Prospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
49(11) 1–12

DOI: 10.1177/03000605211057829
journals.sagepub.com/home/imr
SAGE

Heart rate variability and subsequent psychological distress among family members of intensive care unit patients

Benjamin RE Harris[1], Sarah J Beesley[2,3,4], Ramona O Hopkins[4,5], Eliotte L Hirshberg[2,3,4,6], Emily Wilson[4], Jorie Butler[2,7], Thomas A Oniki[2,3,8], Kathryn G Kuttler[2,3,8], James F Orme[2,3,4] and Samuel M Brown[2,3,4]

Abstract

Objective: To determine whether heart rate variability (HRV; a physiological measure of acute stress) is associated with persistent psychological distress among family members of adult intensive care unit (ICU) patients.

Methods: This prospective study investigated family members of patients admitted to a study ICU. Participants' variability in heart rate tracings were measured by low frequency (LF)/high frequency (HF) ratio and detrended fluctuation analysis (DFA). Questionnaires were completed 3 months after enrollment to ascertain outcome rates of anxiety, depression, and post-traumatic stress disorder (PTSD).

Results: Ninety-nine participants were enrolled (median LF/HF ratio, 0.92 [interquartile range, 0.64–1.38]). Of 92 participants who completed the 3-month follow-up, 29 (32%) had persistent

[1]Department of Medicine, University of Utah School of Medicine, Salt Lake City, UT, USA
[2]Center for Humanizing Critical Care, Intermountain Healthcare, Murray, UT, USA
[3]Pulmonary and Critical Care Medicine, Intermountain Medical Center, Salt Lake City, UT, USA
[4]Pulmonary and Critical Care Medicine, University of Utah School of Medicine, Salt Lake City, UT, USA
[5]Psychology Department and Neuroscience Center, Brigham Young University, Provo, UT, USA
[6]Pediatric Critical Care, University of Utah, Salt Lake City, UT, USA
[7]Geriatrics and Psychology, University of Utah and Salt Lake City Veterans Administration Hospital, Salt Lake City, UT, USA
[8]Care Transformation Information Systems, Intermountain Healthcare, Salt Lake City, UT, USA

Corresponding author:
Benjamin RE Harris, Department of Medicine, University of Utah School of Medicine, 30 North 1900 East, Room 4C104, Salt Lake City, UT 84132, USA.
Email: benjamin.harris@hsc.utah.edu

anxiety. Logistic regression showed that LF/HF ratio (odds ratio [OR] 0.85, 95% confidence interval [CI] 0.43, 1.53) was not associated with 3-month outcomes. In an exploratory analysis, DFA α (OR 0.93, 95% CI 0.87, 0.99), α_1 (OR 0.97, 95% CI 0.94, 0.99), and α_2 (OR 0.94, 95% CI 0.88, 0.99) scaling components were associated with PTSD development.

Conclusion: Almost one-third of family members experienced anxiety at three months after enrollment. HRV, measured by LF/HF ratio, was not a predictor of psychologic distress, however, exploratory analyses indicated that DFA may be associated with PTSD outcomes.

Keywords

Post intensive care syndrome, psychological distress, anxiety, intensive care, family members, heart rate variability

Date received: 21 April 2021; accepted: 12 October 2021

Introduction

The intensive care unit (ICU) is regularly a stressful environment for patients and families, with long-lasting psychological effects.[1–6] Family members of ICU patients have been demonstrated to often experience persistent anxiety, depression, and post-traumatic stress disorder (PTSD),[6–9] with many family members experiencing a poor quality of life that may persist for years,[10] frequently associated with significant financial and emotional burden.[7,11,12] This constellation of psychological, cognitive and functional problems is defined as post intensive care syndrome (PICS), and is considered to have two forms: PICS affecting patients (PICS) and PICS affecting their family members (PICS-F).[5] PICS-F represents psychological distress and significant morbidity among family members themselves that may also significantly disrupt caregiving for the patient during convalescence after an ICU admission.[11,12]

