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Electrocardiographic Derived Cheyne-Stokes Respiration and Periodic Breathing in

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Electrocardiographic Derived Cheyne-Stokes Respiration and Periodic Breathing in Healthy, Hospitalized and Critically Ill Cohorts

by

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DISSERTATION

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Abstract

Electrocardiographic Derived Cheyne-Stokes Respiration and Periodic Breathing in Healthy, Hospitalized and Critically Ill Cohorts

Adelita Tinoco

Cheyne-Stokes respiration (CSR) and periodic breathing (PB) are associated with an increased risk for mortality and may provide an early sign of risk for deterioration. The purpose of this study was to determine whether electrocardiographic (ECG) derived CSR and PB differ among healthy individuals, patients presenting to the emergency department with acute coronary syndrome symptoms and critically-ill patients admitted to the intensive care unit (ICU); and whether CSR and PB provide an early sign of risk for adverse outcome in critically ill patients in the ICU. Adverse events were defined as cardiac arrest, emergency endotracheal intubation, prolonged mechanical ventilation post-surgery, and all cause in-hospital mortality that occurred during admission; and, all-cause 30 day mortality that occurred after patient discharge.

We conducted data analyses in a healthy, a hospitalized and a critically ill group:

Healthy group

A study entitled "*Quantifying Novel Electrocardiographic Monitoring Measurements in Healthy Adults*" (Barbara Drew, PI, funded by NINR T32 NR007088) which prospectively collected 24-hour continuous Holter ECG data from healthy individuals during 2013

Hospitalized group

A study entitled "*Ischemia Monitoring & Mapping in the Emergency Department In Appropriate Triage & Evaluation of Acute Ischemic Myocardium"* (Barbara Drew, PI, funded by NIH, RO1HL69753) which prospectively collected 24-hour continuous Holter ECG data from patients presenting to the emergency department with acute coronary symptoms during 2002-2005

Critically-Ill group

A study entitled "*Analysis of patient monitor alarms in adult intensive care units"* (Barbara Drew, PI; funded by GE Healthcare) which prospectively collected continuous ICU ECG monitor data from patients admitted to the ICU during March 2013

CSR and PB data were measured using SuperECG software (Mortara Instrument, Milwaukee, WI), a computerized ECG measurement algorithm that measures CSR and PB by detecting beat to beat changes in QRS morphology. SuperECG CSR and PB derivation requires sinus rhythm, and patients who had atrial fibrillation, atrial flutter or paced rhythms were not included in analyses. Patients with a minimum of 18 hours of continuous ECG data were included allowing for observation of the variables of interest. Finally, only periods in which the patients breathed spontaneously (i.e., not ventilator dependent) were used for analyses allowing for measurement of CSR and PB. The final group samples included: 100 healthy participants, 90 hospitalized patients and 172 critically-ill patients.

When comparing the hospitalized group presenting to the emergency department with acute coronary symptoms to the healthy group, the hospitalized patients had 7.3 (CI=2.00-28.96) times more CSR episodes and 1.6 (CI=1.15-2.38) times more PB episodes than healthy participants.

Furthermore, when comparing the critically ill group admitted to the ICU to the healthy participant group, the critically ill patients had 1.71 times more CSR (CI=.95-3.52) and 1.35 times more PB (CI=1.07-1.69) than healthy participants.

Lastly, patients who suffered an adverse event in the ICU had 2 times more CSR (CI= .58 - 5.47) and .73 times more PB (CI= .47 – 1.07) than patients who did not suffer an adverse event; however, these increased abnormal breathing patterns were not statistically significant. Kaplan Meier survival curve and the log rank test showed that patients who had ≥15 CSR episodes had a

higher adverse event rate than patients who had <15 CSR episodes (21.7% vs. 12.8%, log rank, p=.52). Cox regression showed that risk for adverse event increases by 4% per every CSR episode increase (CI = .99-1.08, p=.07).

In conclusion, CSR and PB differ between a healthy population and hospitalized or critically ill patients. Critically ill patients have a higher adverse event rate when they have 5 or more CSR episodes and CSR may be predictive of adverse event. More research needs to be done to assess the clinical value of CSR and PB in detecting risk for adverse events.

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Chapter 1: Introduction to Dissertation

Electrocardiographic Derived Cheyne-Stokes Respiration and Periodic Breathing in Healthy, Hospitalized and Critically Ill Cohorts

The term Cheyne-Stokes respiration (CSR) has been used in conjunction with several other breathing patterns, including central sleep apnea, irregular breathing, labored breathing, obstructive sleep apnea, periodic breathing, sleep apnea and sleep disordered breathing.

Sleep-related breathing disorders are commonly categorized as either *obstructive* (i.e., caused by upper airway collapse) or *central* (i.e., caused by brain dysfunction in sending signals to the muscles that control breathing) [1].

CSR and periodic breathing (PB) are a type of central sleep apnea often associated with sickness and worsening health status [1] yet the underlying mechanisms are not completely understood.

Throughout the human lifespan, human beings cycle through multiple states of consciousness and states of arousal, including wakefulness and several stages of sleep. In conditions of normal health, and in all states of consciousness, the body maintains pH homeostasis through breathing—the fine chemical balancing of arterial carbon dioxide concentration and arterial oxygen concentration. CSR ensues when the system is unable to maintain an adequate oxygen and carbon dioxide level [2-3].

Medullary neurons maintain homeostasis through a negative-feedback, closed-loop system in which carbon dioxide and oxygen levels in the blood are kept in balance through ventilation. However, if the central nervous system becomes dysfunctional, chemoreceptors are unable to adequately sense the amount of carbon dioxide in the blood. The individual may then begin to hyperventilate, which results in hypocapnia. When the carbon dioxide level drops, the

individual may then begin to hypoventilate, which will either result in CSR (apnea) or PB (no apnea). Consequently, the carbon dioxide level rises again, producing hypercapnia. In order to lower the carbon dioxide level, a new cycle will start when the individual begins to hyperventilate again [4].

CSR and PB have been associated with increased mortality in heart failure patients [5-9], yet much of the research measuring CSR and PB has been done in sleep laboratories and not in acute care settings. A new software, SuperECG (Mortara Instrument, Milwaukee, WI) uses subtle changes in QRS morphology with breathing to calculate CSR and PB episodes from continuous Holter electrocardiographic (ECG) monitor data and from continuous hospital monitor ECG data. SuperECG allows for the opportunity to study these breathing abnormalities in the acute care setting. It is unknown whether measuring CSR and PB would be of any diagnostic, prognostic, or therapeutic value in the clinical setting. The first step is to conduct an observational study to determine whether the frequency of CSR and PB differs in healthy and sick cohorts.

The purpose of this study was to determine whether ECG derived CSR and PB differ among healthy individuals and patients presenting to the emergency department with acute coronary syndrome symptoms; healthy individuals and critically-ill patients admitted to the intensive care unit (ICU); and whether CSR and PB provide an early sign of risk for adverse outcome in critically ill patients in the ICU.

Specific Aims

In a population of 100 healthy participants and 90 emergency department patients admitted with symptoms of acute coronary syndrome (hospitalized group) over 24 hours of continuous ECG monitoring we aim to:

Aim 1. Measure and compare the frequency of Cheyne-Stokes respiration and periodic breathing in healthy individuals versus hospitalized patients.

Hypothesis 1. Hospitalized patients will have significantly more Cheyne-Stokes respiration and periodic breathing episodes than healthy individuals.

In a population of healthy participants and intensive care unit patients over 24 hours of continuous ECG monitoring we aim to:

Aim 2. Measure and compare the frequency of Cheyne-Stokes respiration and periodic breathing in healthy individuals versus intensive care unit patients.

Hypothesis 2. Intensive care unit patients will have significantly more Cheyne-Stokes respiration and periodic breathing episodes than healthy individuals.

Aim 3. Determine whether Cheyne-Stokes respiration and periodic breathing are associated with adverse outcomes.

Hypothesis 3. Cheyne-Stokes respiration and periodic breathing will be significantly correlated with adverse outcomes.

The early development of cardiac care units brought into focus the importance of nurse observation and monitoring. Nurses detect changes in physiologic monitoring data (vital signs, oxygen saturation, and arrhythmias) that indicate a patient deterioration. A biomarker of *early* deterioration, which can provide additional time to intervene on patient physiological deterioration has the potential to save lives. Knowledge gained from this study can potentially contribute to improved detection of deteriorating health status in hospitalized and critically ill patients; improved health status detection may help direct plan of care and perhaps improve patient's health outcomes. Although CSR and PB counts could be added to computer algorithms to generate alarms with hospital patient monitoring, it is unknown whether such alarms would

have any clinical utility or whether they would just increase the alarm fatigue problem. The current study represents the initial investigations of CSR and PB that are necessary to determine whether a future prospective clinical trial would be justified.

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Chapter 2:

ECG-Derived Abnormal Breathing Patterns: A comparison of Healthy Participants to Hospitalized Patients with Suspected Acute Coronary Syndrome

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Abstract

Background: Cheyne-Stokes respiration (CSR) has been investigated primarily in outpatients with heart failure. The present study was designed to determine the frequency of CSR in other cardiac cohorts.

Methods: We compared CRS and periodic breathing (PB), measured during 24 hours of continuous 12-lead electrocardiographic (ECG) Holter recording, in a group of 90 hospitalized patients presenting to the emergency department with symptoms suggestive of ACS to a group of 100 healthy ambulatory participants. We also examined CSR and PB in the 90 patients presenting with ACS symptoms, divided into a group of 39 (43%) with confirmed ACS, and 51 (57%) with a cardiac diagnosis but Non-ACS. SuperECG software was used to derive respiration and then calculate CSR and PB episodes from the ECG Holter data. Negative binomial regression was used to compare incidence rate ratios for CSR and PB episodes between the healthy versus hospitalized group, and for the ACS versus cardiac Non-ACS group.

Results: Hospitalized patients with suspected ACS had 7.3 times more CSR episodes and 1.6 times more PB episodes than healthy ambulatory participants. Patients with confirmed ACS had 6.0 times more CSR episodes and 1.3 times more PB than cardiac Non-ACS patients.

Conclusion: Patients presenting to the emergency department with ACS symptoms have a significantly higher number of ECG derived CSR and PB measurements than healthy ambulatory individuals. Patients with a positive ACS diagnosis have a higher number of CSR and PB episodes than patients with a cardiac Non-ACS diagnosis. Future research is needed to determine whether these non-invasive ECG-derived respiratory parameters are linked to adverse patient outcomes, which could have implications in clinical practice for identifying high risk patients.

Introduction

Cheyne-Stokes respiration (CSR) and periodic breathing (PB) are a type of central sleep apnea caused by brain dysfunction that impairs signals sent to the muscles that control breathing. In contrast to CSR and PB, obstructive sleep apnea is caused by a mechanical collapse or obstruction of the airway [1]. CSR and PB are abnormal breathing patterns associated with an increased risk for mortality in patients with heart failure [2-5], renal failure [6] and stroke [7]. Prior studies measured CSR and PB using the gold standard polysomnography [3, 5], unattended sleep study [4] and portable systems [2, 5, 7], which are costly, and obtrusive. SuperECG (Mortara Instrument Inc, Milwaukee, WI.) research software capable of measuring both CSR and PB from continuous electrocardiographic (ECG) monitoring has been used to examine both CSR and PB, in heart failure and healthy groups [8].

In a further assessment of this non-invasive method we examined two research aims; (1) compare ECG-derived CSR and PB between a group of healthy ambulatory participants and a group of patients presenting to the emergency department (ED) with symptoms suggestive of Acute Coronary Syndrome (ACS); and 2) compare the rate of CSR and PB between those with and without a final discharge diagnosis of ACS. The SuperECG measurements of CSR and PB were designed for use with 12 leads of ECG information; however, routine hospital monitoring involves the recording of 7 rather than 12 leads. Therefore, a third aim of this study was to determine whether CSR and PB rates differ when using 7 versus 12 ECG leads.

Methods

Study design. Data from two separate studies were used. First, data for the hospitalized patient group came from a subsample of patients enrolled in the prospective study entitled

Ischemia Monitoring & Mapping in the Emergency Department In Appropriate Triage & Evaluation of Acute Ischemic Myocardium (IMMEDIATE AIM, RO1HL69753). The healthy control group data came from a prospective descriptive study entitled Quantifying Novel Electrocardiographic Monitoring Measurements in Healthy Adults (T32 NR007088). The primary aim of this study was to quantify the frequency of 12-lead ECG-derived CSR and PB in healthy ambulatory individuals. The Institutional Review Board at the university approved both studies and research nurses obtained informed consent from all participants.

Study setting and population.

Hospitalized Group. The IMMEDIATE AIM study has been described in detail previously [9]. Briefly, patients presenting to the emergency department at UCSF's Moffitt hospital with symptoms suggestive of ACS from April 2002 to December 2004 were prospectively enrolled [9]. The research nurses in the IMMEDIATE AIM study obtained verbal assent followed by written informed consent from 1308 patients. This consent method was used so that 12-lead Holter recording (Mason-Likar electrode configuration) could be applied as soon as possible following presentation to the ED. The median door-to-Holter time was 44 minutes. Although all 1,308 patients had a Holter recording, only 188 (14%) who were enrolled near the end of the study were monitored with a H12+ device (Mortara Instrument, Milwaukee, WI) that recorded 1000 samples/second which is required for ECG-derived CSR and PB measurement. Of the 188 subjects, 50 (26.6%) were excluded because a cardiac diagnosis was ultimately ruled out, 40 (21.3%) were excluded because they had less than 18 hours of ECG recording, and 8 (4.0%) were excluded because of an arrhythmia that would confound the measurement of CSR and PB (i.e., atrial fibrillation/flutter, or ventricular paced rhythm). Thus, the final sample included in this analysis was 90 patients. The final diagnosis in the 90 patients was cardiac non acute

coronary syndrome (i.e., valvular heart disease, congestive heart failure, pericarditis, new onset arrhythmia, stable angina, hypertension crisis, aortic dissection or aneurysm) in 51 (56.7%), and ACS in 39 (43.3%). Of the 39 patients with ACS, 6 (15.4%) had ST elevation myocardial infarction, 8 (20.5%) had non-ST elevation myocardial infarction, and 25(64.1%) had unstable angina.

Healthy Group. The healthy control group included a convenience sample of 100 participants 18 years of age and older who were recruited between January and March 2013 (T32 NR007088; F31 NR015196). Potential participants were carefully queried about medical history to ensure they met criteria for being "healthy." Exclusion criteria included skin allergy to adhesive used for skin electrodes, current flu symptoms or chronic illnesses including:

- coronary heart disease (angina pectoris, myocardial infarction, coronary bypass surgery, percutaneous coronary intervention [angioplasty, stent procedure])
- heart failure or heart transplantation
- hypertension requiring medication
- abnormal heart rhythm (atrial fibrillation, pacemaker, implantable cardioverter defibrillator, ablation therapy)
- stroke
- diabetes mellitus
- chronic obstructive pulmonary disease (emphysema, chronic bronchitis, restrictive lung disease)
- asthma requiring year-round inhaler use
- sleep apnea, and/or treatment for sleep apnea with continuous positive airway pressure
- cancer with treatment in the past 12 months

- end-stage renal failure or renal dialysis.

In addition, participants were excluded if they were taking nitroglycerin, coumadin, pradaxa, or beta blockers. Finally, potential participants were also screened for sleep apnea with the Geisinger Health Tool and excluded if they answered 'yes' to two or more of the questions [10].

Healthy participants were asked to continue all routine daily activities while wearing a H12+ Holter monitor (Mortara Instrument Inc, Milwaukee, WI.) for 24 hours. The H12+ Holter acquired 12 ECG leads simultaneously with a digital sampling rate of 1,000 samples per second. Electrodes were placed by the primary investigator (AT) using a Mason-Likar [11] electrode configuration. Each electrode site was marked with ink and the participants were instructed on how to replace electrodes and lead wires (i.e., after showering or if electrodes came off).

