TIME SERIES ANALYSIS AND CLUSTERING TO CHARACTERIZE CARDIORESPIRATORY INSTABILITY PATTERNS IN STEP-DOWN UNIT PATIENTS

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Eliezer Linus Bose, PhD

Background: Cardiorespiratory instability (CRI) in noninvasively monitored step-down unit (SDU) patients has a variety of etiologies, and therefore likely manifests in different patterns of vital signs (VS) changes.

Objective: We sought to describe differences in admission characteristics and outcomes between patients with and without CRI. We explored use of clustering techniques to identify VS patterns within initial CRI epoch (CRI_1) and assessed inter-cluster differences in admission characteristics, outcomes and medications.

Methods: Admission characteristics and continuous monitoring data (frequency 1/20 Hz) were recorded in 307 patients. Vital sign (VS) deviations beyond local instability trigger criteria for 3 consecutive minutes or for 4 out of a 5 minute moving window were classified as CRI events. We identified CRI_1 in 133 patients, derived statistical features of CRI_1 epoch and employed hierarchical and k-means clustering techniques. We tested several clustering solutions and used 10-fold cross validation and ANOVA to establish best solution. Inter-cluster differences in admission characteristics, outcomes and medications were assessed.

Main Results: Patients transferred to the SDU from units with higher monitoring capability were more likely to develop CRI (n=133, CRI 44% vs no CRI n=174, 31%, p=.042). Patients

with at least one event of CRI had longer hospital length of stay (CRI 11.3 $\pm$ 10.2 days vs no CRI 7.8 $\pm$ 9.2, p=.001) and SDU unit stay (CRI 6.1 $\pm$ 4.9 days vs no CRI 3.5 $\pm$ 2.9, p< .001). Four main clusters(C) were derived. Clusters were significantly different based on age (p=0.001; younger patients in C1 and older in C2), number of comorbidities (p<0.01; more C2 patients had ≥2), and admission source (p=0.008; more C1 and C4 patients transferred in from a higher intensity monitoring unit). Patients with CRI differed significantly (p<.05) from those without CRI based on medication categories.

Conclusions: CRI_1 was associated with prolonged hospital and SDU length of stay. Patients transferred from a higher level of care were more likely to develop CRI, suggesting that they are sicker. Future study will be needed to determine if there are common physiologic underpinnings of VS clusters which might inform monitoring practices and clinical decision-making when CRI first manifests.

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1.0 INTRODUCTION

Patients are placed in step-down units (SDUs) because their presumed risk for cardiorespiratory instability (CRI) necessitates a higher level of monitoring than is available in general hospital units (Hravnak et al., 2008). In the SDU, patient physiology is either continuously or intermittently monitored using non-invasive vital sign (VS) monitoring devices. These generally include the use of the electrocardiogram (ECG) leads for monitoring vital signs of heart rate (HR) and respiratory rate (RR), as well as plethysmographic monitoring of peripheral capillary oxygen saturation (SpO2). Each of the vital signs (VS) are expected to be within certain predefined "normal" threshold limits, based on normal human physiology, with non-invasive monitors preset to normal limits but also providing in-built capabilities of user-input threshold set limits. While varying criteria for thresholds exist, normal monitoring threshold parameter values include HR between 40 and 140, RR between 8 and 36 and SpO2>85%, with deviations from any of these normal values, while being monitored, considered either as artifact or as potential CRI (Hravnak, DeVita, et al., 2011; Hravnak et al., 2008). Nevertheless, such generic threshold parameters denote instability far into its course. Generic thresholds also do not account for differences in the various pathophysiologic reasons which drive CRI. For example, possibly CRI due to acute onset respiratory failure may present in a different sequence of VS abnormalities than CRI due to hypovolemia or acute onset arrhythmia. Such a variety in

processes and manifestations may make it difficult for clinicians to be certain of the CRI state until well into its course.