Risk factors for PICS-F include female sex, age of family member or patient, history of anxiety, and amount of social support.[13–15] Furthermore, family members have an elevated risk for persistent psychological distress if they were more involved in medical decision making, their relative died in the ICU, or communication between the team of clinicians and the family was felt to be inadequate.[6] To the best of the present authors knowledge, only one previously published study has evaluated physiologic markers of acute stress in family members of adult patients and their association with development of PICS-F.[13]

Heart rate variability (HRV) is a useful measure of sympathovagal balance within the autonomic nervous system, as a surrogate for adrenergic stimulation, and a late mediator of the physiology of the acute stress response through the hypothalamus-pituitary axis (HPA).[14,15] Interbeat variability of a subject's heart rate has been validated as a surrogate marker of sympathovagal balance. Low frequency (LF) and high frequency (HF) power bands (the area under the curve at such frequencies) corresponds to activation by the sympathetic nervous system or the parasympathetic nervous system, respectively. The ratio of these frequencies is a commonly accepted marker of sympathetic activation.[14]

The aim of the present study was to determine whether HRV-based measures of acute stress in family members during the ICU admission of a relative was

associated with family member psychological outcomes 3 months later. The hypothesis that abnormalities in HRV would predict persistent anxiety symptoms, as well as depression and PTSD symptoms at a 3-month follow-up, was evaluated.

Participants and methods

Study population

This was a pre-planned ancillary study of a prospective cohort study examining cortisol responses among ICU family members.[13] In the parent cohort, adult family members of patients newly admitted to a multidisciplinary ICU at the Intermountain Medical Center, Murray, Utah, with an admission Acute Physiology and Chronic Health Evaluation (APACHE) II score >15 (a score associated with at least a 10–20% hospital mortality rate in contemporary environments), were enrolled within the first 24 h of the patient's ICU admission.[13,16] Subjects were enrolled when research staff were available and, to reduce systematic bias, eligible subjects were approached regardless of patient or participant type. Participants were enrolled between January 2015 and January 2016, with follow-up completed by April 2016. Criteria for inclusion were the ability to speak and read English. Study exclusions were atrial fibrillation,[17] use of steroid-containing medications, pregnant or breast-feeding females, prisoners, children (aged < 18 years), or a known history of PTSD, dementia, or schizophrenia.[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 ≥24 h, or who had a previous ICU or long-term acute-care hospital admission within 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 a previously described algorithm, with preference for a spouse or family member who lived with the patient.[13]

This study was approved by the Intermountain Medical Center Institutional Review Board (No. 1040305), and written informed consent was obtained from all participants. Each participant received a $50 gift card upon finishing the initial study visit, and another $50 gift card on completion of the 3-month telephone interview. All subject and patient data included herein has been de-identified, and the reporting of these data conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[19]

Demographic and clinical variables

Data regarding demographic characteristics and medical history of study participants were obtained, including age, race, ethnicity, sex, history of anxiety or depression, and medication use (including medication for treatment of anxiety or depression).[20,21] History of tobacco use versus non-use in the last 12 months,[18,22,23] and significant alcohol use, defined as two or more drinks daily (averaged over a week), were also recorded.[24,25]

Characteristics of the ICU patients were also collected, including admission APACHE II score, Elixhauser comorbidity score,[26,27] age, sex, ICU and hospital length of stay, in-hospital mortality, 3-month mortality, and number of prior ICU admissions for the patient in the last 5 years, based on family member report.

Heart rate variability testing

In order to assay the autonomic nervous system through measurement of HRV, 30 min of 3-lead electrocardiography was

recorded on the day of enrollment with the participant at rest, undisturbed, in a private, quiet room. Paced breathing was not employed. Measurements were obtained using a non-invasive Sotera Visi Mobile™ monitoring device (Sotera Wireless Inc, San Diego, CA, USA). Peaks were detected using Continuous Individualized Multiorgan Variability Analysis (CIMVA™) software,[28] and the Elgendi algorithm.[29] Metrics were calculated for 28 min of data. The prespecified primary predictor was the normalized LF/HF power ratio from the frequency domain (LF: 0.04–0.15 Hz; HF: 0.15–0.4 Hz) of the time series of interbeat intervals, a parsimonious and well-validated measure of sympathovagal balance.[30] Detrended fluctuation analysis (DFA) α, α_1, and α_2, as well as sample entropy of heart rate tracings, were also analyzed as predictors, as follows.