ECG Analysis. Acquired 12-lead ECG data from both studies were downloaded to the H-Scribe computer for off-line analysis (4.34 software, Mortara Instrument Inc. Milwaukee, WI). The ECG data were then processed with research software (Super ECG, Mortara Instrument Inc.) to measure CSR and PB episodes during the recording period for each participant. Details of this process have been published previously by Haigney et al [8]. Briefly, when respiration occurs, tidal volume increases, the heart shifts in the thorax and the QRS waveform changes its morphology. SuperECG uses beat to beat changes in QRS morphology to derive respirations and calculate CSR and PB episodes from Holter ECG recordings. The software first uses QRS amplitude changes to calculate the QRS amplitude mean square variation over 15 seconds (area divided by width in ¼ uV units); and then derives a waveform from the mean QRS amplitude (sample rate of 1 sample per second). The derived waveform is used to measure changes in tidal volume and calculate respiration, CSR and PB. Examples of SuperECG software technology to

detect breathing are displayed in Figure 1 and 2. CSR is identified by the software when three or more consecutive cycles of hyperpnea/hypopnea/apnea respiration with a crescendo-decrescendo breathing pattern occur (Figure 1, top). PB is identified by the software when three or more consecutive cycles of hyperpnea/hypopnea respiration with a crescendo-decrescendo breathing pattern occur (Figure 1, bottom). The distinguishing feature of CSR from PB is that CSR has a period of apnea whereas PB does not.

To measure sensitivity and specificity of the measurement tool, SuperECG, one research nurse randomly selected 10 healthy participants and 10 hospitalized patients and produced one CSR waveform, one PB waveform and one waveform that was not classified by the software as neither CSR nor PB for each patient. A total of 20 resulting waveforms for each CSR, PB and neither CSR nor PB were produced using 12 lead ECG data and 7 lead ECG data. A total of 60 waveforms using 12 lead ECG data and 60 waveforms using 7 lead ECG data were reviewed. Using 12 lead ECG data resulted in agreement between human visual inspection and SuperECG software detection of 40% CSR, 50% PB, and 100% neither CSR nor PB while using 7 lead ECG data resulted in an agreement of 55% for CSR, 60% PB, and 90% for neither CSR nor PB.

Statistical Analysis

Continuous data is reported as mean ±SD. The Wilcoxon rank-sum test was used to compare group means for the variable monitoring time and for the demographic variables age and body mass index (BMI). The Pearson Chi-square test was used to compare group frequencies of the categorical variables gender and ethnicity. The Chi-square test followed by post hoc pairwise comparisons was used for the variable race and the Fisher exact test was used when the assumptions for Pearson Chi-square test were not met. Spearman rank order correlations were used to test for a correlation between demographic variables and the variables

of interest, CSR and PB. The incidence rate ratio between the two groups in each analysis was calculated using negative binomial regression, since the count outcomes were strongly over dispersed [12]. Estimation was carried out using a nonparametric, bias-corrected bootstrap with 5,000 repetitions to reduce the potential influence of several cases with extreme outliers for both outcomes [13-15]. Threshold ordinal variables for the continuous variables CSR and PB were created. An ordinal logistic regression was used to test each threshold probability on all groups followed by Bonferroni post hoc pairwise comparisons. Statistical analyses were conducted using Stata Release 14 (StataCorp, TX, USA). A p value <.05 was considered statistically significant.

Results

Aim 1: Comparison of CSR and PB between healthy participants and patients presenting to the ED with symptoms of ACS.

Patient and participant characteristics. As shown in Table 1, the hospitalized group was more racially diverse than the healthy group and included fewer Caucasians (41% vs. 70%, p<.001). In addition, the hospitalized group was also older (67 vs. 34, p<.001) and had a higher body mass index (BMI) (28 vs. 25, p=.001) than the healthy group.

Correlation of demographics with CSR and PB. Age was correlated to both CSR (r_s= +29, p<.001) and PB ($r_{s=}$ +.36, p<.001) and recognized to be a confounder, as a result, we controlled for age and BMI in all subsequent analyses. The daily mean Holter monitoring time were similar between the hospitalized and the healthy groups (22.99 vs. 23.66, p=.05), however they were also statistically different. Therefore, CSR and PB counts were adjusted in the negative binomial regression model to account for differences in the time span for which data

were collected for each patient; that is, between 18 and 24 hours (Table 2).

Frequency of CSR and PB. Daily mean CSR count was different between the hospitalized and healthy groups (9 vs. 1, p<.001). The daily mean PB count was also different between the hospitalized and healthy (24 vs. 9, p<.001) (Table 2).

We employed negative binomial regression for the analyses of the dependent variables, CSR and PB, because they are positive integer count variables, truncated at zero, skewed to the right and showing over-dispersion [12]. For example, 68 (35.8%) individuals from the healthy and the hospitalized group had zero CSR and 2 (1%) individuals had over 100 episodes each. To estimate the model and obtain parameter estimates uninfluenced by the outliers we ran a negative binomial regression using a nonparametric bias corrected bootstrap with 5000 repetitions.

As seen in Table 3 hospitalized patients had 7.3 times more CSR (CI=2.00-28.96) and 1.64 times more PB (CI=1.15-2.38) than healthy individuals after controlling for age and BMI.

Aim 2: Comparison of CSR and PB between patients with a positive ACS diagnosis and patients with a cardiac Non-ACS diagnosis. We conducted further analysis in the hospitalized group (n=90) to determine whether patients who had a final diagnosis of ACS (n=39) differed in the daily number of CSR and PB counts from those with cardiac but Non-ACS diagnosis (n=51).

Patient and participant characteristics. The groups with and without a final diagnosis of ACS did not differ with respect to age, gender, race, ethnicity, or BMI (Table 4).

Correlation of demographics with CSR and PB. *A*ge and BMI were not correlated to CSR or PB but were controlled for to maintain consistency of statistical analyses. Although mean monitoring time differed by less than an hour between the group with ACS and the cardiac Non-ACS group, it was statistically different (23.49 hours vs. 22.63 hours, p=.002) (Table 4) and

adjusted for in the final negative binomial regression model.

Frequency of CSR and PB. Daily mean CSR count was different between the group of patients with ACS and the group of patients with cardiac Non-ACS group (17 vs. 3, p<.001). The daily mean PB count was also different between the groups (27 vs. 22, p<.001) (Table 4).

Regression showed that patients with a positive ACS diagnosis had 6.01 more CSR (CI=2.78-13.73) and 1.31 times more PB (CI=-0.12-1.90) than those with cardiac Non-ACS diagnosis after controlling for age and BMI. In this analysis, age was correlated to PB with individuals having 2.5 more episodes per every year of age increase (CI=1.01-1.04) after controlling for BMI and group. (Table 5).

Aim 3: Comparison of CSR and PB when using 12-ECG Leads or 7 ECG Leads. The 12-lead ECG includes the 6 limb leads and 6 precordial leads which provide both frontal and horizontal plane waveform data respectively; however, the routine 7-lead monitoring method has become the standard of care for hospital patient monitoring and provides six limb leads and one precordial lead. To study the correlation between 12 lead and 7 lead CSR and PB we used SuperECG research software to derive both respiratory variables out of 12 lead ECG data; and then selected 7 ECG leads (I, II, III, aVR, aVL, aVF and V_1) to derive the same variables, in this manner we insured that each of the 100 healthy participants and 90 hospitalized patients became their own control. Both groups were selected for this analysis as the hospitalized group had higher CSR and PB counts versus the healthy group and we wanted to test if having 7 leads of continuous ECG waveform to derive CSR and PB would affect the sensitivity of the instrument in deriving the variables of interest.

As shown in Table 6, there was a strong positive correlation between 7-lead and 12-lead CSR measurements (r_s= +73, p<.001) and in between 7-lead and 12-lead PB measurements (r_s=

+88, p<.001) in hospital patients. These correlations were moderately positive between 7-lead and 12-lead CSR measurements (r_s= +43, p<.001) and weak between 7-lead and 12-lead PB measurements (r_s= +31, p=.002).

Concentrating in the healthy group and when using 12 lead ECG to derive CSR we found that 44% did not have CSR, 54% had less than 5 episodes, and 2% had 5 or more episodes a day. The prevalence changed to 29% did not have CSR, 69% had 1 to 4 episodes, and 2% had 5 episodes or more when using 7 leads to derive CSR. Examining the CSR data by threshold, showed that when using the 12 lead ECG to derive CSR, 35.9% of patients in the ACS group and 15.6% of patients in the in the cardiac Non-ACS group had 5 or more episodes of CSR a day. The frequency of CSR were similar when using 7 lead ECG to derive CSR, with 38.5% of patients in the ACS group and 13.7% in the cardiac Non-ACS group having 5 or more episodes a day (Table 7).

Table 8 shows that when using 12 lead ECG to derive PB in healthy participants, 1% did not experience PB, 92% had less than 15 episodes, and 7% had 15 or more episodes of PB a day versus 0%, 91% and 9% respectively when using 7 lead ECG to derive PB. When using 12 lead ECG to derive PB, 56.4% of patients in the ACS group and 41.2% in the cardiac Non-ACS group had 15 or more episodes a day; similarly 7 lead ECG derived PB showed prevalence of 69.2% in the ACS group and 39.2% in the cardiac Non-ACS group for a threshold of 15 or more PB episodes a day.

Discussion

This is the first study to investigate the use of ECG-derived CSR and PB measurements for patients in a hospital setting. Our findings indicate that ECG-derived CSR rates are more than 7 times higher in cardiac patients being evaluated in the emergency department compared with

healthy individuals. Moreover, the subgroup with acute coronary syndrome had the highest rate of CSR (average, 17.3 episodes per 24-hour period).

Using ECG-derived measurements, Haigney et al. [8] reported an average of 2.6 CSR episodes per 24-hour period in healthy subjects. We also observed a small number of CSR episodes (average, 1.04 per 24-hour period) in healthy subjects.

In addition, we found healthy subjects experienced PB (average, 9.24 per 24-hr period). These findings support the knowledge that irregular breathing patterns naturally exist in health and assist in maintaining physiological stability [16, 17].

Central Sleep Apnea (CSA) and CSR have been found in combination with Obstructive Sleep Apnea (OSA) in the heart failure population [18-20]. Javaheri et al found a 51% sleep apnea prevalence in outpatient heart failure patients who had a gold standard polysomnography (PSG) study, these patients had a mean number of 24 CSA, seven OSA and one mixed apnea episodes per hour of sleep [19]. Sin et al found that 72% of heart failure patients who underwent PSG testing had a mix of CSA and OSA episodes; of these patients, 33% had CSA defined as having ≥50% central episodes and 38% had OSA defined as having ≥50% obstructive episodes [20].

Few studies have evaluated CSA or OSA in patients with ACS. De Jesus et al. used the Berlin Questionnaire to measure sleep disordered breathing and found 47% of patients admitted to the chest pain unit with ACS were likely to have OSA [21]. Areias et al. used a portable instrument, the Apnea link, and found a 43.1% sleep apnea-hypopnea prevalence in ACS patients admitted to the coronary intensive care unit [22]. Correia et al. also used the Berlin Questionnaire and found a 73% prevalence of OSA in ACS patients admitted to the cardiac care unit; the difference in the prevalence found between De Jesus and Correia might be explained to

the different protocols used in administration of the Berlin Questionnaire, with Correia allowing patients to self-report and self-take the questionnaire [23]. Leao also used a portable device, the Stardust II, to assess for OSA in patients admitted to the cardiac intensive care unit for ACS and found a74% prevalence [24].

To our knowledge this is the first study to use 12-lead ECG Holter data to measure CSR and PB, a central sleep apnea form of sleep disordered breathing, in patients with developing ACS, initiated within a median of 44 minutes from presentation in the emergency department setting. Our results support those of Van den Broecke et al. [25] who performed a sleep study using a tele-monitoring system which remotely monitored 27 patients within 72 hours (median 2 days) of admission to the coronary care unit. Van den Broecke et al. found that 82% of patients had at least one episode of CSR or PB. Correspondingly, 87% of patients in our ACS group had at least one episode of CSR.

Our results support the notion that there is a link between sleep disordered breathing and cardiovascular disease. Further research is needed to assess for CSR, PB, and OSA prevalence in patients with ACS and to evaluate if this disorder is associated with adverse events. Because there is treatment available to treat sleep disordered breathing, new research studies are needed to determine the impact of this pathology so timely treatment can be initiated, which could potentially improve patient outcomes.

Our results showed higher Spearman correlations for both CSR and PB when using only the hospitalized group versus using the healthy group; and may indicate that 7 lead measurement has a higher sensitivity in people who have higher CSR and PB counts. These findings indicate that 7 lead ECG derived CSR and PB could be comparable to 12 lead ECG derived CSR and PB in individuals who experience a higher episode frequency.

Further research testing a threshold of 5 or more episodes of CSR a day and 15 or more episodes of PB a day when using standard in-hospital ECG monitoring and SuperECG to determine the presence of abnormal central apnea is needed to help us identify patients at higher risk for ACS.

In congruence with other studies [26-29] we also found a correlation between age and both CSR and PB. However, controlling for this variable showed that age had a significant effect in how patients experience PB but not CSR, with people showing a higher PB frequency as they grow older.

Limitations. This study included a small sample consisting of 100 healthy participants and 90 hospitalized patients. Although a thorough interview was conducted to assess participants' health' status for inclusion, it was self-reported. Patients in the hospitalized group were enrolled from a single emergency room. While target monitoring time was 24 hours, missing data resulted in inclusion of cases that had at least 18 hours of continuous ECG recording. Variables of interest, CSR and PB, were not measured with the gold standard, polysomnography.

Conclusion

Continuous 12-lead ECG data appears to measure Cheyne-Stokes and periodic breathing patterns in hospitalized patients. CSR and PB counts were significantly different between healthy and hospitalized patients and in in ACS and cardiac Non-ACS patients. Hospitalized patients, especially those with ACS discharge diagnosis had more CSR and PB than healthy and cardiac non-ACS groups. Further research is needed to determine whether these ECG-derived respiratory parameters are linked to adverse patient outcomes and whether continuous measurement would be valuable in clinical practice to identify patients with sleep disordered breathing.