Non-invasive monitoring of VS in SDUs are performed to assess patient departure from a stable state and prevent complications. Complications are undesirable outcomes (due to adverse physiologic events) developed by a patient during the course of their hospital stay. Hravnak et al. monitored 326 patients using an electronically integrated continuous monitoring system and reported that patients on SDUs became unstable as long as 6 hours prior to a medical emergency team (MET) call (Hravnak, DeVita, et al., 2011). The underlying theory supporting this project is the concept of Failure to Rescue (FTR), first proposed by Silber et al. (Silber, Williams, Krakauer, & Schwartz, 1992). Failing to notice instability onset and rescue a deteriorating patient promptly and appropriately can lead to negative patient outcomes including increased morbidity and mortality, increased requirement for intensive care, and elevated costs (Hravnak, Schmid, Ott, & Pinsky, 2011). The premise for this study is that failure to identify these complications quickly, by noticing the impending pattern changes prior to overt CRI, can contribute to FTR. CRI is generally a process that occurs over minutes to hours, and offers numerous subtle warning signs and symptoms that could be identified from non-invasive monitoring prior to a patient ever crossing a CRI VS threshold. The hypothesis for this study is that early identification and accurate characterization of the patterns of physiological deviations that lead to overt CRI may aid existing monitoring technologies in earlier detection, thus improving patient outcomes and preventing FTR.

1.1 SPECIFIC AIMS

Purpose: Current physiologic monitoring tools in SDU patients use simultaneous continuous monitoring of individual VS, but do not characterize inter-temporal patterns in multiple VS during the time of overt CRI (CRI epoch).

The proposed study on adult SDU patients has the following specific aims

1. Identify and compare the admission characteristics of patients who develop overt CRI (unstable) with patients who do not develop CRI (stable)
2. For the unstable patient's first occurrence of CRI (CRI_1)--characterize the first VS over stability threshold, extract numeric features within CRI_1 epoch, and use clustering to study interaction of other VS within each cluster.
3. Explore inter-cluster differences based on admission characteristics and whether various CRI_1 patterns are linked to specific disease states.

1.1.1 Definition of Terms

CRI: VS excursions beyond local criteria for instability concern (HR< 40 or > 140, RR< 8 or > 36, SpO2< 85%) not due to artifact were defined as CRI if they persisted for a minimum duration of 3 minutes, or for 4 minutes out of a 5-minute moving window (80% duty cycle) with or without changes in other VS.

CRI epoch: Defined as the first time a VS exceeded normality thresholds and continues until the time the VS returns to normality.

CRI_1: The patient's first instance of CRI epoch not caused by artifactual VS cross of threshold.

CRI_1 Driver: The first VS to cross the CRI stability thresholds within CRI_1 epoch.

1.2 CURRENT BACKGROUND AND REVIEW OF LITERATURE

1.2.1 MET Teams to prevent FTR

Within hospitals, medical emergency teams (METs) are typically composed of medical, nursing, and respiratory therapy staff who can be summoned immediately at any time for prompt evaluation, triage, and treatment of patients with signs of impending clinical deterioration at a much earlier stage in the development of CRI (Chan, Jain, Nallmothu, Berg, & Sasson, 2010). Hravnak et al. recorded 111 MET activation criteria events caused by CRI in 59 patients, but MET activation for this cause occurred in only 7 patients (Hravnak et al., 2008). Schmid-Mazzoccoli et al. have reported that there was a delay in activation of the MET by > 30 minutes with greater delays occurring often during the night shift.(Schmid-Mazzoccoli, Hoffman, Wolf, Happ, & Devita, 2008). The exact reason for such delay in MET activations remains unclear but appears to be multifocal. Ludikhuize et al. identified that the delay could be due to differences in personal perceptions about how nurses, resident physicians and medical specialists and experts judged deteriorating patients and their VS patterns on medical wards, and that there was a wide difference in personal perceptions and a lack of clarity among the various care providers (Ludikhuize et al., 2012). Thus METs can be deployed only when bedside clinicians notice overt CRI. A better approach would be to assist clinicians to notice overt CRI, and even more importantly, become aware of evolving changes in VS prior to CRI manifestation. Such an

approach could assist clinicians to not only treat CRI earlier, but target therapy to a specific disease etiology if CRI patterns unique to pathophysiologic disease processes can be determined.