An exploratory analysis was performed to determine the value of DFA in predicting the development of psychological outcomes. DFA has previously been used to analyze non-linear time series, essentially identifying significant trends within data that are otherwise not linear.[31] Briefly, the interval time between heart beats is graphed and sectioned into windows of equal number of heart beats. Linear regression is then completed on each window, effectively providing the mean of the window. This regression line is then subtracted from the window, detrending each window. A plot of the window size and fluctuation within the window is then graphed and the scaling component alpha (α) can be determined based on the behavior of root-mean-squares of different time scales. This can then be further broken down into short- and long-term scaling components, α_1 and α_2, respectively.[32,33] DFA has previously been shown to correlate with acute psychological stress in subjects, decreasing in amplitude with increasing stress.[34,35]

Finally, sample entropy was evaluated based on HRV. Among subjects who experience acute stress, sample entropy (that determines the randomness of biological time series such as HRV) tends to be lower in subjects with a history of major depressive disorder.[36] Furthermore, increased anxiety is reported to be associated with a lower sample entropy.[37]

Outcome instruments

The primary outcome was anxiety, measured using the Hospital Anxiety and Depression Scale (HADS)-Anxiety (A) during a telephone follow-up interview at 3 months (+/− 1 month) after enrollment.[38] The HADS screens for anxiety and depression with a 14-item scale with scores ranging from 0 to 21 for anxiety and depression. A HADS score $\geq$8 on either section is indicative of possible or probable anxiety or depression.[38–40] HADS-A scores were dichotomized using a HADS-A score $\geq$8 to indicate anxiety. This dichotomous assignment was used instead of continuous measures in all analyses due to highly influential outliers. In addition to the primary outcome, depression (using HADS-Depression [D])[38] and PTSD (using Impact of Event Scale-Revised [IES-R])[41] were also screened during the 3-month follow up. The IES-R is a 22-item scale measuring intrusion, avoidance and hyperarousal; a mean score of $\geq$1.6 indicates PTSD symptoms.[41,42]

Statistical methods

Continuous data are presented as mean $\pm$ SD or median (interquartile range [IQR]) and categorical data are presented as *n* (%) prevalence. The pre-specified primary analysis was a logistic regression of the association between LF/HF ratio and anxiety, adjusting for a subject's history of anxiety, age, and sex. In a pre-specified

secondary analysis, the primary analysis was repeated using the outcomes of depression and PTSD, adjusting for a subject's history of depression or anxiety, respectively, as well as age and sex. In exploratory analyses, DFA scaling components α, α_1, and α_2, as well as sample entropy, were analyzed as predictors of anxiety, depression, and PTSD outcomes in logistic regression models. Due to very small odds ratios (ORs) and confidence intervals (CIs) in the logistical regression models for PTSD outcomes, DFA outcomes were multiplied by 100. Between-group differences in continuous data were analyzed using Wilcoxon signed–rank test, χ^2-test or Student's *t*-test, as appropriate.

Because this was an ancillary study, a formal sample size and power calculation was not completed outside the parent study. Data were analyzed using R software (R Core Team, 2020 version; https://www.R-project.org), and a P value <0.05 was considered to be statistically significant.

Results

A total of 100 subjects were enrolled into the parent study, with one participant withdrawing after enrollment. All remaining participants ($n = 99$) underwent HRV testing, and the 3-month follow-up assessment was completed for 92 (92%) of those enrolled.

The median age of study participants was 54 ± 14 years and 63 (64%) were female. Seventy (71%) of participants lived with the patient prior to ICU admission, and 52 (53%) were the patient's spouse. A history of anxiety was reported by 26 (26%) participants and a history of depression was reported by 30 (30%). No participants reported a history of PTSD. Additional demographic data for the study population are presented in Table 1.