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Figures and Tables

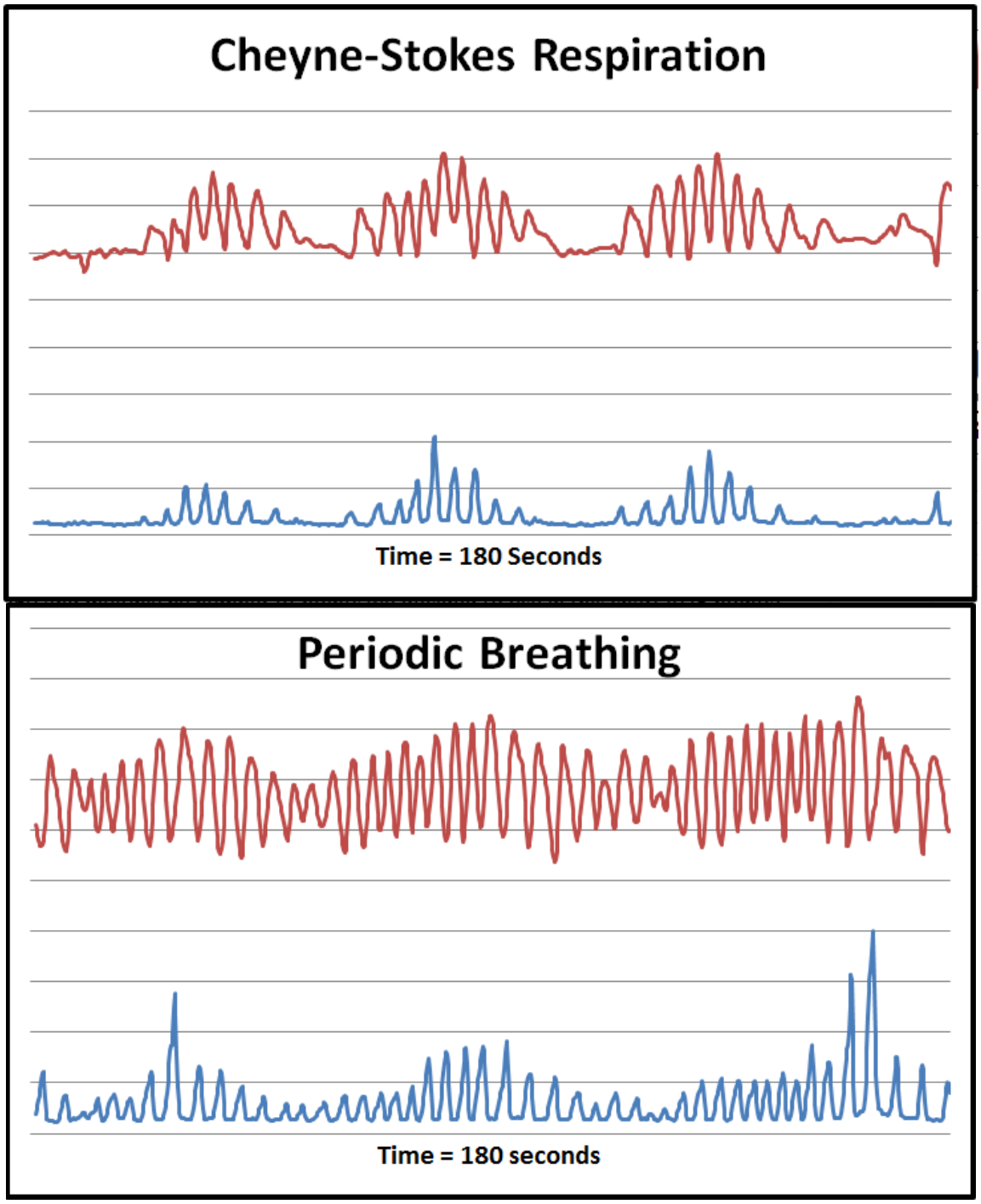

Figure 1. Cheyne-Stokes respiration and periodic breathing. Top: Cheyne-Stokes respiration, top; periodic breathing, bottom over 180 seconds. The top line is the mean QRS amplitude in ¼ microvolts and is used to derive respiratory effort. The bottom line is a myogram signal with arbitrary units used to detect respiratory effort. In Cheyne-Stokes respiration apnea is seen as a flat line in both the QRS amplitude and the myogram waveforms.

Table 1. Demographic characteristics of hospitalized and healthy groups.

Variable	Hospitalized	Healthy	P value
Number	90	100	
Age in years, mean± SD/median	67±14 / 68	34±10 /33	<.001[a]
Male, n (%)	42 (47)	35 (35)	.10[b]
Race			<.001[b]
White, n (%)	37 (41)	70 (70)	H>I[c]
African American, n (%)	20 (22)	11(11)	.58[c]
Asian, n (%)	20 (22)	19 (19)	.04[c]
American Indian/Alaskan Native, n (%)	13 (14)	0 (0)	H<h[c,d]
Hispanic, n (%)	16 (18)	26 (26)	.17[b]
BMI, kg/m², mean ±SD/median	28±7 /27	25±4 /24	.001[a]

Wilcoxon rank-sum test =a, Chi-square test=b, post hoc pairwise comparison of each category for race against the remaining categories=c, Fisher exact test =d. SD = Standard deviation; H= hospitalized group; h= healthy group; BMI= body mass index

Table 2. Frequency of Cheyne-Stokes respiration and periodic breathing in hospitalized and healthy groups.

Variable	Hospitalized	Healthy	P value
Monitoring time, mean hours/SD/median	23±2 /24	24±1 /24	.05[a]
Cheyne-Stokes respiration, entire monitoring period mean/SD/median	9±23 /2	1±1 /1	<.001[a]
Cheyne-Stokes respiration range	0-165	0-7	
Periodic breathing, entire monitoring period mean/SD/median	24±27 /14	9±3 /9	<.001[a]
Periodic breathing range	3-170	0-18	

Wilcoxon rank-sum test =a. SD= standard deviation.

Table 3. Regression for Cheyne-Stokes respiration and periodic breathing in hospitalized patients and healthy subjects.

Variable	Incidence Rate Ratio	Confidence Interval (Bias-Corrected)
Cheyne-Stokes respiration		
Hospitalized vs. Healthy	7.28	2.00-28.96
Reference group, Healthy		
Periodic breathing		
Hospitalized vs. Healthy	1.64	1.15-2.38
Reference group, Healthy		

Table 4. Frequency of Cheyne-Stokes respiration and periodic breathing in patients with and without ACS.

Variable	ACS 39 (57%)	Cardiac Non-ACS 51 (43%)	P value
Monitoring time, mean hours ±SD /median	23±1 /24	23±2 /24	.002[a]
12 Lead Cheyne-Stokes respiration, entire monitoring period mean ±SD /median	17±33 /3	3±7 /1	<.001[a]
12 Lead Cheyne-Stokes respiration, range	0-165	0-38	
12 Lead Periodic breathing, entire monitoring period mean ±SD /median	27±22 /18	22±30 /11	.11[a]
12 Lead Periodic breathing , range	4-88	3-170	

Wilcoxon rank-sum test =a. SD = Standard deviation. ACS=Acute coronary syndrome.

Table 5. Regression for Cheyne-Stokes respiration and periodic breathing in ACS and cardiac Non-ACS groups.

Variable	Incidence Rate Ratio	Confidence Interval (Bias-Corrected)
Cheyne-Stokes respiration Acute Coronary Syndrome vs. Cardiac Non-Acute Coronary Syndrome Reference group, Cardiac Non-Acute Coronary Syndrome	6.01	2.78-13.73
Periodic breathing Acute Coronary Syndrome vs. Cardiac Non-Acute Coronary Syndrome Reference group, Cardiac Non-Acute Coronary Syndrome	1.31	-0.12-1.90

ACS=Acute coronary syndrome.

Table 6. 12 lead to 7 lead correlation using data.

Spearman Correlation	12 Lead CSR versus 7 Lead CSR	P Value	12 Lead PB versus 7 Lead PB	P Value
Hospitalized	.73	<.001	.88	<.001
Healthy	.43	<.001	.31	=.002

CSR= Cheyne-Stokes respiration; PB= periodic breathing

Table 7. 12 lead and 7 lead Cheyne-Stokes respiration thresholds.

Cheyne-Stokes Respiration (# Episodes)	12 Lead ECG Derived Cheyne-Stokes Respiration			
	ACS N (%)	Cardiac Non-ACS N (%)	Healthy N (%)	Significance
0	5 (13)	19 (37)	44 (44)	.001a; H>ACS[b]
1-4	20 (51)	24 (47)	54 (54)	NS[a]
≥5	14 (36)	8 (16)	2 (2)	<.001[a]; ACS>H[b]
Cheyne-Stokes Respiration (# Episodes)	7 Lead ECG Derived Cheyne-Stokes Respiration			
	ACS N (%)	Cardiac Non-ACS N (%)	Healthy N (%)	Significance
0	8 (21)	11(22)	29 (29)	NS[a]
1-4	16(41)	33(65)	69 (69)	NS[a]
≥5	15(39)	7 (14)	2(2)	<.001[a]; ACS>H[b]

Ordinal logistic regression=a, Bonferroni post hoc pairwise comparison of each threshold category for Cheyne-Stokes respiration against the remaining threshold categories=b ($p<.017$ considered significant). H=healthy; ACS=acute coronary syndrome; CNACS=cardiac non-acute coronary syndrome; NS=Not significant.

Table 8. 12 lead and 7 lead periodic breathing thresholds.

Periodic Breathing (# Episodes)	12 Lead ECG Derived Periodic Breathing			
	ACS N (%)	Cardiac Non-ACS N (%)	Healthy N (%)	Significance
0	0 (0)	0 (0)	1 (1)	NS[a]
1-14	17(44)	30 (59)	92(92)	NS[a]
≥15	22(56)	21 (41)	7(7)	<.001[a] ACS>H[b]; CNACS>H[b]
Periodic Breathing (# Episodes)	7 Lead ECG Derived Periodic Breathing			
	ACS N (%)	Cardiac Non-ACS N (%)	Healthy N (%)	Significance
0	0(0)	0(0)	0(0)	NA
1-14	12(31)	31(61)	91(91)	<.001a H>ACS[b]; H>CNACS[b]
≥15	27(69)	20(39)	9(9)	<.001[a] ACS>H[b]; CNACS>H[b]

Ordinal logistic regression=a, Bonferroni post hoc pairwise comparison of each threshold category for periodic breathing against the remaining threshold categories=b (p<.017 considered significant). H=healthy; ACS=acute coronary syndrome; CNACS=cardiac non-acute coronary syndrome; NS=Not significant; NA=not available.

Chapter 3:

Comparing Cheyne-Stokes Respirations in Healthy and Critically-Ill Cohorts Measured with Continuous Electrocardiographic Monitoring

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Target Journal**:** Journal of Electrocardiology

Keywords: Cheyne-Stokes respirations, disordered breathing, critically ill, periodic breathing, intensive care unit, electrocardiogram.

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Abstract

Background: Cheyne-Stokes respiration (CSR) and periodic breathing (PB) are abnormal breathing patterns associated with mortality, which have been largely studied during the night in outpatient sleep study populations. CSR and PB have not been studied in intensive care unit (ICU) patients. In a prior study, we showed that CRS and PB could be measured non-invasively using the electrocardiogram (ECG) among hospitalized patients. The purpose of this study was to compare CSR and PB in healthy individuals and critically ill patients admitted to the ICU.

Methods: Special ECG software was used to measure CSR and PB rates in 172 critically ill patients compared with 100 healthy subjects. Regression analysis was used to compare mean CSR and PB episodes between the healthy and ICU patients. The ICU group was further subdivided and regression analyses were used to compare CSR and PB among the subgroups.

Results: Regression showed that the ICU patients had 1.71 times more CSR (CI=.95-3.52) and 1.35 times more PB (CI=1.07-1.69) than healthy participants. ICU patients discharged with a cardiovascular diagnosis had over 3.0 times more CSR than patients discharged with a medical/surgical diagnosis (CI=.56-10.15) and 2.0 times more CSR than patients discharged with a neurological/neuro-surgical diagnosis (CI=.33-7.71). Patients in the cardiovascular group also had over 2.0 times more PB than the medical/surgical group (CI=1.31-3.37) and 1.46 times more PB than patients in the neurological/neuro-surgical group (CI=.85-2.35).

Conclusion: Measurement of abnormal breathing patterns from continuous ECG data detects different rates of CSR and PB between critically ill and healthy subjects. Patients with a cardiovascular diagnosis have more episodes of CSR and PB than patients with any other non-cardiac diagnosis. Future research is required to determine whether ECG-derived detection of abnormal breathing patterns has diagnostic, prognostic, or therapeutic clinical value.

Introduction

Most of the research assessing Cheyne-Stokes respiration (CSR) and periodic breathing (PB) has been conducted in the outpatient setting, or in sleep laboratories by physicians screening and treating patients for sleep disordered breathing [1-9]. These studies have focused on measuring irregular respiratory patterns in patients with heart failure, mostly during sleep [1-7, 10-12], during short periods of wakefulness [2,7-8,13] or over 24 hours [9]. Although heart failure patients who have CSR have been found to have a higher mortality rate than those without CSR [1,3,5-6,9], only a few studies have examined this pathology in patients in the acute care setting [10,11,13] or in the intensive care unit (ICU) [12,14,15] where patients who have sleep disordered breathing are at high risk for physiological deterioration. Recently, investigational research software that uses continuous electrocardiographic (ECG) waveforms to measure CSR and PB (Mortara Instrument Inc, Milwaukee, WI) was used to study these respiratory variables in an outpatient population [16]. The present study was designed to further explore this methodology in critically-ill ICU patients who routinely have continuous ECG monitoring.

This study was designed to: 1) measure the frequency of ECG derived CSR and PB in a group of ICU patients; 2) determine whether CSR and PB differ between healthy individuals and ICU patients; and 3) determine if CSR and PB differ among ICU patients with a cardiovascular, neurological/neuro-surgical or medical/surgical discharge diagnosis. Current standard of care for patients in the ICU includes continuous monitoring providing readily available 7 lead ECG waveform data that can be used by SuperECG to derive CSR and PB. This study will inform us of CSR and PB presence and frequency among critically ill patients allowing us to identify potential patient groups that might benefit from monitoring for these abnormal breathing

disturbances using ECG data already collected for detection of arrhythmias.

Methods

Study design. This is a secondary analysis of data from two prospective studies. The first study (UCSF Alarm Study funded by GE Healthcare) included all consecutive patients admitted to the five adult ICUs at the UCSF Medical Center over a one-month period (n=461) [17]. The second study included 100 community-based adults who were enrolled to examine ECG-derived CSR and PB in a normal population (T32 NR007088). The university's Institutional Review Board approved both studies. A waiver of consent was approved by the university's Committee on Human Research for patients in the critically ill group allowing inclusion of all consecutive patients admitted to the ICU. A research nurse obtained written informed consent for participants in the healthy group.

Study setting, population and protocol.

Intensive Care Unit Group. The critically ill group included 461 consecutive patients 18 years of age or older who were treated in one of the adult ICUs (cardiac, neurological/neuro-surgical, medical-surgical) at a teaching medical center in California during March, 2013 [17].

All patients were monitored with a Solar 8000i monitor as part of their routine ICU care (version 5.4 software, GE Healthcare, Milwaukee, WI) using a five electrode lead configuration resulting in 7 lead (leads I, II, III, aVR, aVL, aVF and V_1) ECG data. The data was then securely transferred (CARESCAPE Gateway system, GE Healthcare, Milwaukee, WI) to an external server (BedMaster, Excel Medical Electronics, Inc, Jupiter, FL) for off-line analysis. The ECG data was first stored in BedMaster in flat format, then changed into Extensible Markup Language (XML) format using BedMaster software, and finally changed into binary files (AD Instruments,

Dunedin, New Zealand) by our research team. Patient demographic and clinical data were obtained from electronic medical records (Epic software, Madison, WI) (Figure 1) [17].

All 461 patients in the UCSF Alarm study had ECG waveform data recorded and stored for their entire ICU stay. However, for the present analysis, we used just the first 48 hours of ECG monitoring data because patients' acuity is likely to be higher in the first days of ICU stay [18]. To allow an appropriate length of time to observe CSR and PB we excluded 176 (38.2%) patients with less than 18 hours of continuous ECG recording. In addition, we excluded 98 (21.2%) patients who were not breathing spontaneously (i.e., ventilator, bilevel positive airway pressure, continuous positive airway pressure) for at least 18 hours. Lastly, ECG derived CSR and PB requires patients to be in sinus rhythm and not in a ventricular paced rhythm, consequently we excluded 15 (3.3%) patients who had atrial fibrillation or a paced rhythm. Hence, the final ICU group used for this analysis included 172 (37.3%) patients.

Healthy Group. The healthy group included 100 participants 18 years of age or older enrolled between January and March 2013. A research nurse interviewed potential participants and excluded those who had flu symptoms; chronic illnesses (coronary heart disease, heart failure, heart transplantation, hypertension requiring medication, abnormal heart rhythm, stroke, diabetes mellitus, chronic obstructive pulmonary disease, asthma requiring year-round inhaler use, sleep apnea, cancer with treatment in the past 12 months, end-stage renal failure); were taking certain medications (nitroglycerin, coumadin, pradaxa, beta blockers); or responded affirmatively to two or more of the Geisinger Health Tool criteria questions for sleep apnea [19].