1.2.2 Early warning scores for early identification of CRI

Many different techniques of early identification of at-risk patients using charted VS, both of single VS abnormalities (Cretikos et al., 2007; Lee, Bishop, Hillman, & Daffurn, 1995; G. B. Smith, Prytherch, Schmidt, Featherstone, & Higgins, 2008) as well as multiple simultaneous abnormalities (Bleyer et al., 2011; G. B. Smith, Prytherch, Schmidt, & Featherstone, 2008; Subbe, Kruger, Rutherford, & Gemmel, 2001) have been explored in an effort to identify overt CRI earlier. Still others have developed aggregate weighted systems (Gao et al., 2007; Paterson et al., 2006) by categorizing VS deviations into step-wise degrees of physiological abnormality based on expert-opinion, prior literature and trial and error, and then computing a score for each of the variables used within the system. However, most of the studies in this area are based upon a single discrete point in time (e.g.: NEWS, MEWS etc.) and treat CRI as a homogenous entity, with no differentiation between the different types of physiologic processes which occur prior to overt CRI. We have anecdotally observed that CRI is an evolving process in time and not an event, and further manifests as different patterns leading up to different CRI etiologies. This study seeks to confirm those observations. These observations are supported by the literature regarding instability physiology and known patterns.

1.2.3 Characteristics other than VS that impact CRI

Previous studies have shown that mortality prediction models which include demographic and clinical diagnoses besides only the monitored VS, after development of CRI, were able to achieve better prediction capabilities. Smith et al. (G. B. Smith, Prytherch, Schmidt, Featherstone, Kellett, et al., 2008)) showed that adding age to a single-VS CRI model (RR<5 or > 36, HR<40 or > 140, systolic blood pressure < 90 mm Hg, sudden decrease in consciousness) or intermittently determined MEWS improved mortality prediction. Higher age also increased mortality prediction as MEWS score increased. Yousef et al. used a multivariable logistic regression model on static variables (age, race, gender etc.) and demonstrated that using the Charlson Comorbidity Index (CCI) could differentiate between patients with and without CRI with high specificity (97%) (Yousef, Pinsky, DeVita, Sereika, & Hravnak, 2012).

1.2.4 Instability physiology and known patterns

1.2.4.1 Low pulse oximetry as an input signal to CRI in SDU patients

Peripheral pulse oximetry is aimed at detecting changes in oxygen saturation of peripheral arterial blood noninvasively (SpO_2), and is utilized as a marker for hypoxemia and therefore CRI. The pulse oximeter probe used on patients in the SDU is designed to target the pulsatile flow arising from the arterial bed, causing signal changes in the waveform via plethysmography. The “order” in which low SpO_2 manifests itself relative to other VS changes might provide clues to the reason for hypoxemia. For example, if a patient becomes overly sedated, one would expect to see a low RR (the CRI ‘driver”) precede decreased oxygen uptake which then manifests as

low SpO_2. Conversely, if a patient develops lung atelectasis and diminished alveolar surface area, a lower SpO_2 might be the first manifestation of decreased oxygen uptake, followed in short order by increased RR and HR to increase circulation and therefore oxygen delivery to compensate for the oxygen uptake shortfall.

Nevertheless, peripheral pulse oximetry is subject to error. Peripheral hypoperfusion from hypothermia, low cardiac output or vasoconstrictive drugs usually prolong the detection time for a hypoxic event due to reduced perfusion at the site of measurement (Jubran, 1999). Bradycardia and its accompanying low perfusion state (low cardiac output) as well as motion artifacts are the main sources of varying patterns in the plethysmographic signal, with usually a very low SpO_2 value in such states. Motion artifacts also imitate low pulse oximetry states and typically, in SDU patients, can be caused due to shivering, agitation or twitching. Peripheral hypoperfusion due to bradycardia and thus a low cardiac output as well as artifact related low perfusion produce lower than normal values and a waveform pattern that appears with very little variation in the signal. Oscillatory patterns of the SpO_2 signal, with corresponding oscillatory changes in the HR and the RR suggest a “real” CRI with lesser suspicion of an artifact. Weak signal strength is indicated by a decrease in the amplitude of the waveform with prolonged “real” low value leading up to potential CRI.