Median age of the 99 related ICU patients was 60 ± 17 years, 50 (51%) were female, and the majority (89%) were White. Mean APACHE II score on admission was 26 ± 6, and 63 (64%) patients required intubation during their time in the ICU. Median ICU length of stay was 3.3 (IQR 1.9–8.4) days. Forty-seven (47%) of these patients had experienced a previous ICU admission in the last 5 years, and 30 (30%) had experienced two or more ICU admissions over this same time period. In-hospital mortality rate was 21% and 3-month mortality was 29%.

Among the 99 participants who underwent HRV testing, the mean heart rate was 76 ± 12 beats/min, and the median LF/HF ratio was 0.92 (IQR 0.64–1.38).

Table 1. Demographics of family members of patients admitted to the intensive care unit.

Variable	Number
Total participants	99
Age, years	54 ± 14
Sex, female	63 (64)
Race	
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	
Hispanic or Latino	8 (8)
Not Hispanic or Latino	90 (91)
Not reported	1 (1)
Relationship to patient	
Spouse of patient	52 (53)
Child of patient	26 (26)
Parent of patient	11 (11)
Sibling of patient	5 (5)
Other family relationship	4 (4)
Close friend of patient	1 (1)
Live with patient	70 (71)
Self-reported medical history	
History of depression, yes	30 (30)
History of anxiety, yes	26 (26)

Data presented as mean $\pm$ SD or *n* (%) participant prevalence.

Out of the 92 participants with 3-month follow-up data, 29 (32%) had a HADS-A score ≥8, indicating anxiety. Fifteen participants (16%) had a HADS-D score ≥8, indicating depression, and 14 participants (15%) had IES-R scores consistent with PTSD. The median LF/HF ratios of the dichotomized outcomes for anxiety, depression, and PTSD are presented in Table 2.

In the primary analysis, the logistical regression model showed LF/HF ratio (OR 0.85, 95% confidence interval 0.43, 1.53) was not associated with anxiety outcomes at the 3-month follow-up (Table 3) after adjusting for age, sex and history of anxiety. In further exploratory analyses, DFA α, α_1, and α_2, and sample entropy were also not associated with HADS-A ≥8 (Table 3).

Table 2. Summary statistics for individual outcomes in 92 family members of patients admitted to the intensive care unit.

Variable	Overall	Anxious HADS-A ≥8 ($n=29$)	Not anxious HADS-A <8 ($n=63$)	Statistical significance
LF/HF ratio	0.92 (0.64–1.38)	0.97 (0.67–1.12)	0.86 (0.60–1.30)	NS
DFA α	0.85 ± 0.13	0.86 ± 0.12	0.85 ± 0.14	NS
DFA α_1	0.96 ± 0.26	0.95 ± 0.24	0.95 ± 0.26	NS
DFA α_2	0.94 ± 0.14	0.84 ± 0.12	0.84 ± 0.15	NS
Sample entropy	1.13 ± 0.38	1.11 ± 0.39	1.14 ± 0.39	NS
Heart rate	76.1 ± 11.7	78.9 ± 10.8	74.4 ± 11	NS
Variable	Overall	Depressed HADS-D ≥8 ($n=15$)	Not depressed HADS-D <8 ($n=77$)	Statistical significance
LF/HF ratio	0.92 (0.64–1.38)	0.79 (0.60–1.03)	0.92 (0.63–1.33)	NS
DFA α	0.85 ± 0.13	0.86 ± 0.11	0.85 ± 0.13	NS
DFA α_1	0.96 ± 0.26	0.93 ± 0.24	0.95 ± 0.26	NS
DFA α_2	0.94 ± 0.14	0.86 ± 0.12	0.84 ± 0.14	NS
Sample entropy	1.13 ± 0.38	1.01 ± 0.44	1.15 ± 0.38	NS
Heart rate	76.1 ± 11.7	82.7 ± 14.1	74.2 ± 9.8	$P=0.03$
Variable	Overall	PTSD IES-R ≥1.6 ($n=14$)	No PTSD IES-R <1.6 ($n=78$)	Statistical significance
LF/HF ratio	0.92 (0.64–1.38)	0.95 (0.67–1.07)	0.86 (0.62–1.32)	NS
DFA α	0.85 ± 0.13	0.82 ± 0.12	0.95 ± 0.13	NS
DFA α_1	0.96 ± 0.26	0.89 ± 0.26	0.96 ± 0.25	NS
DFA α_2	0.94 ± 0.14	0.80 ± 0.09	0.95 ± 0.15	NS
Sample entropy	1.13 ± 0.38	1.16 ± 0.47	1.12 ± 0.37	NS
Heart Rate	76.1 ± 11.7	77.8 ± 7.6	75.2 ± 11.5	NS