Participants in the healthy group wore an H12+ Holter recorder (Mortara Instrument Inc, Milwaukee, WI) for 24 hours using the Mason-Likar [20] electrode configuration. While all 12-ECG leads were recorded, only the seven leads that matched the hospital monitoring leads in

study #1 (I, II, III, aVR, aVL, aVF and V_1), were analyzed for CSR and PB. A prior study by our group found the correlation between 12-lead ECG and 7-lead ECG for CSR to be (S_r= +73, p<.001) for hospitalized patients and (S_r = +.43, p<.001) for healthy individuals. Furthermore, the correlation between 12-lead PB and 7- lead PB was +.88, p<.001 for hospitalized patients and +.31, p=.002 for healthy individuals.

ECG Analysis. In order to analyze comparable periods of time between groups and to ensure quality of data used to derive CSR and PB we used H-Scribe (4.34 software, Mortara Instrument Inc, Milwaukee, WI) software to review ECG recording time and waveform data from the healthy group; and Lab Chart 7.2.1 software (AD Instruments) to review ECG recording time and waveform data from the ICU patient group. SuperECG research software (Mortara Instrument, Inc., Milwaukee, WI) was used to measure CSR and PB, and has been used by other investigators [16] to measure these respiratory variables. SuperECG uses changes in the QRS complex waveform to derive respiration and calculate CSR and PB episodes from continuous ECG data. CSR is defined as three or more consecutive cycles of hyperpnea/hypopnea/apnea respiration with a crescendo-decrescendo breathing pattern (Figure 2, top) and PB as three or more consecutive cycles of hyperpnea/hypopnea respiration with a crescendo-decrescendo breathing pattern (Figure 2, bottom).

Statistical Analysis

Continuous data is reported as mean ±SD. The Wilcoxon rank-sum test was used to compare group means for the variables monitoring time, age and body mass index (BMI) between the ICU and healthy groups. A Kruskal-Wallis rank test was used to compare the same variables among the ICU subgroups followed by Pairwise post hoc pairwise Wilcoxon comparisons with a Bonferroni correction. The Pearson Chi-square test was used to compare

group frequencies of the categorical variables gender and ethnicity. The Chi-square test followed by post hoc pairwise comparisons was used for the variable race and the Fisher exact test was used when the assumptions for Pearson Chi-square test were not met. Spearman rank order correlations were used to test the association between demographic variables and the variables of interest, CSR and PB. The incidence rate ratio between the groups in each analysis was calculated using negative binomial regression, since the count outcomes were strongly overdispersed [21]. Estimation was carried out using a nonparametric, bias-corrected bootstrap with 5,000 repetitions to reduce the potential influence of several cases with extreme outliers for both outcomes [22-24]. Threshold ordinal variables for the continuous variables CSR and PB were created. An ordinal logistic regression was used to test each threshold probability on all groups followed by Bonferroni post hoc pairwise comparisons. Statistical analyses were conducted using Stata Release 14 (StataCorp, TX, USA). A p-value <.05 was considered statistically significant.

Results

Aim 1: Frequency of ECG derived CSR and PB in a group of ICU patients and healthy participants.

Patient and participant characteristics. As shown in Table 1, the ICU group included more males (53.3% vs. 35.0%, p=.006) and fewer Caucasians (58.14% vs. 70%) that the healthy group. Patients in the ICU group were also of older age (60.56 vs. 33.96, p<.001) and had a higher BMI (27.41 vs. 24.78, p.005) than subjects in the healthy group.

Correlation of demographics with CSR and PB. A correlation between age and PB was significant (r_s = +.22, p<.001). Accordingly, we controlled for age and BMI in the following

analyses. In addition, although the monitoring time was similar between the two groups (22.43 hours vs. 23.66 hours, p<.001) they were significantly different; as a result, CSR and PB counts were adjusted in the negative binomial regression model to account for differences in ECG monitoring time.

Frequency of CSR and PB. Patients in the ICU group had a higher CSR average count in a 24 hour period (2.10 vs. 1.19, p=.20) and a higher PB average count in a 24 hour period (17.59 vs. 9.28, p=.002) than individuals in the healthy group (Table 2).

Aim 2: Determining whether CSR and PB differ between healthy individuals and ICU patients. Regression showed ICU patients had 1.71 times more CSR (CI=.95-3.52) and 1.35 times more PB (CI=1.07-1.69) than participants in the healthy group. In addition, people experienced 1.15 more PB episodes per every year of age increase (CI=1.01-1.02) (Table 3).

Aim 3: Determining if CSR and PB differ among ICU patients with a cardiovascular, neurological/neuro-surgical or medical/surgical discharge diagnosis. We reviewed patient's final discharge diagnosis and separated the ICU group into three sub-groups: a cardiovascular group, a neurological/neuro-surgical group, and a medical/surgical group.

Patient and participant characteristics. The ICU subgroups had similar gender, racial, and ethnic compositions. The subgroups differed significantly in age (p<.01) and patients in the cardiovascular subgroup were of higher age than patients in the neurological/neuro-surgical subgroup (70 vs. 58, p=.007) and patients in the medical/surgical subgroup (70 vs. 59, p=.003). BMI was not significantly different among the subgroups. Monitoring time was not found to be significantly different among the subgroups but the monitoring time ranged between 18 and 24 hours for all ICU patients. Age and BMI were controlled for in further analyses because age was significantly different among the subgroups and BMI has been correlated to central sleep CSA

by prior research groups [25-26]. To allow for unbiased analyses among the subgroups we adjusted for monitoring time in all subsequent analyses.

Frequency of CSR and PB. Mean daily CSR was not significantly different among the cardiovascular, neurological/neuro-surgical and medical/surgical subgroups (4.58 vs. 2.17 vs. 1.44). However, mean daily PB episodes were significantly different ($p<.001$) and pairwise Wilcoxon test showed that the cardiovascular subgroup had significantly more PB episodes a day than the medical/surgical subgroup (31.38 vs. 13.41, $p<.001$) and that the neurological/neuro-surgical subgroup had more PB episodes a day than the medical/surgical group (18.96 vs. 13.1, $p=.01$) (Table 4).

Bootstrapped regression analyses were used to analyze CSR and PB counts among 24 (14.0%) patients in the cardiovascular group, 52 (30.2%) patients in the neurological/neuro-surgical group, and 96 (55.8%) patients in the medical/surgical group. A large effect size [27-29] was found among patients in the cardiovascular group, who had 3.15 times more CSR than patients in the medical/surgical group (CI=.56-10.15) and two times more CSR than the patients in the neurological/neuro-surgical group (CI=.33-7.71). Also, patients in the neurological/neuro-surgical group had 1.58 times more CSR than patients in the medical/surgical group (CI=.67-3.31) (Table 5).

Regression also revealed that patients in the cardiovascular group had 2.2 times more PB than patients in the medical/surgical group (CI=1.31-3.37) and 1.46 times more PB than patients in the neurological/neuro-surgical group (CI=.85-2.35). Moreover, patients in the neurological/neuro-surgical group had 1.50 times more PB than patients in the medical/surgical group (CI=1.06-2.19) (Table 5).

Examination of CSR frequencies measured in the healthy and ICU groups showed that

2% of the healthy participants had five or more episodes of CSR a day in comparison to 9.4% patients with a medical/surgical discharge diagnosis, 17.3% with a neurological/neuro-surgical discharge diagnosis and 20.8% with a cardiovascular discharge diagnosis (Table 6).

Additionally, only 10% of healthy participants had a frequency of 15 or more episodes of PB a day in comparison to 25% of patients with a medical/surgical discharge diagnosis, 38.5% with a neurological/neuro-surgical discharge diagnosis and 66.7% with a cardiovascular discharge diagnosis (Table 7).

Discussion

To our knowledge this is the first study to use 7 lead continuous ECG monitoring to derive CSR and PB in an ICU group and a healthy group. In a prior study we used 12 lead continuous ECG data to derive CSR and PB; the mean daily values for the healthy participant group using 12 leads versus 7 leads are quite similar at (12 lead=1.04 vs. 7 lead=1.19) for CSR and (12 lead = 9.24 vs. 7 lead = 9.28) for PB. Consequently, using the already available 7 ICU monitor leads might be sufficient to derive CSR and PB in hospitalized patients. The 7 lead derived CSR daily mean of 1.19 episodes in the healthy population is in agreement of research by Haigney et al. [15] who reported a 12 lead derived CSR daily mean of 2.6 episodes.

Comparing the ICU patients to the healthy participants showed that daily mean CSR was not significantly higher in the ICU group versus the healthy group; this finding might be due to the nature of the ICU sample which included patients with cardiovascular, neurological and medical/surgical discharge diagnoses. In contrast, daily mean PB was significantly different between the ICU group and the healthy group; the higher PB frequency seen in critically ill patients might represent a natural physiological response to regulate arterial carbon dioxide and arterial oxygen levels [30].

Few studies have investigated CSR or PB in the ICU, and when doing so, careful criteria was selected to include patients with a primary cardiovascular [11, 14, 31], or neurological [32-37] or respiratory [15] condition. In this study we first compared all ICU patients which included cardiovascular, neurology/neurosurgical and medical/surgical conditions to healthy participants. Our results showed that ICU patients have 71% more CSR and 30% more PB than healthy participants; however significance ($p<.05$) was only achieved in the PB analysis. The mild effect size of 30% in the PB analysis and the lack of significance in the CSR analysis might be due to the wide range of diagnosis included in the ICU group, specifically the medical/surgical subgroup which included 96 patients (56% ICU group).

A clear difference emerged when subgrouping the ICU group by discharge diagnosis, showing that the cardiovascular subgroup had the highest daily mean values for both CSR and PB, followed by the neurological/neuro-surgical group and lastly by the medical/surgical group. These results are not surprising as sleep disordered breathing has been previously linked to cardiovascular disease in outpatients [1-9] and in critically ill patients [11, 14, 31].

There exist few studies that have investigated sleep disordered breathing in patients with cardiovascular conditions in the ICU. Padeletti et al. used overnight polysomnography and found a 97% CSA prevalence (>5 Apnea-Hypopnea Index) in patients with acute decompensated heart failure [11]. Areias et al. used the apnea link, a portable device, and found a 43.1prevalence (≥10 Apnea-Hypopnea Index) in patients with acute coronary syndrome [14]. Van Den Broecke et al. used sleepbox, portable device, and found that 82% had CSR or PB and 63% had ≥5 CSR or PB episodes in patients with acute coronary syndrome [31]. In congruence with these findings, we found that 21% of patients with a cardiovascular diagnosis had ≥5 episodes of CSR and 67% of patients had ≥15 episodes of PB.

Some researchers have studied abnormal breathing patterns in patients admitted to the ICU with neurological/neuro-surgical diagnoses. In 1976 Lee and colleagues used impedance pneumography to study CSR in patients with acute brain stem infarction and who had been admitted to the neurological ICU, he found 17% patients experienced CSR and another 17% PB [32]. North and Jeneett also used impedance pneumography to study CSR and PB in 225 patients admitted to the neurosurgical wards, however, his study included a wide range of diagnosis: head injury, subarachnoid hemorrhage, intracranial tumor and cerebrovascular disease. They found that 24% of patients had PB and 15% patients had CSR [33]. Vapalahti and Troupp found 32% CSR prevalence in patients with brain surgery and who had been referred to a neurosurgical clinic [34]. CSR has also been studied in patients with hemorrhages. In 2014 Shibazaki and colleagues used the SmartWatch, a portable device to measure sleep disordered breathing in patients admitted to the hospital with intracerebral hemorrhage, they found 94% of the patients had an apnea-hypopnea index of 5 or more and 30% had an apnea-hypopnea index of 30 or more [35]. There has also been interest in the investigation of sleep apnea in patients with Chiari malformations. Henriques-Filho & Pratesi used full night polysomnography to study sleep apnea in patients diagnosed with Chiari malformation. They found 59% of patients had central sleep apnea and an apnea-hypopnea index of ≥5 [36]. Lastly Lee et al. studied four children who had posterior fossa neoplasms and who underwent surgical resection. The children had a polysomnography study done after parents reported snoring, apnea and restlessness while asleep or clinicians described desaturation while undergoing tests. The investigators found that while sleeping all four children spent a percentage of their sleep time with sleep disordered breathing and included one child who spent 60% of their sleep time with CSA, one child who spent 5% of their sleep time with CSA, one child who spent 100% of their sleep time with OSA, and one

child who had a mix of both CSA and OSA [37].

Mahmoud et al. used Somnoscreen plus, a portable polysomnography to study sleep disordered breathing in patients admitted to the respiratory ICU. Mahmoud found that 39 out of 51 (76%) patients had OSA and 2 out of 51 (4%) had CSA. The top two co-morbidities experienced by patients in this study were cardiovascular in nature, the first hypertension (74.5%), and the second cardiovascular diseases (52.9%); thus indicating that patients with cardiovascular disease have more sleep apnea than patients with other diagnosis in a respiratory ICU [15].

In reviewing the effect sizes and statistical significance when comparing CSR and PB among the three subgroups, the analyses involving CSR had a medium (d=.05) and large (d≥.8) effect sizes but statistical significance (p<.05) was not achieved. In contrast, two out of three analyses involving PB achieved statistical significance (cardiovascular vs. medical/surgical and neurological/neuro-surgical vs. medical/surgical). In essence, the magnitude or large effect size for each analyses shows that patients in the cardiovascular subgroup had the largest frequency of CSR and PB, followed by the neurological/neuro-surgical subgroup and lastly by the medical/surgical subgroup. The lack of statistical significance might be due to the small subgroup sample sizes [28]. The difference between CSR and PB as measured in this study is that CSR has apnea while PB does not; our results might indicate that patients in the cardiovascular subgroup and the neurological/neuro-surgical subgroup have more marked PB as a way to maintain pH homeostasis and chemical control. Patients in our cardiovascular group have chronic comorbidities including heart failure and coronary artery disease. Research shows that patients with these comorbidities experience higher rates of CSR and PB as a way to maintain levels of carbon dioxide and oxygen in the arterial blood [40]. The neurological/neuro-

surgical group may have CSR and PB as a result of injury to the pons [32] or cerebellum [33, 37] which in turn impact the breathing center.

This study supports findings that CSR and PB are found in patients with a cardiovascular diagnosis [11, 14, 31] and that these abnormal respiratory patterns are also found in ICU patients with a neurological discharge diagnosis [32-37]. It is important to conduct further research to understand if CSR and PB might help identify patients who are at higher risk for adverse event in the ICU. In addition, patients who suffer CSR or PB experience apnea which leads to oxygen desaturation and sleep fragmentation. ICU patients suffer from sleep deprivation which in turn can affect the immune system and cognitive level [38-39]. Identifying patients who have sleep disordered breathing, OSA, CSA, CSR or PB may also help clinicians develop strategies to improve sleep in this group. Lastly, because only 2% of healthy participants had ≥5 episodes of CSR and 10% of healthy participants had ≥15 episodes of PB perhaps these cutoff values or thresholds could be used to identify abnormal respiratory thresholds in critically ill patients in the ICU.

Limitations. This study was limited by a small sample size of 100 healthy participants and 172 critically ill patients. In addition, only a small proportion of patients with a cardiovascular discharge diagnosis were included in this study. Healthy participant group health status was evaluated by patient self-report. CSR and PB were measured with research technology not yet validated with the gold standard, polysomnography.

Conclusion

This study demonstrates that measurement of ECG derived CSR and PB in critically ill patients while in the ICU is feasible. In addition, a discernible difference in CSR and PB frequencies among the groups were found in which critically ill patients had more CSR and PB

than healthy participants. Moreover, critically ill patients discharged with a cardiovascular diagnosis have more CSR and PB than patients with any other discharge diagnosis. Future research is needed to determine whether CSR or PB are linked to adverse patient outcomes in the critically ill and whether continuous measurement would be valuable in clinical practice.

