
Small amount	7 (7)
Moderate amount	18 (18)
Large amount	27 (27)

who completed follow-up, we had complete samples for AUC_g in 80 participants and for CAR in 77 participants, with seven being excluded because more than 90 minutes elapsed between the samples. No cortisol measurements were greater than 3 SDs from the mean.

At 3-month follow-up, among the 92 participants with recorded outcomes, 29 participants (32%) had HADS-A score greater than or equal to 8 indicating possible or probable anxiety. Fifteen (16%) participants had HADS-D score greater than or equal to 8, indicating possible or probable depression, and 14 participants (15%) had IES-R scores consistent with PTSD (≥ 1.6). For our primary outcome, we used a dichotomous assignment instead of continuous measures in all analyses due to an influential outlier in HADS-A scoring.

In our primary analysis, normalized AUC_g was not significantly associated with anxiety (odds ratio [OR], 0.94; CI, 0.69–1.26; $p = 0.70$), after controlling for a history of anxiety. In the prespecified secondary analysis, however, CAR was significantly associated with anxiety (OR, 1.08; CI, 1.01–1.15; $p = 0.02$) after controlling for a history of anxiety (**Fig. 2**). In sensitivity analysis, CAR was also significantly associated with 3-month anxiety after controlling for the patient's admission APACHE II score and history of anxiety (OR, 1.08; CI, 1.01–1.16; $p = 0.02$). CAR also remained significantly associated with 3-month anxiety after controlling for PSS and history of anxiety (1.09; CI, 1.02–1.17; $p = 0.02$). An effect plot which depicts the relationship between predictor (CAR) and outcome (3-mo anxiety) at different levels of the predictor while controlling for a history of anxiety is represented in **Figure 3**. In a sensitivity analysis using backward stepwise logistic regression, the association between CAR and anxiety remained significant (OR, 1.10; CI, 1.03–1.18; $p = 0.009$) when controlling for other relevant covariates (sex, history of anxiety, and previous ICU admission) (**Table 2**).

DISCUSSION

In a prospective, observational study of family members of ICU patients, the CAR, a measure of hypothalamic-pituitary activation commonly associated with physiologic stress (33), was associated with anxiety at 3 months. Although this finding was a prespecified secondary analysis, the association between CAR and anxiety persisted in sensitivity analyses that controlled for patient baseline severity of illness, a participant self-reported history of anxiety, and PSS scores at study enrollment.

The impact of a critical illness on family members of ICU patients has received increasing recognition (6, 34). Many questions remain about the best interventions, both in and after the ICU, to ameliorate or prevent PICS-F and how to identify those family members most at risk for PICS-F. To our knowledge, ours is the first study in family members of adult ICU patients investigating the link between an acute physiologic disturbance and subsequent anxiety.

Our results confirm the concept that a family member's vulnerability to anxiety after a loved one's ICU admission is comprised of both physiologic and psychologic characteristics. Our findings additionally suggest that acute physiologic stress (measured here by salivary cortisol) might identify individuals at highest risk for post-ICU anxiety and raise the possibility that reducing physiologic stress through specific support strategies may lessen post-ICU anxiety. CAR may serve as a physiologic indicator of identifying individuals who may respond

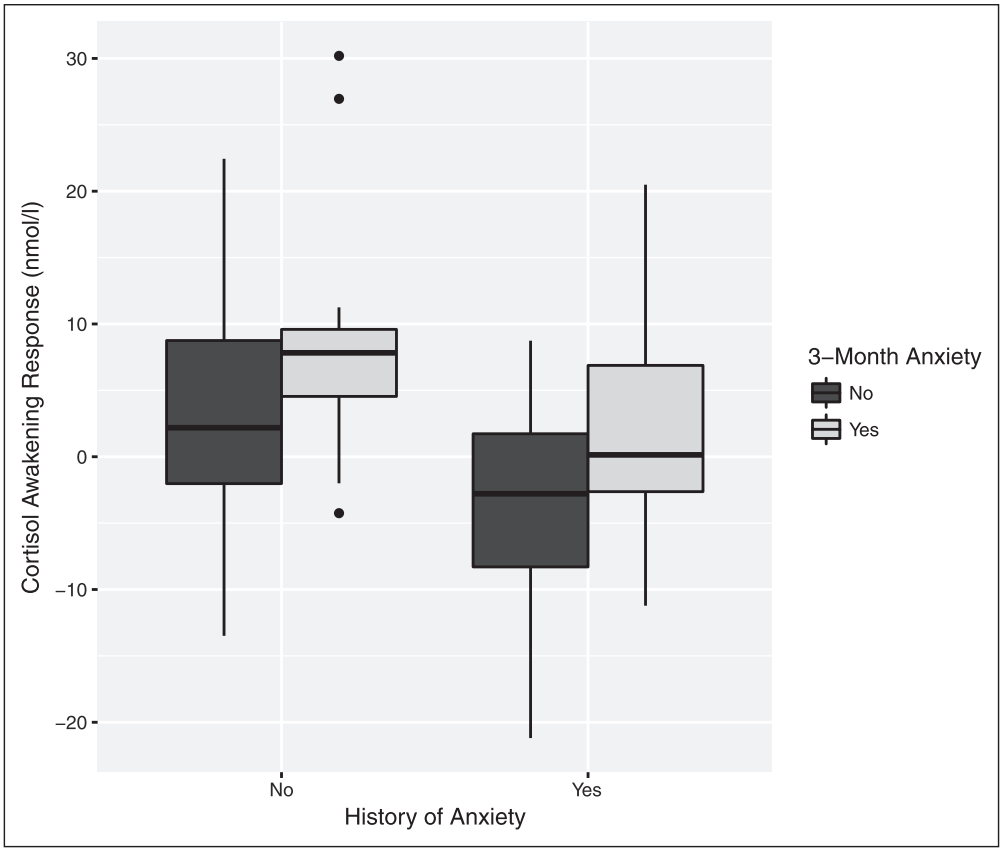

Figure 2. Cortisol awakening response and 3-mo anxiety.