Data presented as median (interquartile range) or mean ± SD.

HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression; PTSD, post-traumatic stress disorder; IES-R, Impact of Event Scale-Revised; LF, low frequency; HF, high frequency; DFA, detrended fluctuation analysis.

$P<0.05$, statistically significant between-group difference (Wilcoxon signed–rank test or Student's *t*-test).

NS, no statistically significant between-group difference ($P\geq0.05$).

Table 3. Logistic regression analyses of the association between baseline heart rate variability parameters and anxiety, depression, and PTSD outcomes in 92 family members of patients admitted to the intensive care unit.

	Odds ratio	95% confidence intervals	
Anxiety (HADS-A $\geq$8)			
LF/HF ratio	0.85	0.43	1.53
DFA α	0.09	0	6.09
DFA α_1	0.27	0.03	2.62
DFA α_2	0.09	0	3.79
Sample entropy	0.57	0.13	2.44
Depression (HADS-D $\geq$8)			
LF/HF ratio	0.73	0.23	1.64
DFA α	0.12	0	33.28
DFA α_1	0.13	0	2.64
DFA α_2	0.45	0	62.3
Sample entropy	0.17	0.02	1.02
PTSD (IES-R $\geq$1.6)			
LF/HF ratio	0.41	0.07	1.14
DFA α*	0.93	0.87	0.99
DFA α_1*	0.97	0.94	0.99
DFA α_2*	0.94	0.88	0.99
Sample entropy	0.61	0.1	3.67

HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression; PTSD, post-traumatic stress disorder; IES-R, Impact of Event Scale-Revised; LF, low frequency; HF, high frequency; DFA, detrended fluctuation analysis.

*Statistically significant association with PTSD.

Pre-specified secondary outcomes included PTSD and depression, defined as an IES-R score of $\geq$1.6 and a HADS-D score of $\geq$8, respectively. When dichotomizing PTSD outcomes, the LF/HF ratio was not associated with PTSD outcomes at the 3-month follow-up (OR 0.41, 95% CI 0.07, 1.14) in logistical regression analysis. However, in exploratory analyses, it was found that DFA α (OR 0.93, 95% CI 0.87, 0.99), DFA α_1 (OR 0.97, 95% CI 0.94, 0.99), and DFA α_2 (OR 0.94, 95% CI 0.88, 0.99) were all statistically significantly associated with PTSD at the 3-month follow-up (Table 3). Notably, sample entropy was not associated with PTSD outcomes (Table 3). Depression at 3 months was not associated with LF/HF ratio (OR 0.73, 95% CI 0.23, 1.64), nor was it associated with DFA α, α_1, α_2, or sample entropy (Table 3) on logistic regression.

Associations between DFA results and PTSD were further explored in terms of covariate contribution to overall average DFA trends. Females were found to be more likely to have a statistically significant, or trend toward significant, difference, measured by their mean DFA between PTSD outcomes, while their male counterparts did not (Table 4). This was also the case when looking at younger subjects (aged $<$ 65 years), but elderly subjects did not show any significantly associated differences between these measurements (Table 4). When evaluating how the coefficients contributed to these models, female sex was found to be positively associated with PTSD outcomes within the DFA α, α_1, and α_2 logistical regression models (β coefficient 2.60, $P = 0.023$ for DFAα), and age was inversely associated within these

Table 4. Mean DFA value for each covariate within the PTSD logistical regression models.