1.2.4.2 Tachycardia and bradycardia as CRI inputs in SDU patients

Tachycardia is defined as heart rate > 100 beats per minute (bpm). Sinus tachycardia is the most common dysrhythmia encountered in SDU patient population, which often occurs as a response to any sympathetic stimulus (e.g.: hypoxia, pain, dehydration or hyperthyroidism)(M. P. Fink, Abraham, Vincent, & Kochanek, 2005). The signal patterns seen in this dysrhythmia include

normal threshold deviations which could last from a few seconds to several hours. In post-surgical patients, tachycardia could be a secondary compensatory physiological sign of bleeding and/or hypovolemia. Sinus tachycardia in the presence of an elevated blood pressure could be manifestations from opioid withdrawal. With a higher prevalence of the older population (age>65 yrs.), atrial fibrillation and atrial flutter with either the presence or absence of structural heart diseases could also lead to tachycardic rhythms (Nattel, 2011). Prolonged tachycardia has been shown to be a major risk factor for cardiac arrests in monitored patients (Sander, Welters, Foëx, & Sear, 2005) as well as in post-operative patients (Landesberg et al., 1993) and could portend impending CRI.

Bradycardia is defined as heart rate < 60 bpm. Frequent causes of bradycardia in SDU patients include but are not limited to degeneration of heart tissue due to aging, damage of heart tissue due to heart attack or heart diseases, hypertension, hypothyroidism, imbalance of electrolytes (especially potassium) contributing to arrhythmogenesis (Miura et al., 2012), obstructive sleep apnea, inflammatory diseases such as lupus and some of the commonly used medications such as beta blockers or calcium channel blockers (Kwon et al., 2012). Signal patterns in such states usually show slower rhythms close to the lower normal thresholds, with a decreasing trend and low signal variability. Patients with any or all of the above physiologic abnormalities and signal patterns are more prone to developing CRI, with varying physiologic causes producing different types of monitoring patterns prior to CRI.

1.2.4.3 Tachypnea and bradypnea as CRI inputs in SDU patients

Abnormal RR has shown in numerous studies to be an important predictor leading up to serious cardiac arrest or transfer to an intensive care unit (escalation of care). (Cretikos et al., 2007;

Fieselmann, Hendryx, Helms, & Wakefield, 1993; Goldhill, McNarry, Mandersloot, & McGinley, 2005; Hodgetts, Kenward, Vlachonikolis, Payne, & Castle, 2002; Subbe, Davies, Williams, Rutherford, & Gemmell, 2003). Subbe et al. noted that in unstable patients (defined as patients who were dying, suffering cardiac arrest or being admitted to critical care) relative changes in RR were much greater than changes in HR or systolic blood pressure, and that RR was likely to be a better means of discriminating between stable patients and unstable patients. (Subbe et al., 2003). Pathologic conditions which cause metabolic acidosis (ketosis, uremia, salicylates, methanol, alcohol, lactic acidosis) lead to increased hydrogen ion concentrations, which in turn lead to increased CO_2 production thus increasing the tidal volume and RR. Furthermore, pathologic conditions which cause hypercarbia (COPD, asthma, MG, ALS etc.) or hypoxia (pulmonary edema, severe ARDS etc.) also increase alveolar ventilation. Besides the above, hypoxia and hypercarbia in SDU patients could also occur from the use of opiate medications (for pain control) which depress the RR. Signal patterns in tachypnea can be either regular or irregular above threshold limits, or with a progressively increasing trend, while bradypnea is usually maintained as a slow RR that is deep (larger amplitude) with a regular rhythm. Cretikos et al, in a prospective case-control study reported that RR might be the VS with the best combination of sensitivity and specificity for the prediction of major adverse events leading up to CRI in hospitalized ward patients (Cretikos et al., 2007). Changes in RR (tachy or brady) is an indicator of abnormality in several body systems, as well as acid-base status and is an important precursor to impending CRI, albeit due to a variety of pathophysiologic causes as described above.