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Figures and Tables

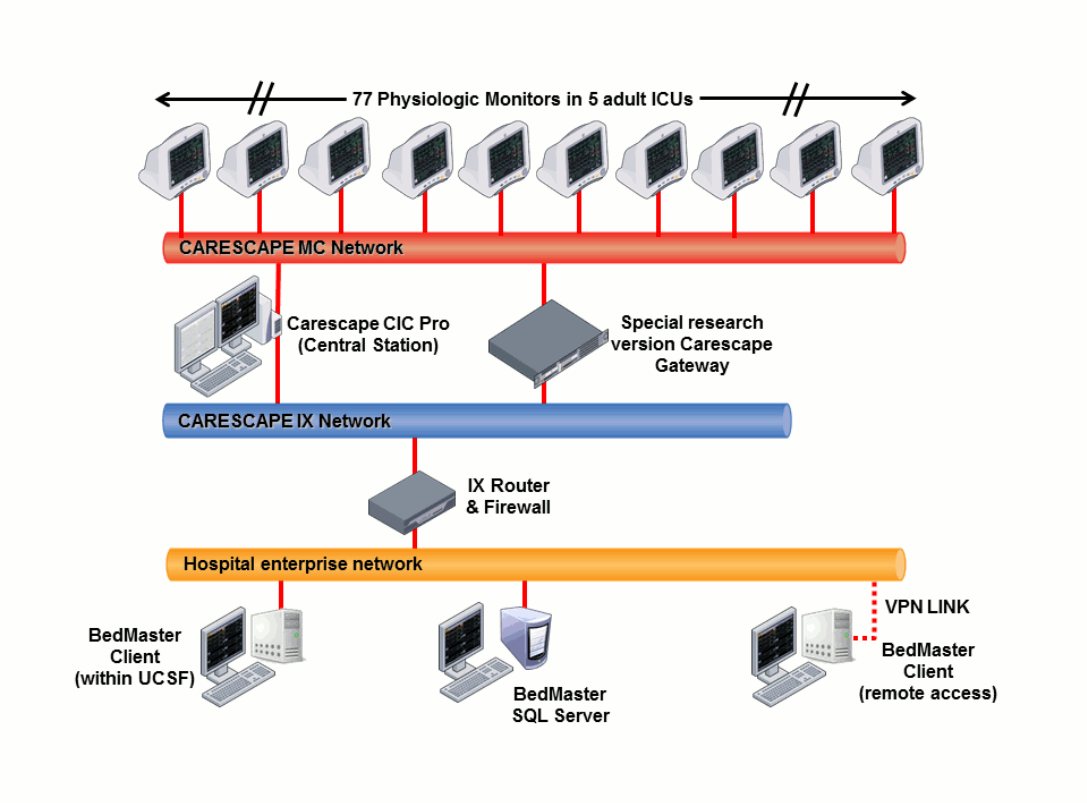

Figure 1. Hospital infrastructure to automatically store all physiologic monitor waveform and alarm data (used with permission from Drew BJ, et al. PLoS ONE 2014; 9(10): e110274).

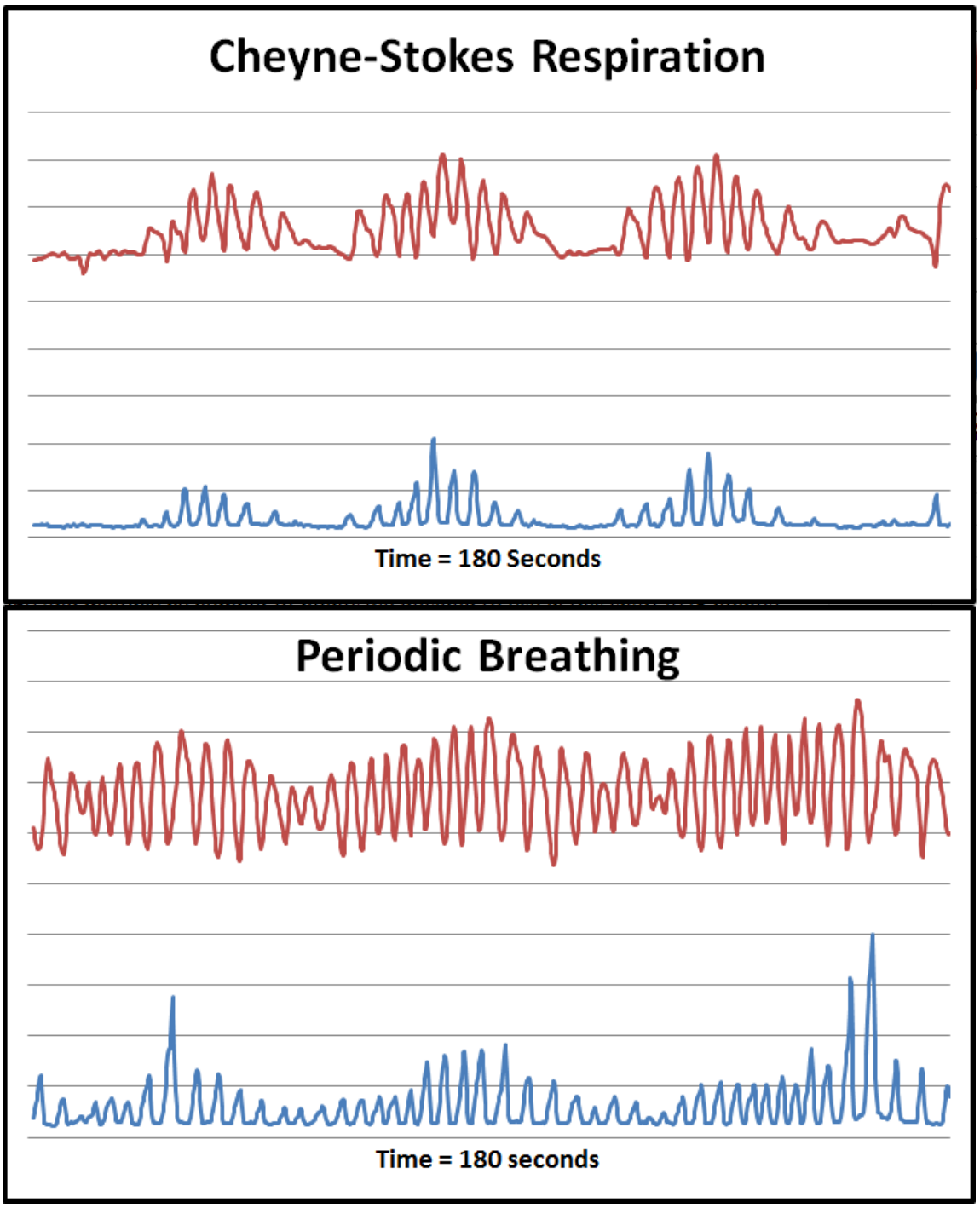

Figure 2. Cheyne-Stokes respiration and periodic breathing. Top: Cheyne-Stokes respiration, top; periodic breathing, bottom over 180 seconds. The top line is the mean QRS amplitude in ¼ microvolts and is used to derive respiratory effort. The bottom line is a myogram signal with arbitrary units used to detect respiratory effort. In Cheyne-Stokes respiration apnea is seen as a flat line in both the QRS amplitude and the myogram waveforms.

Table 1. Demographic characteristics of intensive care unit and healthy groups.

Variable	ICU	Healthy	P value
Number	172	100	
Age in years, mean ±SD / median	61±17 /61	34±10 /33	<.001[a]
Male, n (%)	90 (52)	35 (35)	.006[b]
Race			<.001[b]
White, n (%)	100 (58)	70 (70)	H>ICU[c]
African American, n (%)	15 (9)	11(11)	.54[c]
Asian, n (%)	31 (18)	19 (19)	.84[c]
Hawaiian/Pacific Islander, n (%)	3 (2)	0 (0)	.25[c,d]
Unknown	23 (13)	0 (0)	H<ICU[c,d]
Hispanic, n (%)	17 (10)	26 (26)	<.001[b]
Body Mass Index, kg/m², mean ±SD, median	27±7 /26	25±4 /24	.005[a]

Wilcoxon rank-sum test =a, Chi-square test=b, post hoc pairwise comparison of each category for race against the remaining categories=c, Fisher exact test =d. SD = standard deviation. H=Healthy group; ICU= Intensive care unit group.

Table 2. Frequency of Cheyne-Stokes respiration and periodic breathing in intensive care unit patients and healthy subjects.

Variable	ICU	Healthy	P value
Body Mass Index, kg/m², mean/SD, median	27±7 /26	25±4 /24	.005[a]
Monitoring time, mean hours/SD/median	22±2 /24	24±1 /24	<.001[a]
Cheyne-Stokes respiration, entire monitoring period, mean/SD/median	2±5 /1	1±1 /1	.20[a]
Cheyne-Stokes respiration, range	0-52	0-7	
Periodic breathing, entire monitoring period, mean/SD/median	18±19 /11	9±4 /9	.002[a]
Periodic breathing, range	2-110	1-19	

Wilcoxon rank-sum test =a. ICU= Intensive care unit group; SD = standard deviation.

Table 3. Regression for Cheyne-Stokes respiration and periodic breathing in intensive care unit patients and healthy subjects.

Variable	Incidence Rate Ratio	Confidence Interval (Bias-Corrected)
Cheyne-Stokes respiration, Intensive Care Unit vs. Healthy Reference group, Healthy	1.71	.95-3.52
Periodic breathing, Intensive Care Unit vs. Healthy Reference group, Healthy	1.35	1.07-1.69

Table 4. Baseline characteristics of intensive care unit groups.

Variable	Cardiovascular	Neurological/ Neurosurgical	Medical/Surgical	P value
Monitoring time, mean hours ±SD/median	23±2 /24	22±2 /24	23±2 /24	.39[a]
Cheyne-Stokes respiration, entire monitoring period, mean ±SD/median	5±11 /0	2±4 /1	1±3 /5	.69[a]
Cheyne-Stokes respiration, range	0-52	0-22	0-14	
Periodic breathing, entire monitoring period, mean ±SD/median	31±26 /29	19±19 /13	13±15 /9	<.001[a] C>MS[b] N>MS[b]
Periodic breathing, range	3-89	2-103	2-110	

Kruskal Wallis rank test =a, Pairwise Wilcoxon test=b ($p<.017$ considered significant). SD = standard deviation; C = Cardiovascular; N = Neurological/Neuro-surgical; MS = Medical/Surgical

Table 5. Regression for Cheyne-Stokes respiration and periodic breathing in cardiovascular, neurological/neuro-surgical and medical/surgical patients.

Groups	Incidence Rate Ratio	Confidence Interval (Bias-Corrected)
Cheyne-Stokes respiration, Medical/Surgical vs. Cardiovascular Reference group, Medical/Surgical	3.15	.56-10.15
Cheyne-Stokes respiration, Medical/Surgical vs. Neurological/Neurosurgical Reference group, Medical/Surgical	1.58	.67-3.31
Cheyne-Stokes respiration, Neurological/Neurosurgery vs. Cardiovascular Reference group, Neurological/Neurosurgical	2.00	.33-7.71
Periodic breathing, Medical/Surgical vs. Cardiovascular Reference group, Medical/Surgical	2.20	1.31-3.37
Periodic breathing, Medical/Surgical vs. Neurological/Neurosurgical Reference group, Medical/Surgery	1.50	1.06-2.19
Periodic breathing, Neurological/Neurosurgery vs. Cardiovascular Reference group, Neurological/Neurosurgical	1.46	.85-2.35

Table 6. Cheyne-Stokes respiration thresholds in intensive care unit and healthy groups.

Cheyne-Stokes respiration (# Episodes)	Cardiovascular N (%)	Neurological/ Neurosurgical N (%)	Medical/ Surgical N (%)	Healthy N (%)	P Value
0	13(54)	22(42)	48(50)	29(29)	NS[a]
1 – 4	6(25)	21(40)	39(41)	69(69)	<.001[a] H>CV[b] H>NNS[b] H>MS[b]
≥5	5(21)	9(17)	9(9)	2(2)	NS[a]

Ordinal logistic regression=a, post hoc pairwise comparison of each threshold category for Cheyne-Stokes respiration against the remaining threshold categories=b ($p<.0125$ considered significant). H=healthy; CV=cardiovascular diagnosis group; NNS=neurology/neurosurgical diagnosis group; MS= medical/surgical diagnosis group; NS=not significant.

Table 7. Periodic breathing thresholds in intensive care unit and healthy groups.

Periodic Breathing (#Episodes)	Cardiovascular N (%)	Neurological/ Neurosurgical N (%)	Medical/ Surgical N (%)	Healthy N (%)	P Value
0	0(0)	0(0)	0(0)	0(0)	NA
1 – 14	8(33)	32(62)	72(75)	90(90)	<.001[a] H>CV[b] H>NNS[b] MS>CV[b]
≥15	16(67)	20(38)	24(25)	10(10)	<.001[a] CV>H[b] NNS>H[b] CV>MS[b]

Ordinal logistic regression=a, post hoc pairwise comparison of each threshold category for periodic breathing against the remaining threshold categories=b ($p<.0125$ considered significant). H=healthy; CV=cardiovascular diagnosis group; NNS=neurology/neurosurgical diagnosis group; MS= medical/surgical diagnosis group; NS=not significant. NA=not available.

Chapter 4:

Value of ECG-Derived Cheyne-Stokes respiration and Periodic Breathing in Predicting Adverse Outcomes in Hospitalized Intensive Care Unit Patients

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Target Journal**:** Journal of Electrocardiology

Keywords: ECG, Cheyne-Stokes, periodic breathing, disordered breathing, respiration, intensive care unit.

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Abstract

Background: It has been reported that signs of patient deterioration are likely present before a hospital cardiopulmonary arrest, yet clinicians may not be aware. Cheyne-Stokes respiration (CSR) and periodic breathing (PB) are associated with an increased risk for mortality and a higher susceptibility to arrhythmias in out-patients with heart failure, renal failure and stroke, yet, no study has investigated whether CSR or PB can predict critically ill patients at risk for acute deterioration. We studied whether CSR or PB can identify patients who may experience an adverse event in the intensive care unit (ICU).

Methods: SuperECG software was used to derive CSR and PB from continuous bedside monitoring electrocardiographic (ECG) data in 172 patients admitted to the ICU. The electronic medical record was used to identify 24 (14.0%) patients who suffered an adverse event, defined as cardiac arrest, emergency endotracheal intubation, prolonged mechanical ventilation post-surgery, all cause in-hospital mortality and all-cause 30 day mortality) Negative binomial regression analysis was used to compare mean CSR and PB episodes between ICU patients who experienced an adverse event to those who did not experience an adverse event. Survival curves were analyzed with the Kaplan-Meier test and groups compared with the Log Rank test. The Cox Proportional Regression Model was used to analyze the prognostic value of CSR and PB to adverse event.

Results: Patients who had an adverse event had 2 times more CSR (CI= .58 - 5.47) and .73 times more PB (CI= .47 – 1.07) than patients who did not suffer an adverse event. Patients who had more than 5 episodes of CSR had a higher adverse event rate than patients who had less than 5 CSR episodes (21.7% vs. 12.8%, log rank, p=.52). Risk for adverse event increases by 4% for every CSR episode (CI = .99-1.08, p=.07).

Conclusion: CSR, detected with bedside ECG data, may be a useful measure to identify ICU patients at risk for adverse events. Further research and a larger sample size are needed to further understand the predictive value of both CSR and PB in the critically ill.

Introduction

The National Patient Safety Agency reports that 11% of in-hospital deaths occur as a result of patient deterioration that is not recognized [1]. In the Intensive Care Unit (ICU) where patients with the highest risk for deterioration and death are treated, clinicians rely on physiologic monitoring devices, or bedside monitors, to detect cardiac arrhythmias and acute vital sign changes. Cheyne-Stokes respiration (CSR) is an abnormal breathing pattern that has been observed and investigated in ICU settings [2-3]. During normal respiration, oxygen and carbon dioxide levels are kept in balance. However, if the central nervous system becomes dysfunctional chemoreceptors may sense the amount of carbon dioxide in the blood inadequately, and overly respond or hyperventilate. Hyperventilation can result in either below-apnea-threshold hypocapnia and periodic breathing (PB) or above-apnea-threshold hypocapnia and CSR. Both PB and CSR have a crescendo-decrescendo breathing pattern; however, CSR is uniquely characterized by a period of apnea (Figure 1) [4].