	Male			Female		
	No PTSD ($n=33$)	PTSD ($n=1$)	Statistical significance	No PTSD ($n=45$)	PTSD ($n=13$)	Statistical significance
DFA α	0.82 ± 0.14	0.85	NS	0.89 ± 0.12	0.82 ± 0.12	NS
DFA α_1	0.90 ± 0.30	0.92	NS	1.00 ± 0.20	0.89 ± 0.27	NS
DFA α_2	0.80 ± 0.13	0.84	NS	0.88 ± 0.15	0.80 ± 0.10	$P=0.03$
	Age <65 years			Age ≥65 years		
	No PTSD ($n=55$)	PTSD ($n=13$)	Statistical significance	No PTSD ($n=23$)	PTSD ($n=1$)	Statistical significance
DFA α	0.90 ± 0.10	0.83 ± 0.11	NS	0.77 ± 0.15	0.68	NS
DFA α_1	1.03 ± 0.21	0.91 ± 0.26	NS	0.79 ± 0.27	0.66	NS
DFA α_2	0.89 ± 0.13	0.81 ± 0.08	$P=0.04$	0.75 ± 0.15	0.64	NS
	No history of anxiety			History of anxiety		
	No PTSD ($n=59$)	PTSD ($n=9$)	Statistical significance	No PTSD ($n=19$)	PTSD ($n=5$)	Statistical significance
DFA α	0.85 ± 0.14	0.81 ± 0.13	NS	0.90 ± 0.10	0.83 ± 0.09	NS
DFA α_1	0.94 ± 0.27	0.85 ± 0.32	NS	1.02 ± 0.18	0.97 ± 0.08	NS
DFA α_2	0.83 ± 0.15	0.79 ± 0.10	NS	0.88 ± 0.13	0.82 ± 0.09	NS

Data presented as mean ± SD.

DFA, detrended fluctuation analysis; PTSD, post-traumatic stress disorder.

$P<0.05$, statistically significant difference between PTSD and no PTSD within subgroups (Student's *t*-test).

NS, no statistically significant difference ($P \geq 0.05$).

models (β coefficient –0.060, $P=0.059$ for DFAα) (Table 5).

To better understand the cohort in terms of which population had persistent anxiety or depression based on the HADS scoring system, the frequency of subjects with a reported personal history of anxiety and depression who also had these outcomes at the 3-month follow-up was investigated in an exploratory analysis. Those with a personal history of anxiety were found to be significantly more likely to report a HADS-A score of >8 at 3 months (22% without anxiety versus 58% with anxiety; $P=0.002$; χ^2-test). This was also true for those with a reported history of depression (6% without depression versus 37% with depression; $P<0.001$; χ^2-test).

Discussion

In this study, HRV was examined as a physiologic marker of stress and as a predictor of subsequent psychological outcomes: anxiety, depression, and PTSD at a 3-month follow-up. The primary analysis found no significant association between sympathetic activation, measured by the LF/HF ratio, and anxiety, depression, or PTSD in family members of ICU patients. In an exploratory analysis, increased complexity of HRV, measured by DFA, was found to be associated with decreased development of PTSD, an effect observed among women and younger subjects.

Prior studies using similar HRV analysis and psychological outcomes have been limited to evaluation of an acute stressor on

Table 5. Beta coefficients of covariates within the PTSD logistical regression models.

		Logistical regression model		
		DFA α Coefficient (*P*-value)	DFA α_1 Coefficient (*P*-value)	DFA α_2 Coefficient (*P*-value)
Covariate	DFA variable	–0.072 (0.022)	–0.029 (0.044)	–0.063 (0.032)
	Anxiety	0.30 (0.66)	0.31 (0.65)	0.30 (0.65)
	Age	–0.060 (0.059)	–0.040 (0.010)	–0.049 (0.076)
	Female	2.60 (0.023)	2.29 (0.039)	2.60 (0.022)
	AIC	73.526	75.397	74.05

PTSD, post-traumatic stress disorder; DFA, detrended fluctuation analysis; AIC, Akaike Information Criterion.