1.2.5 Compensatory hemodynamic mechanisms

There are a number of compensatory feedback mechanisms in the human body with a variety of "sensors" to detect slight changes either in the pH of the blood (chemoreceptors) or the pressure of the blood flow (baroreceptors).

1.2.5.1 Chemoreceptors

The control of the respiratory activity in the body is carefully regulated by the central or medullary chemoreceptors and peripheral chemoreceptors (present in the aortic arch and carotid bodies) and a constant interaction between the central and peripheral chemoreceptors. Ventilation to the alveoli of the lungs is regulated chemically by the partial pressure of carbon dioxide ($PaCO_2$) as well as the partial pressure of oxygen (PaO_2), with $PaCO_2$ being the primary driver of RR. Alveolar ventilation (V_A) is a product of the RR and tidal volume, as

$$V = V_A + V_D = V_T * f$$

where V_A = alveolar minute ventilation, V_D = dead space volume, V_T = tidal volume and f = respiratory rate. The conditions of hypoxemia (↓ PaO_2) and hypercarbia (↑ $PaCO_2$) are corrected by increasing both the tidal volume as well as the respiratory rate. Chemoreceptors detect the levels of carbon dioxide in the blood. In order to do this, they monitor the concentration of hydrogen ions in the blood, which cause a decrease in the pH of the blood due to increasing $PaCO_2$. The physiologic response is that the respiratory center located in the medulla sends nervous impulses to the external intercostal muscles and the diaphragm, to increase breathing rate (increasing trend in the signal pattern) to blow off the excessive accumulating CO_2. While the response to stimulation of chemoreceptors on the HR is complicated and obscure, stimulation

of peripheral chemoreceptors usually directly activates the medullary vagal center and slows the HR, triggering a surge of catecholamines to increase HR (Levy & Pappano, 2007). Figure 1 illustrates the case of a SDU patient who developed CRI due to SpO_2, (in the CRI epoch) but prior to it, had developed a decrease in RR, with a compensatory change of increase in HR, within 2 minutes.