The high patient acuity seen in the ICU setting is a barrier to commonly used CSR and PB measurement devices such as the gold standard polysomnography (PSG) and unattended sleep studies using screening devices; hence very few studies in this population and setting exist [5-6]. We have shown that research software (SuperECG, Mortara Instrument, Milwaukee, WI) that uses continuous acquired hospital ECG monitor data to derive CSR and PB and can be used to study CSR and PB in healthy, acute and critically ill patients. In an expansion of these prior studies we examine the following research questions:

1. Do patients who have an adverse event (cardiac arrest, emergency endotracheal intubation, unexpected prolonged mechanical ventilation post-surgery, all cause in-hospital mortality

and all-cause 30 day mortality) experience different CSR or PB counts than ICU patients who do not have adverse event?

2. Is adverse event outcome probability different in ICU patients comparing patients with ≤ 5 CSR episodes to patients with > 5 CRS episodes?
3. Is adverse event outcome probability different in ICU patients comparing patients with ≤ 15 PB episodes to patients with > 15 PB episodes?
4. Effect of CSR and PB to time to adverse event.

Monitoring for CSR and PB using continuous ECG monitoring in critically ill patients may help identify patients who are at greater risk of adverse outcome and help clinicians guide their plan of care.

Methods

Study design. Existing data from a prior study entitled *Analysis of patient monitor alarms in adult intensive care units* was used for this study, the design of which has been described previously [7]. The data for this study was prospectively collected to examine alarm rates generated from bedside monitoring devices in the ICU [7]. The university's Institutional Review Board approved the study. In order to include all consecutive patients admitted to the ICU a waiver of consent was approved by the university's Committee on Human Research.

Study setting and population. This study included all patients, 18 years of age and older who were admitted to one of the five adult ICUs during March 2013. The five adult ICU's include two medical-surgical units (32 beds), one cardiac care unit (16 beds), and two neurological/neuro-surgical units (29 beds) [7].

Study protocol. Routine care in the ICU units included continuous ECG monitoring with a 5-electrode lead configuration resulting in the acquisition of 7 Mason-Likar leads (leads I, II,

III, aVR, aVL, aVF and V_1). Solar 8000i monitors (version 5.4 software, GE Healthcare, Milwaukee, WI) were used to monitor patients, CARESCAPE Gateway system (GE Healthcare, Milwaukee, WI) was used to securely transfer in-network data to an external server with BedMasterEx software (Excel Medical Electronics, Inc, Jupiter, FL) (Figure 2) [7]. These data were stored in flat file format, and then extracted in Extensible Markup Language (XML) file format. The investigators converted the XML files into binary files (AD Instruments, Dunedin, New Zealand) and used Lab Chart 7.2.1 software (AD Instruments) to review the stored ECG recordings for time and waveform data. The electronic medical record (Epic software, Madison, WI) was used to obtain patient's demographic, clinical data, and adverse events.

Adverse Events. Adverse events were obtained from electronic health records and could include any one of the following:

- Cardiac arrest: Patients requiring cardiopulmonary resuscitation, defibrillation and advanced cardiac life support medication administration.
- Emergency endotracheal intubation: Patients requiring endotracheal intubation followed by mechanical ventilation (ECG derived CSR and PB were not measured while patients were mechanically ventilated).
- Prolonged mechanical ventilation post-surgery: Patients requiring mechanical ventilation during surgery and who had prolonged ventilated post-surgery upon return to the ICU. (ECG derived CSR and PB were not measured while patients were mechanically ventilated).
- All cause in-hospital mortality: death during hospital admission.
- All-cause 30 day mortality: death within 30 days after hospital discharge.

Adverse events were identified through thorough review of the electronic medical record by reviewing procedure notes, flowsheets, medication administration record, clinician's progress

notes and clinician's discharge note. While each adverse event was examined, due to the low number of adverse event per category a composite adverse event variable was also created for analysis. In patients who suffered multiple adverse events the first adverse event in the electronic medical record was selected for analysis. An Acute Physiology and Chronic Health Evaluation (APACHE III) score was calculated from the electronic medical record and used to control patient acuity on admission to the ICU.

ECG Analysis. Subtle changes in ECG waveforms occur during inspiration and expiration and can be captured during continuous ECG data acquisition. SuperECG software was used in this study to derive CSR and PB and has been previously studied by Haigney et al [8]. SuperECG software (Mortara Instrument Inc.) uses QRS beat to beat changes in morphology to derive CSR and PB. In this study CSR is defined as three or more consecutive cycles of hyperpnea/hypopnea/apnea respiration with a crescendo-decrescendo breathing pattern (Figure 3) and PB as three or more consecutive cycles of hyperpnea/hypopnea respiration with a crescendo-decrescendo breathing pattern (Figure 4). The presence of apnea characterizes a CSR cycle and is missing in the PB cycle.

Statistical Analysis

Continuous data is reported as means ± standard deviation (SD). The variables age, body mass index and time monitored were not normally distributed; accordingly, the Wilcoxon rank-sum test was used to compare group mean ranks between the groups. The Pearson Chi-square test was used to compare group proportions for the categorical variables gender and ethnicity. The Chi-square test was used to test the variable race between the two groups followed by post hoc pairwise comparisons to see where the differences were while the Fisher exact test was used when the assumptions for Pearson Chi-square test were not met. The incidence rate ratio between

patients who experienced an adverse event versus patients who did not experience an adverse event was calculated using negative binomial regression, because the count outcomes were strongly over-dispersed [9]. Estimation was carried out using a nonparametric, bias-corrected bootstrap with 5,000 repetitions to reduce the potential influence of several cases with extreme outliers for both outcomes [10-12]. The Kaplan Meier method was used to analyze time to adverse event. The log rank test was used to do a comparison between patients who had ≥5 CSR episodes versus patients who had <5 CSR episodes; and to compare patients who had ≥15 PB episodes versus patients who had <15 PB episodes. Cox proportional hazard univariate analysis was used to test CSR, PB, age, body mass index, heart rate, systolic blood pressure and blood urea nitrogen as independent predictors of adverse event. Statistical analyses were conducted using Stata Release 14 (StataCorp, TX, USA). A p value of <.05 was considered statistically significant; however more liberal alpha levels have been used when sample sizes are small [13-15].

Results

A total of 461 patients were monitored in the ICU during March 2013 (range one to 31 days). However, because the focus of this study was to determine the effect of CSR and PB before an adverse event, we restricted our analysis to the first 48 hours of ICU admission. Of the 461 patients, 176 (39%) patients were excluded because their continuous ECG recording lasted less than 18 hours, which we determined to be an inadequate period of time to observe CSR and PB. In addition, 98 (21%) patients were excluded due to their inability to breathe spontaneously and required need for breathing support from a ventilator (bi-level positive airway pressure machine or continuous positive airway pressure machine). Finally, 15 (3%) patients were excluded because their baseline rhythm was atrial fibrillation or ventricular paced rhythms,

which cannot be analyzed to for ECG derived CSR and PB with SuperECG software. Hence, the sample available for this analysis was 172 patients (37%).

Aim 1: Do patients who have an adverse event (cardiac arrest, emergency endotracheal intubation, unexpected prolonged mechanical ventilation post-surgery, all cause in-hospital mortality and all-cause 30 day mortality) experience different CSR or PB counts than ICU patients who do not have adverse event?

Adverse events. Of the 172 ICU patients, 148 (86%) did not experience an adverse event. A total of 24 (14%) had at least one adverse event; 19 (11.0%) had one adverse event, 4 (2.3%) had two adverse events and 1 (.6%) had three adverse events. For patients who had more than one adverse event we choose the first adverse event for analysis. Table 1 shows all adverse event counts and adverse event counts chosen for analyses of aim 2, 3 and 4. Out of the 24 adverse events chosen for analyses there were 3 (1.7%) cardiac arrest with cardiac resuscitation; 4 (2.3%) acute respiratory distress and emergency endotracheal intubation; 6 (3.5%) surgery with general anesthesia requiring prolonged mechanical ventilation post-surgery; 7 (4.1%) in-hospital mortality and 4 (2.3%) 30-day post-hospital discharge mortality. Due to the small number of cases for every adverse event category we created a composite variable of all adverse events; this variable includes 24 patients (14%) who had at least one adverse event and was used for analyses in this study.

Patient and participant characteristics. Table 2 shows demographic and the respiratory variables. Demographic variables were not significantly different between the 24 patients who had an adverse event and the 148 patients who did not have an adverse event.

Monitoring time between groups. ECG monitoring time was not normally distributed with patients who did not experience an adverse event having a mean monitoring time of 22.24

hours and a median monitoring time of 23.88 hours; moreover, monitoring time ranged between 18 and 24 hours and was found to be significantly different between the two groups (adverse event group 23.63 hours vs. no adverse event group 22.24 hours, p=.002); as a result CSR and PB counts were adjusted in the following regression analysis .

Frequency of CSR and PB. Mean CSR episodes between the two groups were not significantly different; however, patients who had an adverse event had more CSR than patients who didn't have an adverse event (3.96 vs. 1.80, p=.80). Inversely, patients who had an adverse event had fewer episodes of PB than patients who didn't have an adverse event (14.21 vs. 18.14, p=.29) (Table 3)

Regression analyses. Regression showed that the ICU patients who an adverse event had a large incidence rate ratio (effect size) [16-18] of 2.0 times more CSR (CI= .58 - 5.47) and 0.73 times more PB (CI= .47 – 1.07) than patients who didn't have an adverse event (Table 4).

Aim 2: Is adverse event outcome probability different in ICU patients comparing patients with ≤ 5 CSR episodes to patients with > 5 CRS episodes?

Prior work from our group showed that 98% healthy individuals have < 5 episodes of CSR a day. Using these values from a healthy group, the ICU patients were divided by CSR groups based on number of CSR/day, and included a subgroup of 23(13.3%) patients who had ≥ 5 CSR episodes during monitoring time and a subgroup of 149 (86.6%) patients who had < 5 CSR episodes during the monitoring period.

Demographic variables were not different between the subgroups; and more patients who had had ≥ 5 CSR episodes were mechanically ventilated post-surgery than patients who have less < 5 CSR episodes per day (13.1% vs. 2.7%, p=.02) (Table 4).). Figure 2 shows the Kaplan Meier survival curves for the two subgroups; among the 23 patients who had had ≥ 5 CSR

episodes, five had an adverse event (21.7%); whereas from the 149 patients who had < 5 CSR episodes, 19 had a an adverse event (12.8%). While a higher proportion of the group with ≥ 5 CSR episodes had an event as compared to those with ≤ 5 CSR, the two subgroups did not differ significantly in their adverse event rate (log rank, p=.52) (Figure 2).

Aim 3: Is adverse event outcome probability different in ICU patients comparing patients with ≤ 15 PB episodes to patients with > 15 PB episodes?

Again, prior work from our group showed that 91% of healthy individuals have < 15 episodes of PB a day. Therefore, we also divided the original group of 172 ICU patients into a subgroup of 60 (34.9%) patients who had ≥ 15 episodes of PB during monitoring time and 112 (65.1%) patients who had < 15 episodes of PB during monitoring time. Comparison between the two subgroups showed that the patients who had ≥ 15 episodes of PB were older than patients who had < 15 episodes of PB (64.67 vs. 58.36, p=.03) (Table 5); however, due to the small sample size of the subgroups, age was not controlled for. Comparing the subgroups showed that out of the 60 patients who had had ≥ 15 episodes of PB, 8 had an adverse event (event rate 13.3%); and out of the 112 patients who had < 15 episodes of PB, 16 had an adverse event (event rate 14.3%). These two subgroups did not differ significantly in their adverse event rate (log rank, p=.48) (Figure 3).

Aim 4: Effect of CSR and PB on time to adverse event.

To control for patient's severity of disease on admission to the ICU the acute physiology, age, chronic health evaluation (APACHE) score III was calculated. Calculation of the APACHE score requires obtaining and scoring the patient's age, chronic health history, and 17 physiologic variables; the resulting score ranges from 0 to 299 with a higher score

symbolizing worse prognosis [19]. The physiologic variables albumin (g/dl), bilirubin (mg/dl), partial pressure of carbon dioxide (mmHg), partial pressure of oxygen (mmHg), and pH are required during the scoring but were often missing in this study's data set. Because only 31 out of 172 patients (18% of the sample) had all variables needed to calculate the APACHE III score and only six patients out of these 31 had an adverse event; consequently, the APACHE III score was not used to control for patient's severity of disease in this Cox regression analysis (Table 6 and 7).

Prior research groups have found age [20-22], body mass index [20, 22], heart rate [22], systolic blood pressure [22-23] and creatinine [23] to be predictive of time to adverse outcome when using univariate analysis. Consequently, we used univariate Cox proportional hazards regression analysis for these variables which are reported in table 8. In our analysis, CSR was the only variable that was close to achieve significance in predicting adverse event. Our results show that per every one CSR episode increase that a patient has their chances of adverse event increase by 4%. (CI = .99-1.08, p=.07), although statistical significance was .07 it has been documented that studies with small sample sizes have a higher chance of Type II error and setting a more liberal alpha level would be reasonable [13-15].

Discussion

Aim 1: Do patients who have an adverse event (cardiac arrest, emergency endotracheal intubation, unexpected prolonged mechanical ventilation post-surgery, all cause in-hospital mortality and all-cause 30 day mortality) experience different CSR or PB counts than ICU patients who do not have adverse event?

The presence of cardiac arrest and emergency endotracheal intubation are a great concern

to all clinicians in the ICU. Between 2000 and 2009, the inpatient cardiac arrest rate in the United States was 4.54 per 1,000 admissions. Although a hospital-wide response team was called in 78.2% of cases and chest compressions started in 97.1% of the responses, the median survival rate was only 18.8% [24]. It is important to have reliable tools such as CSR that can identify signs of deterioration in high acuity populations in the ICU and which could help clinicians improve patient's outcomes.

Although most of our results did not achieve statistical significance at the $p<.05$ level, the findings are supportive of work by other research groups. We found that patients who experienced an adverse event had two times the number of CSR episodes (CI= .58 - 5.47) when compared to patients who did not have an adverse event. A similar finding was reported by Amir et al, who found that heart failure patients who died had more CSR than those who survived p=.02 [25]. Ancoli-Israel also found that mortality increased from 37% in medical ward patients without CSR to 87% in medical ward patients with severe CSR [20]. Silva et al. found that congestive heart failure patients who survived had 32% CSR while non-survivors had 53% CSR [26].

Aim 2: Is adverse event outcome probability different in ICU patients comparing patients with ≤ 5 CSR episodes to patients with > 5 CRS episodes?

We found a higher proportion of patients, 21.7%, who had an adverse event in the high CSR threshold (≥5 episodes) versus 12.8% patients in the lower CSR threshold (<5 episodes) (log rank, p=.52). Although not significant, our results also support findings by several reseach groups including: a) Ancoli-Israel et al who found medical ward patients with severe CSR had significantly shorter time to adverse event (p=.043, mean follow up 2000 days) versus patients without severe CSR [20]; b) Brack et al, who found that heart failure patients who spent >10% of

the daytime in CSR lived shorter than patients who spent less than 10% of their daytime in CSR (mantel cox, p=.04, mean follow up 836 days) [27]; c) Poletti et al, who found that mortality was higher in congestive heart failure patients with CSR vs. patients without CSR (log rank, P<.01, mean follow up 33 months) [21]; d) Silva et al, found a higher mortality in congestive heart failure patients with CSR during daytime vs. those without CSR during the daytime (log rank, p=.01. mean follow up 25 months) [26]; e) Hanly and Zuberi-Khokar found a lower cumulative survival in 77.8% heart failure patients with CSR versus 14.3 heart failure patients without CSR (cox regression, p=.04, mean follow up 44 months) [28]; and f) Andreas et al, found that 20% of heart failure patients with > 20% CSR died versus 6.2% of patients with <20% CSR (chi square, p=.24, mean follow up 3 months) [29].