HRV. In one study ($n = 106$), a diagnosis of social anxiety and psychological distress was associated with reduced HRV, measured by DFA.[43] In two studies of healthy adults ($n = 42$ and $n = 57$, respectively), acute stress was associated with a decrease in HRV, measured by DFA.[34,35] Based on these prior findings, it may have been expected that, in the present study, the acute stressor (ICU admission) would lead to a decreased HRV by DFA as well as increased psychological distress (such as increased PTSD). Instead, increased complexity in the HRV (measured by DFA) was revealed to be possibly protective against the development of negative psychological outcomes (PTSD). This might suggest that, while acute sympathovagal balance is not strongly associated with subsequent psychological symptoms, other markers of disruption of the normal complexity of HRV are. Crucially, the observations related to DFA are exploratory and should be confirmed in an additional study.

While further exploring the logistical regression models, the female sex covariate was found to have a significant effect on the outcomes of the model (Table 5). There was also a large difference in mean DFA α and α_2 values between females with and without PTSD. Because of these results, future studies should assess this relationship further with DFA as the primary exposure.

Additionally, HRV, measured by LF/HF ratio, was not associated with psychological outcomes. Relevant to this observation, LF/HF is primarily a measure of acute sympathovagal balance, whereas DFA and cortisol levels are related to more complex features of the stress response, and DFA relates more straightforwardly to disruptions in heart rate complexity over longer time periods. One explanation for the lack of association between LF/HF ratio and psychological outcomes is that LF/HF ratios were measured at time intervals that differed from the measurement of cortisol levels within this same population (as part of the parent study).[13] Cortisol samples were collected throughout the day,[13] whereas subjects' heart rates were measured at the beginning of enrollment for just 30 minutes.

Nearly half of the patients whose relatives were studied had at least one previous ICU admission, which could have led to blunting of the physiologic effects that were under investigation. Essentially, those with a previous ICU experience may have been primed against acute stress and from a psychological standpoint, these subjects may have a better understanding of what to expect in an ICU. This may have significantly affected the present outcomes, as those with chronic stress have been shown to be less likely to respond to acute

physiologic stress.[44,45] The present study may be limited in generalizability due to only enrolling English-speaking patients as a criterion for being able to complete the study, and due to the subjects being primarily non-hispanic whites. While this is representative of the local Utah population, it is not representative of other parts of the USA or the rest of the world. The study is also limited by the fact that some family members may not have consented to enrollment due to not wanting to leave the patient's room, even for a short time, to participate in the study procedures (HRV and questionnaires) that were performed in a quiet room around the corner from the ICU. It is possible that these family members were the most stressed and anxious, and as they chose not to be included in the study, this may have biased the findings and further limited the generalizability. The study room was serene, quiet and comfortable, and the primary research coordinator who performed enrollment and study procedures is also a comforting person; thus, there is a possibility that her attention and the study room environment might have created a stress-reducing situation that may have blunted sympathetic activation. A final important limitation is that data regarding baseline use of beta blockers were not collected from study participants, which might have influenced the HRV results.

In conclusion, further work to understand PICS-F, including predictors of acute stress in the ICU, and development of future anxiety, depression, and PTSD, is critical to ongoing support of family members at a vulnerable time. While the work presented herein investigates a marker of acute stress, it may be beneficial to also measure subacute stress using a marker of physiological stress at multiple points throughout an ICU stay, as prolonged anxiety and stress beget future stress.[45]

Author contributions

Conception (SMB, ELH, JO, ROH, KGK), data acquisition (SJB, SMB, EW, KGK, ELH), data analysis (SJB, EW, SMB, BREH, EH), manuscript writing (SMB, SJB, BREH, EH), manuscript revision for important intellectual content (all authors), and approval of the final copy (all authors).

Data accessibility

As this research involved human subjects, access to the primary data would require appropriate IRB/ethics board approvals. Conditional on such approvals, deidentified study data would be shared.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and publication of this article: This study and the parent study were funded by an Intermountain Research and Medical Foundation Grant and a Ruth L Kirschstein National Research Service Award Institutional Research Training Grant (T32 5T32HL105321-05) (SJB).

ORCID iD

Benjamin RE Harris https://orcid.org/0000-0003-1459-1473

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