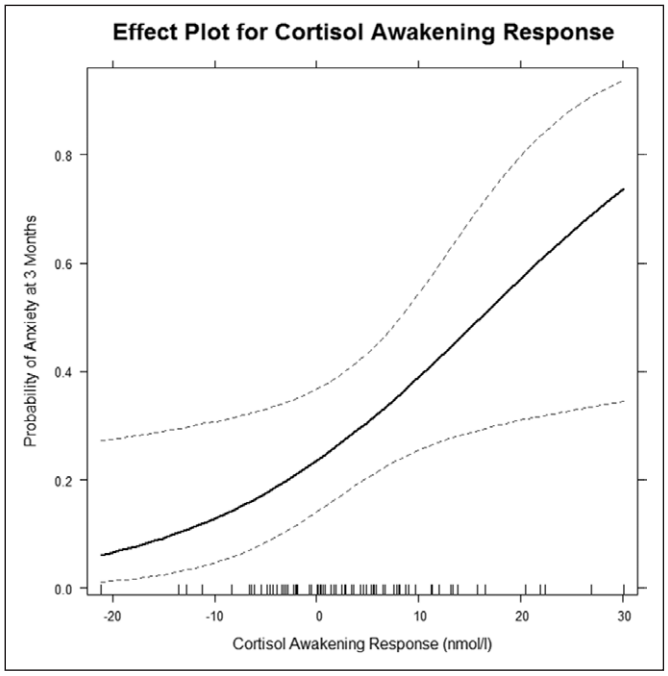

Figure 3. Effect plot for cortisol awakening response.

to support interventions during the ICU experience. Previous studies of family members of chronically ill patients found that providing communication and emotional support to family members reduces anxiety (35, 36).

The ideal procedures for measurement of physiologic stress in ICU family members remain unclear and are likely dependent on the complex relationship between acute and chronic stress and cortisol secretion. High stress can impair HPA functioning, resulting in either chronically elevated or blunted cortisol, both of which may be linked to important health outcomes (37, 38). This blunting effect may have been seen in the participants with chronic stress in our study, possibly due to a chronically ill loved one or other stressors that were not measured in this study. Within each individual, the response to stress is multifaceted and variable—our results reflect these complexities. Given that this population is presumed to be under acute stress, we predicted an activated HPA and elevated levels of salivary cortisol (reflected in both an increased AUC_g and CAR) would predict later anxiety. The CAR was associated with post-ICU anxiety in this population, while our primary analysis using AUC_g was nonsignificant. The CAR and AUC_g reflect discrete parts of the cortisol secretory cycle (39); because the CAR is distinct from other earlier and later circadian cortisol secretion, it may be more sensitive to sleep quality (40)—a potentially salient influence in an ICU setting.

We are unable with this study design to distinguish between acute and chronic stress as causes of patterns of cortisol secretion. As indicated, 47% of participants had a family member with a prior admission to an ICU and as such may have acute stress superimposed on chronic stress. Research is needed to understand the interplay between acute and acute-on-chronic stress for ICU patients and their family members.

Our study has several potential limitations. First, as part of a substudy, participants in this study were asked to leave the patient's room for additional testing. Some family members declined the study, as they did not want to leave the patient's room, even for a short time, to meet with the research coordinator. It is possible that those family members have higher stress, and they were not included in this study. This selection bias may limit the generalizability of our findings. However, our rates of declined consent were low, suggesting relatively minor risk of bias. Owing to resource limitations, we were only able to enroll one participant per day, as such many potentially eligible participants were not approached. We do not believe that the

TABLE 2. Multivariate Backwards Stepwise Logistic Regression of Hospital Anxiety and Depression Scale-Anxiety

Variables	OR (95% CI)	*p*
Cortisol awakening response	1.10 (1.03–1.18)	**0.009**
Female	3.59 (0.99–15.93)	0.07
History of anxiety	6.70 (1.89–26.69)	**0.004**
Previous ICU admit	3.04 (0.94–10.87)	0.07

OR = odds ratio.
Boldface values indicate $p < 0.05$.

process of approaching participants introduced systematic bias, as coordinators approached family members without any preferences for patient or participant types.

We did not collect detailed data on participant's other potential stressors or baseline medical history, so we may have missed some factors that may influenced the cortisol values and study outcomes. Additionally, it is possible that some participants did not accurately record the timing of their cortisol collection, and our results may have been skewed by inaccurate salivary cortisol data. However, no values in our participants were outside the expected range, suggesting that such an effect was unlikely. To reduce the burden on family members, we only collected salivary cortisol samples on 1 day and thus did not capture intraindividual fluctuations in CAR (41). Finally, we did not measure sleep or sleep quality (42) or regulate all substances and habits known to interact with cortisol secretion.

Family members of ICU patients are a select population vulnerable to long-term effects from the stress precipitated by a loved one's critical illness. Not all family members develop PICS-F, and identification of at-risk individuals is a key aspect of interventions to prevent or ameliorate the morbidities associated with this syndrome. We identified elevated CAR as a predictor of subsequent anxiety in family members of adult ICU patients. This study is a novel, important step in characterizing physiologic processes that could allow for early targeted therapies to mitigate post-ICU anxiety.

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