Aim 3: Is adverse event outcome probability different in ICU patients comparing patients with ≤ 15 PB episodes to patients with > 15 PB episodes?

Most research has focused in the study of CSR and not PB, which makes our study unique, and shows a gap in the literature for this type of disordered breathing. However, in this study, the event rate was not different between patients who had ≥ 15 episodes of PB (13.3%) versus those who < 15 episodes of PB (14.3%) (log rank, p=.48).

Kaplan-Meier analyses for event rate using a CSR threshold of ≥5 CSR vs. <5CSR or a PB threshold of ≥15 PB vs. <15PB may not be significant due to the samples small size, because the test does not take into account continuous data, or because the threshold used for analyses is inappropriate.

Aim 4: Effect of CSR and PB to time to adverse event.

The APACHE III score was calculated for the ICU patients in an effort to control for

severity of disease on admission to the ICU unit. However only 31 patients or 18% of the group had the required variables to calculate the APACHE score; while arterial blood gas variable data were missing in 90 patients (52.3%) and albumin and/or bilirubin variable data were missing in 51 patients or 29.7% of the sample. The inability to calculate the APACHE score on all patients is partially due to the large number of variables needed and which require clinician's order; which limits the researcher's ability to calculate severity of disease or evaluate for in-hospital mortality risk.

Cox regression showed that ICU patients have a 4% adverse event risk increase per every extra episode of CSR; our results support findings by Amir et al, where log Cheyne-Stokes breathing was found to be a predictor of mortality ($p=.02$) [25]; Brack et al, where having >10% CSR of the time was found to be a predictor of mortality ($p<.05$) [27]; and Poletti et al, where CSR was found to be a predictor of mortality ($p=.07$) [21].

Limitations. This study was limited by a small sample size of 172 ICU patients, of which only 24 experienced at least one adverse event. Patients were enrolled from highly specialized ICU's in a large academic medical center and therefore may not represent accurately critically ill patients in other hospitals. Target monitoring time was 24 hours but missing data resulting from patient procedures, surgeries, or bathing care resulted in inclusion of cases that had at least 18 hours of continuous ECG recording. Variables of interest, CSR and PB, were not measured with the gold standard, polysomnography. SuperECG can't be used in patients who have non-sinus-rhythm or paced ventricular rhythms. Variables used in the calculation of APACHE score and adverse event data was retrieved by one research nurse.

Conclusion

This study found a difference in the mean CSR and mean PB counts experienced by

patients who suffer an adverse event and those who didn't suffer an adverse event in the ICU. Furthermore, CSR can be useful in identifying patients at risk for adverse event in the ICU. Further research and a larger sample size are needed to further understand the predictive value of both CSR and PB in the critically ill. If CSR and PB prove valuable for early detection of patient deterioration, then the algorithm could be tested in a future prospective randomized clinical trial to determine whether monitoring these new parameters would lead to better patient outcomes.

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Figures and Tables

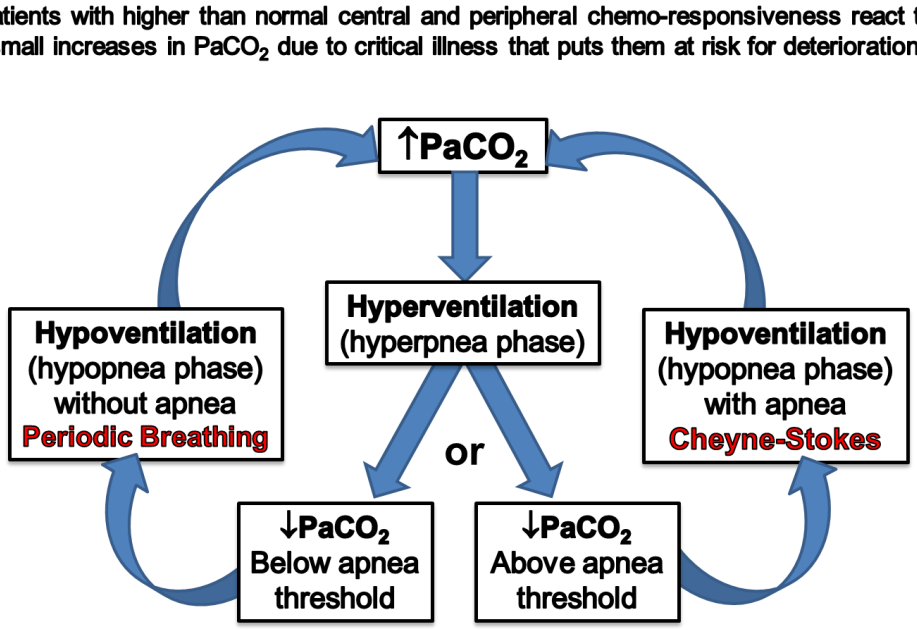

Figure 1. Cheyne-Stokes respiration and Periodic Breathing Model. By Barbara J. Drew, PhD, 2013.

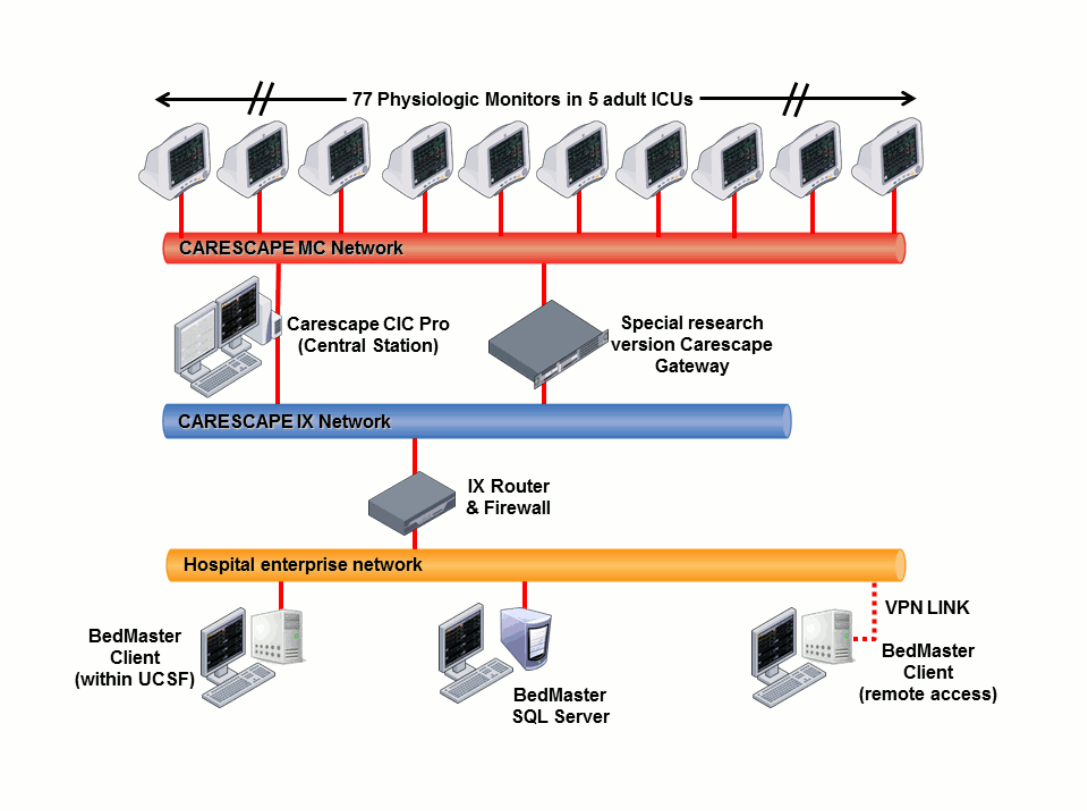

Figure 2. Hospital infrastructure to automatically store all physiologic monitor waveform and alarm data (used with permission from Drew BJ, et al. PLoS ONE 2014; 9(10): e110274).

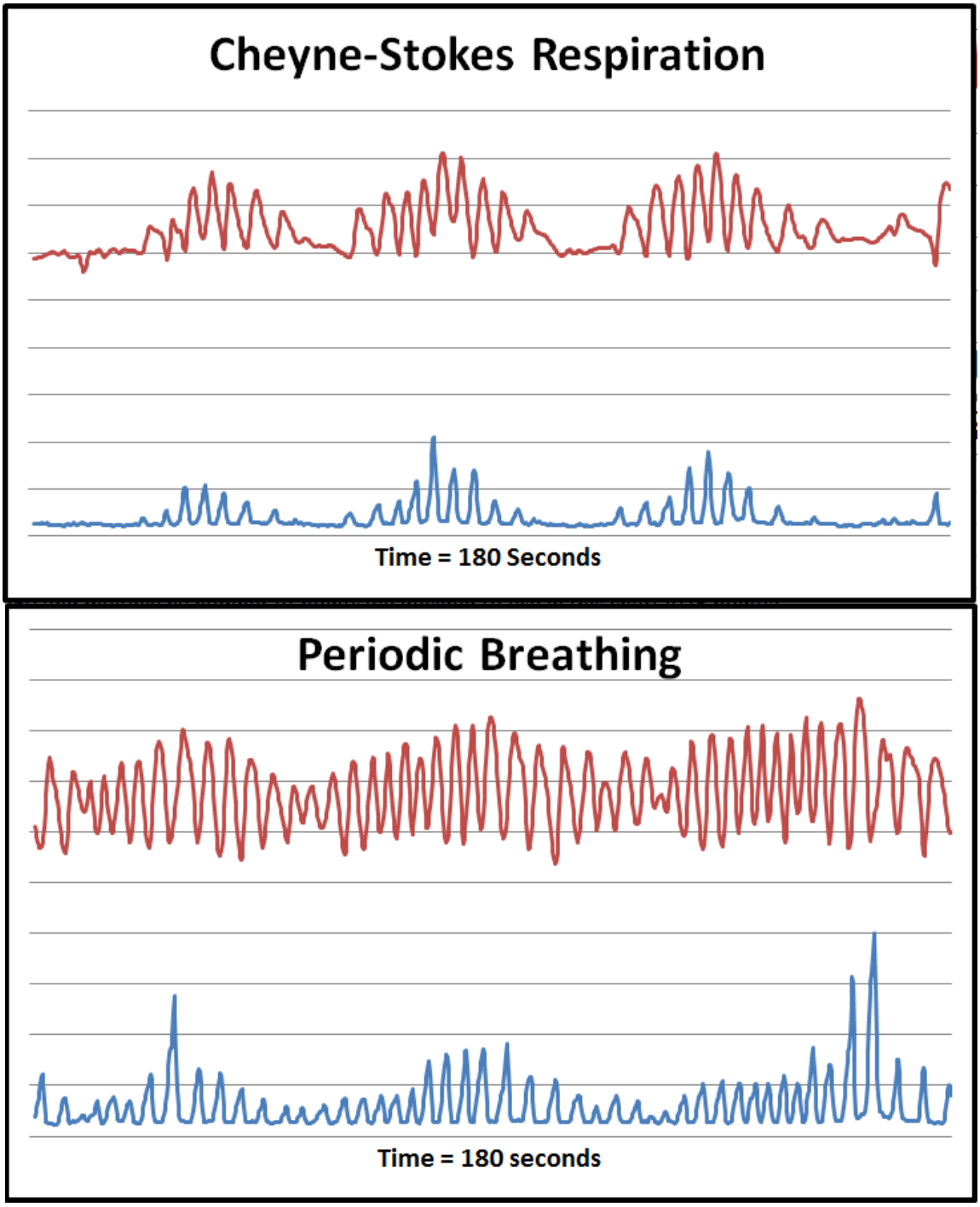

Figure 3. Cheyne-Stokes respiration and periodic breathing. Top: Cheyne-Stokes respiration, top; periodic breathing, bottom over 180 econds. The top line is the mean QRS amplitude in ¼ microvolts and is used to derive respiratory effort. The bottom line is a myogram signal with arbitrary units used to detect respiratory effort. In Cheyne-Stokes respiration apnea is seen as a flat line in both the QRS amplitude and the myogram waveforms.

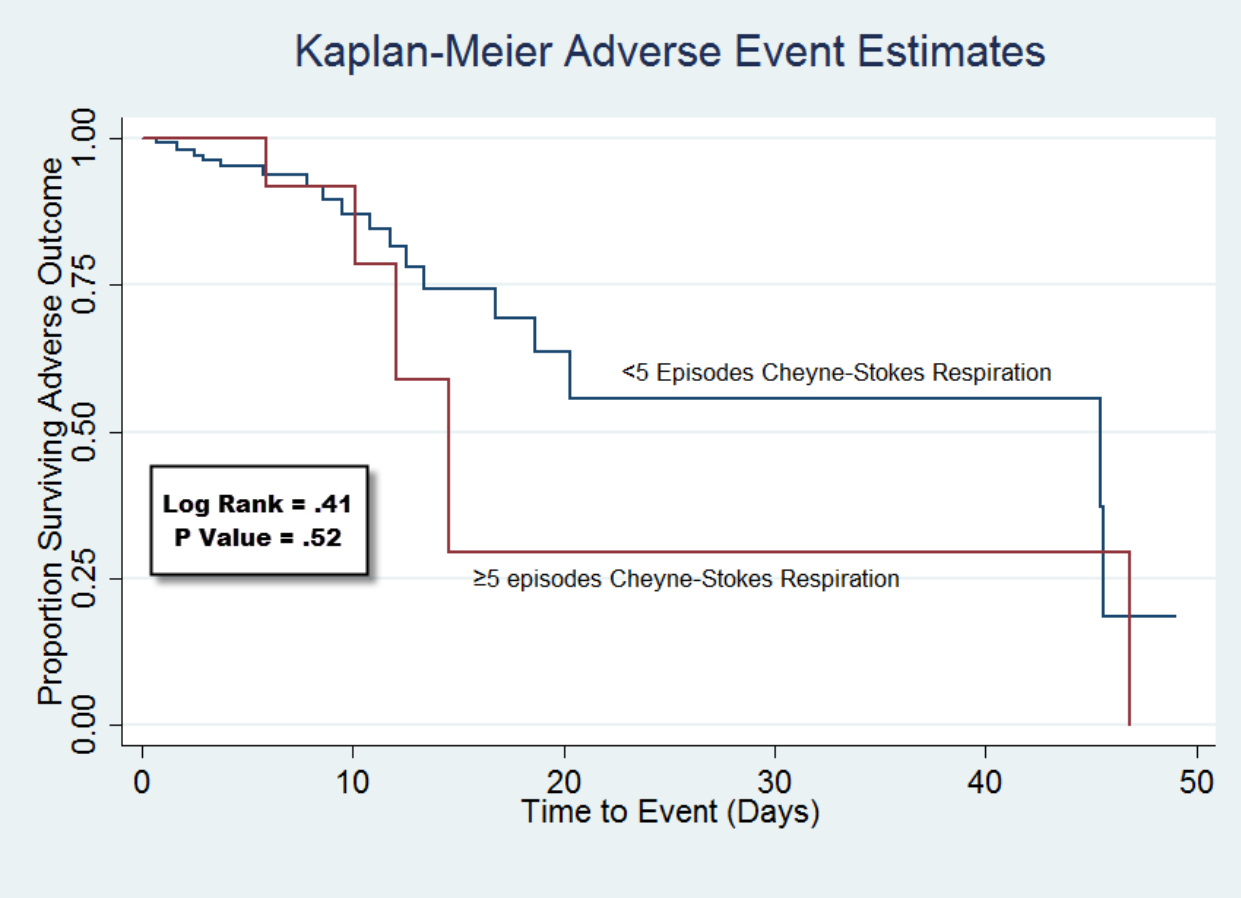

Figure 4. Cheyne-Stokes respiration and adverse event rate in intensive care unit patients (cardiac arrest, emergency intubation, continued mechanical ventilation post-surgery, in-hospital mortality and 30 day mortality). Kaplan-Meier survival estimates dichotomized as patients who had ≥ 5 episodes of Cheyne-Stokes respiration versus patients who had < 5 episodes of Cheyne-Stokes respiration over monitored time.

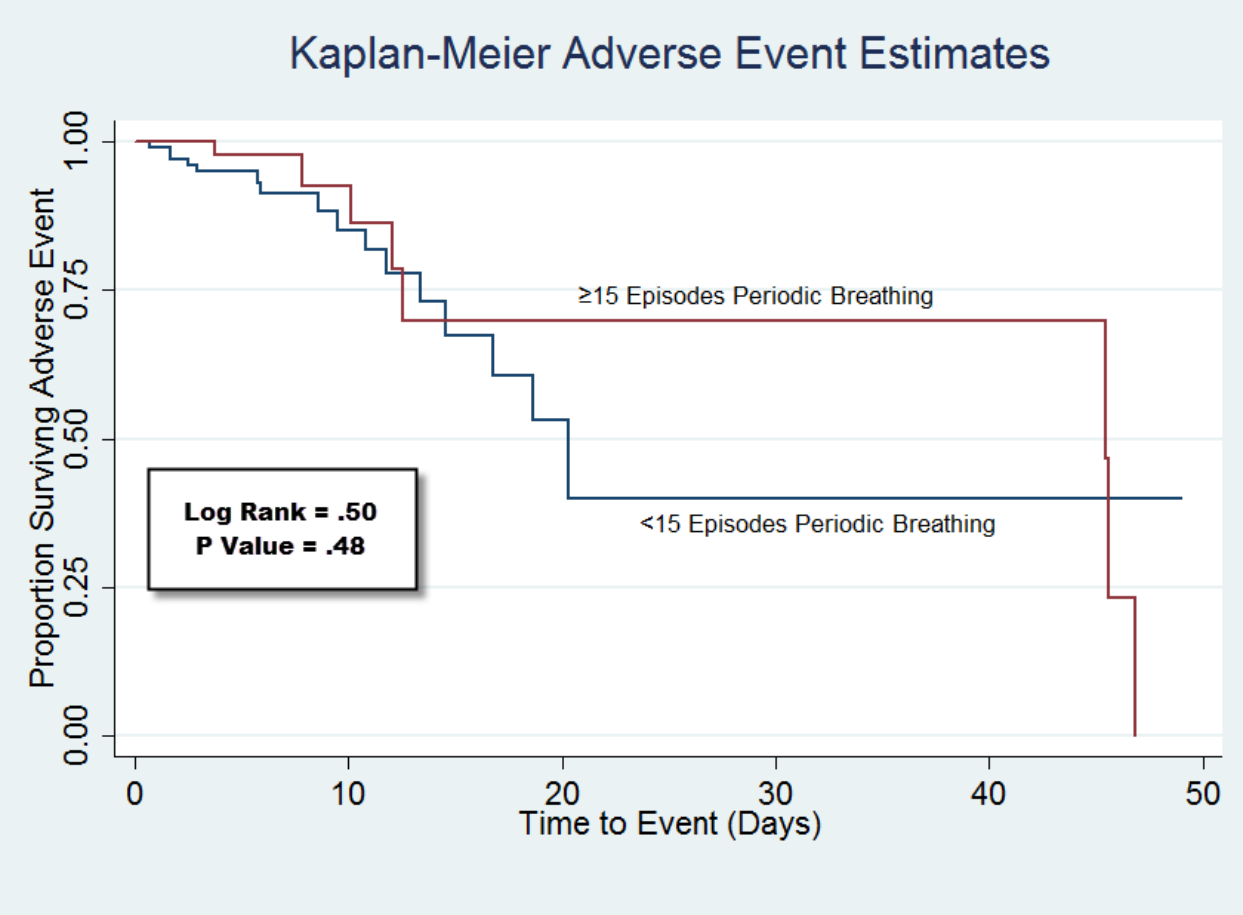

Figure 5. Periodic breathing and adverse event rate in intensive care unit patients (cardiac arrest, emergency intubation, continued mechanical ventilation post-surgery, in-hospital mortality and 30 day mortality). Kaplan-Meier survival estimates dichotomized as patients who had ≥ 15 episodes of periodic breathing versus patients who had < 15 episodes of periodic breathing over monitored time.

Table 1. 24 ICU patients who had a total of 31 adverse events.

Outcome	All events n (%)	First Event Selected for Analysis
Patients, n	24	24
Composite All Adverse Event	30 (100)	24 (100)
Cardiac Arrest	6 (20)	3 (13)
Emergency Endotracheal Intubation	4 (13)	4 (17)
Mechanical Ventilation Post-Surgery	7 (23)	6 (25)
All Cause In Hospital Mortality	9 (30)	7 (29)
All Cause 30 Day Mortality	4 (13)	4 (17)

For patients with multiple adverse event, the first adverse event to occur was selected for analysis under the artificially created variable name “composite all adverse event”.

Table 2. Demographic characteristics of 172 intensive care unit patients with and without an adverse event.

Variable	Composite All Adverse Events	No Adverse Events	P value
Number	24	148	
Age in years, mean ±SD/ median	65±18 /67	60±16 /61	.20[a]
Male, n (%)	12 (50.0)	78 (53)	.81[b]
Race			.99[b]
White, n (%)	14 (58)	86 (58)	.98[b]
African American, n (%)	2 (8)	13(9)	.94[c,d]
Asian, n (%)	5 (21)	26 (18)	.70[c,d]
Unknown	3 (13)	20 (14)	.89[c,d]
Hawaiian or Pacific Islander, n (%)	0 (0)	3 (2)	.48[c,d]
Hispanic, n (%)	3 (13)	14 (10)	.64[b,d]
Body Mass Index, kg/m², Mean ±SD, median	28±10 /26	27±7 /26	.99[a]

Wilcoxon rank-sum test =a, Chi-square test=b, post hoc pairwise comparison of each category for race against the remaining categories=c, Fisher exact test =d. SD = Standard deviation.

Table 3. Frequency of Cheyne-Stokes respiration and periodic breathing in 172 intensive care unit patients with and without an adverse event.

Variable	Composite All Adverse Events	No Adverse Events	P value
Monitoring time, mean hours ±SD/median	24±1 /24	22±2 /24	.002[a]
Cheyne-Stokes respiration, entire monitoring period mean ±SD/median	4/11/0	1/4/1	.80[a]
Cheyne-Stokes respiration, range	0-52	0-22	
Periodic breathing, entire monitoring period mean ±SD/median	14±13 /10	18±20 /11	.29[a]
Periodic breathing, range	2-46	2-110	

Wilcoxon rank-sum test =a. SD = Standard deviation.

Table 4. Regression for Cheyne-Stokes respiration and periodic breathing in 172 intensive care unit patients with and without an adverse event.

Variable	Incidence Rate Ratio	Confidence Interval (Bias-Corrected)
Cheyne-Stokes respiration, Adverse Event vs. no Adverse Event Reference group, ICU no adverse event	2.02	.58-5.47
Periodic breathing, Adverse Event vs. no Adverse Event Reference group, ICU no adverse event	0.73	.47-1.07

ICU= Intensive care unit.

Table 5. Demographic characteristics of intensive care unit patients who had ≥5 episodes of Cheyne-Stokes respiration and intensive care unit patients who had <5 episodes of Cheyne-Stokes respiration.

Variable	≥5 Episodes Cheyne-Stokes Respiration	<5 Episodes Cheyne-Stokes Respiration	P value
Number	23	149	
Age in years, mean ±SD/ median	63±14 /66	60±17 /61	.51[a]
Male, n (%)	14 (61)	76 (51)	.38[b]
Race			.67[b]
White, n (%)	16 (70)	84 (56)	.23[c]
African American, n (%)	2 (9)	13 (9)	.99[c,d]
Asian, n (%)	2 (9)	29 (19)	.21[c,d]
Unknown	3 (13)	20 (13)	.96[c,d]
Hawaiian or Pacific Islander, n (%)	0 (0)	3 (2)	.49[c,d]
Hispanic, n (%)	2 (9)	15 (10)	.84[b]
Body Mass Index, kg/m², mean ±SD, median	29±8 /29	27±7 /26	.29[a]

Table 6. Adverse event distribution in intensive care patients who had ≥5 episodes of Cheyne-Stokes respiration and intensive care unit patients who had <5 episodes of Cheyne-Stokes respiration.

Variable	≥5 Episodes Cheyne-Stokes Respiration	<5 Episodes Cheyne-Stokes Respiration	P value
Monitoring time, mean hours ±SD/median	22±2 /24	22±2 /24	.71[a]
Cheyne-Stokes respiration, entire monitoring period mean/SD/median	11±10 /7	1±1 /0	<.001[a]
Cheyne-Stokes respiration, range	5-52	0-4	
Periodic breathing, entire monitoring period mean ±SD/median	37±24 /36	15±/16 /10	<.001[a]
Periodic breathing, range	5-103	2-110	
All Adverse Event, n (%)	7 (23)	23 (77)	.27[b]
Cardiac Arrest, n (%)	2 (29)	4 (17)	.14[c,d]
Emergency Endotracheal Intubation, n (%)	0 (0)	4 (17)	.43[c,d]
Prolonged Mechanical Ventilation Post-Surgery, n (%)	3 (43)	4 (17)	.02[c,d]
All Cause In Hospital Mortality, n (%)	1 (14)	8 (35)	.84[c,d]
All Cause 30 Day Mortality, n (%)	1 (14)	3 (13)	.49[c,d]

Wilcoxon rank-sum test =a, Chi-square test=b, post hoc pairwise comparison of each category for race against the remaining categories=c, Fisher exact test =d. SD = Standard deviation.

Table 7. Demographic characteristics of intensive care unit patients who had ≥15 episodes of periodic breathing and intensive care unit patients who had less <15 episodes of periodic breathing.

Variable	≥15 Episodes Periodic Breathing	<15 Episodes Periodic Breathing	P value
Number	60	112	
Age in years, mean ±SD/ median	65±16 /66	58±17 /61	.03[a]
Male, n (%)	34 (57)	56 (50)	.40[b]
Race			.45[b]
White, n (%)	36 (60)	64 (57)	.72[c]
African American, n (%)	4 (7)	11(10)	.49[c,d]
Asian, n (%)	8 (13)	23 (21)	.24[c]
Unknown	10 (17)	13 (12)	.35[c]
Hawaiian or Pacific Islander, n (%)	2 (3)	1 (1)	.24[c,d]
Hispanic, n (%)	7 (12)	10 (9)	.57[b]
Body Mass Index, kg/m², mean ±SD, median	27±7 /26	28±8 /26	.77[a]

Table 8. Adverse events in intensive care patients who had ≥15 episodes of periodic breathing and intensive care unit patients who had <5 episodes of periodic breathing.

Variable	≥15 Episodes Periodic Breathing	<15 Episodes Periodic Breathing	P value
Monitoring time, mean hours ±SD/median	22±2 /24	23±2 /24	.91[a]
Cheyne-Stokes respiration, entire monitoring period mean ±SD/median	5±8 /2	1±1 /0	<.001[a]
Cheyne-Stokes respiration, range	0-52	0-7	
Periodic breathing, entire monitoring period mean ±SD/median	35±23 /28	8±3 /8	<.001[a]
Periodic breathing, range	15-110	2-14	
All Adverse Event, n (%)	13 (43)	17 (57)	.88[b]
Cardiac Arrest, n (%)	4 (31)	2 (12)	.01[c,d]
Emergency Endotracheal Intubation, n (%)	2 (15)	2 (12)	.52[c,d]
Mechanical Ventilation Post-Surgery, n (%)	2 (15)	5 (29)	.72[c,d]
All Cause In Hospital Mortality, n (%)	3 (23)	6 (35)	.92[c,d]
All Cause 30 Day Mortality, n (%)	2 (15)	2 (12)	.52[c,d]

Wilcoxon rank-sum test =a, Chi-square test=b, post hoc pairwise comparison of each category for race against the remaining categories=c (significance p<.01), Fisher exact test =d. SD = Standard deviation

Table 9. APACHE score calculated for patients who had all available data and also for those who were missing data.

Patients have:	Group 1 N=172	Group 2 N=82	Group 3 N=31
All variables available	N=31	N=31	N=31
Are missing variables albumin and bilirubin	N=51	N=51	
Are missing variables PCO2, PO2 and pH	N=90		

APACHE III = Acute Physiology, Age, Chronic Health Evaluation. Scoring System In Critically Ill Patients; PaCO2 = Partial pressure of carbon dioxide in the arterial blood; PaO2 = Partial pressure of oxygen in the arterial blood.

Table 10. Calculating APACHE III Score with Missing Data.

Variable	Group 1	Group 2			Group 3				
	All	AE	Number AE	All	AE	Number AE	All	AE	Number AE
Patients (N)	172	24	148	82	14	68	31	6	25
Mean	49.1	46.0	68.3	53.71	72.7	49.8	59.7	78.8	55.0
SD	22.8	21.5	21.1	21.0	17.5	19.6	22.4	22.3	20.3
Median	45	43	66	52	76.5	47	59	81	54
Min	0	0	38	9	45	9	24	45	24
Max	158	158	110	116	102	116	105	102	105

APACHE III = Acute Physiology, Age, Chronic Health Evaluation. Scoring System In Critically Ill Patients; Max= Maximum; Min= Minimum; N= Number of patient; PaCO2 = Partial pressure of carbon dioxide in the arterial blood; PaO2 = Partial pressure of oxygen in the arterial blood; SD= Standard deviation; AE= Adverse events.

Table 11. Unadjusted Risk for Adverse Event (Cox Regression) in 24 intensive care unit patients who had an adverse event and 148 intensive care unit patients who did not have an adverse event.

Variable	Hazard Ratio	95% Confidence Interval	P Value
Cheyne-Stokes respiration	1.04	.99-1.08	.07
Periodic Breathing	.99	.95-1.02	.40
Age	1.02	.99-1.05	.16
Body Mass Index. kg/m^2	.99	.93-1.06	.81
Heart Rate	1.00	.98-1.02	.87
Systolic Blood Pressure	1.00	.99-1.01	.82
Creatinine	1.01	.98-1.01	.56

Chapter 5: Conclusion

Electrocardiographic Derived Cheyne-Stokes Respiration and Periodic Breathing in Healthy, Hospitalized and Critically Ill Cohorts

In conclusion, the electrocardiographic (ECG) derived respiratory variables Cheyne-Stokes respiration (CSR) and periodic breathing (PB) were different among the three groups of interest. Patients hospitalized with acute coronary syndrome (ACS) had higher counts of CSR and PB than healthy participants and further analyses showed that those with a positive diagnosis of ACS had higher CSR and PB counts than patients who did not have an ACS diagnosis.

This study also showed that critically ill patients have higher counts of CSR and PB than healthy participants and further analyses showed that patients with a cardiac discharge diagnosis or a neurological/neuro-surgical discharge diagnosis have higher counts of CSR and PB than patients with a medical/surgical discharge diagnosis. Understanding which patients have a higher CSR and PB prevalence ensures that their monitoring is emphasized adequately.

Lastly, analyses showed that critically ill patients who suffered an adverse event had higher CSR counts, a threshold of five or more CSR episodes differentiated between the adverse event group and the no adverse event group, the risk of adverse event increases as CSR increases. These results did not gain statistical significance and might be due to the small sample size. Yet, both populations, hospitalized patients with symptoms of ACS and critically ill patients are both routinely monitored and monitoring for CSR and PB would be inexpensive and non-invasive. Larger sample sizes and analyses are needed to verify these findings.

Future work includes

- Prospectively following hospitalized patients from start of ICU admission to adverse event to understand CSR and PB daily changes in incidence
- Studying CSR and PB as risk predictors to adverse event in a large group allowing for multivariate analyses
- Studying hourly changes in CSR and PB rate in the hours prior to adverse event
- Studying CSR and PB in mechanically ventilated critically ill patients to understand prevalence and physiological background.

Clinicians rely on physiological monitoring devices to alert them to patient deterioration, but most physiological changes are recognized when patient deterioration is difficult to reverse. CSR and PB might provide an early warning sign before patient deterioration is irreversible allowing clinicians time for targeted interventions.

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