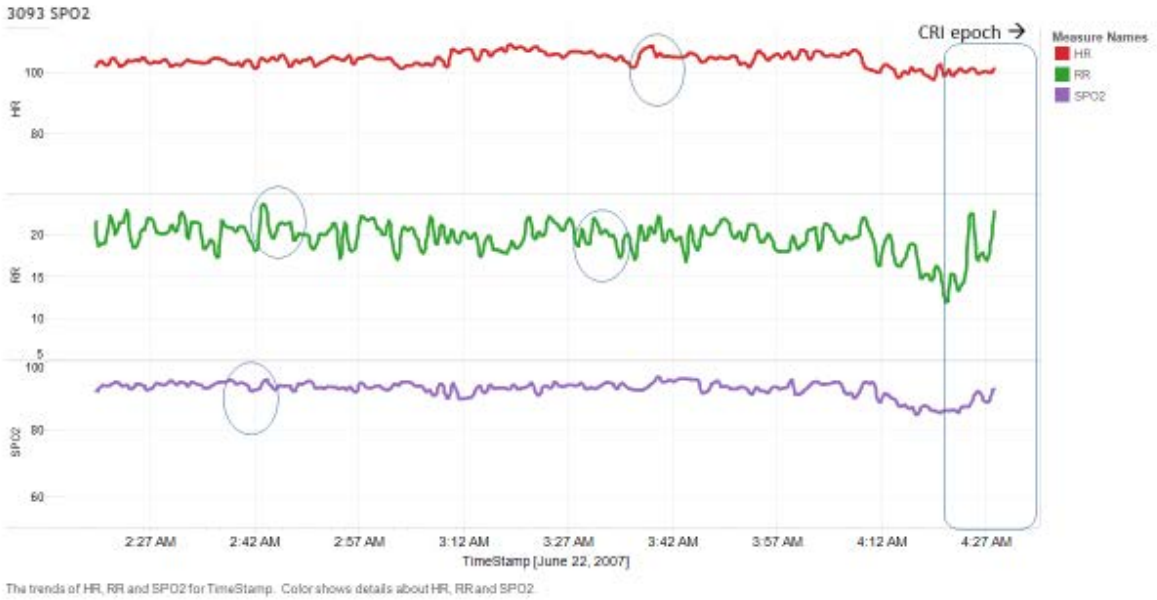

Figure 1. Tableau plot of compensatory changes—decreasing RR, causes increase in HR

1.2.5.2 Baroreceptors

Baroreceptors detect the amount of stretch of the blood vessel walls, and send the signal to the nervous system. Arterial baroreceptors are stretch receptors that are stimulated by changes in both the mean blood pressure as well as the rate of change in the pressure with each arterial pulse. This signal is then transmitted to the nucleus tractus solitarii in the brainstem, which then

through autonomic neurons trigger increases or decreases in HR. If blood pressure (BP) falls, such as in orthostatic hypotension or in various types of shock states (Bose, Hravnak & Pinsky, 2014) (see preliminary work 13.1) baroreceptor reflexes act to help restore blood pressure by increasing HR.

Thus, when patients become unstable and develop CRI, physiologic changes occur with deviations from normal threshold values or the patient's baseline values, and the compensatory changes would be interactive within the three VS of HR, RR and SpO_2.

1.2.6 MET Syndromes—MET calls due to Different Etiologies

MET calls are placed after a patient has developed overt CRI and has been recognized from the monitored variables by the bedside clinicians. While there is an abundance of literature on before and after studies of METs within hospitals (DeVita et al., 2006; Hillman et al., 2005; Lee et al., 1995), a few studies have also attempted to document that there are different causes of MET calls, with differing approaches to the management of the causes. Lee and colleagues, in the original study on METs (Lee et al., 1995), discovered that out of the 522 MET calls, the most common causes were acute respiratory failure, status epilepticus, coma and severe drug overdose. Kenward et al., in a study of 136 MET calls over a 12-month period, discovered that altered consciousness, hypoxia, tachypnea, hypotension and tachycardia were the most common causes of MET calls (Kenward, Castle, Hodgetts, & Shaikh, 2004). Jones et al. studied 400 MET calls and found that the underlying reasons for initiating MET calls were hypoxia (41%), hypotension (28%), altered consciousness (23%), tachycardia (19%), tachypnea (14%) and oliguria (Daryl Jones et al., 2006). He termed these etiologies for MET calls as "MET

syndromes." Jones et al. further elaborated that the accompanying physiological causes for such aberrations included infections, pulmonary edema and arrhythmias. Jones et al. were the first to suggest in literature that if there are differing causes for MET calls, there must be differing patterns in the monitored variables for CRI. However, no studies to date have analyzed the patterns of CRI from the monitored variables of HR, RR and SpO_2.

1.2.7 CRI is a process and not an event

Goldhill et al. (Goldhill & McNarry, 2004) showed that 84% of in-hospital cardiorespiratory arrests are preceded by slow deterioration in vital signs. Buist et al. (Buist, Bernard, Nguyen, Moore, & Anderson, 2004) found that in 76% of adverse events occurring in non-ICU patients, CRI was present for more than one hour before the event with a median duration of 6.5 hours. In one third of these adverse events, documented instability had continued for more than 24 hours. Although CRI is occasionally instantaneously and unmistakably apparent (lethal arrhythmia, massive pulmonary embolism, severe hemorrhage pathologies), it more often evolves over time, with an emerging constellation of subtle abnormality in one or more vital signs as shown in Figure 2. Patients repeatedly display physiologic compensation before compensatory mechanisms are exhausted. Therefore, when CRI occurs it is usually a process and not an event.

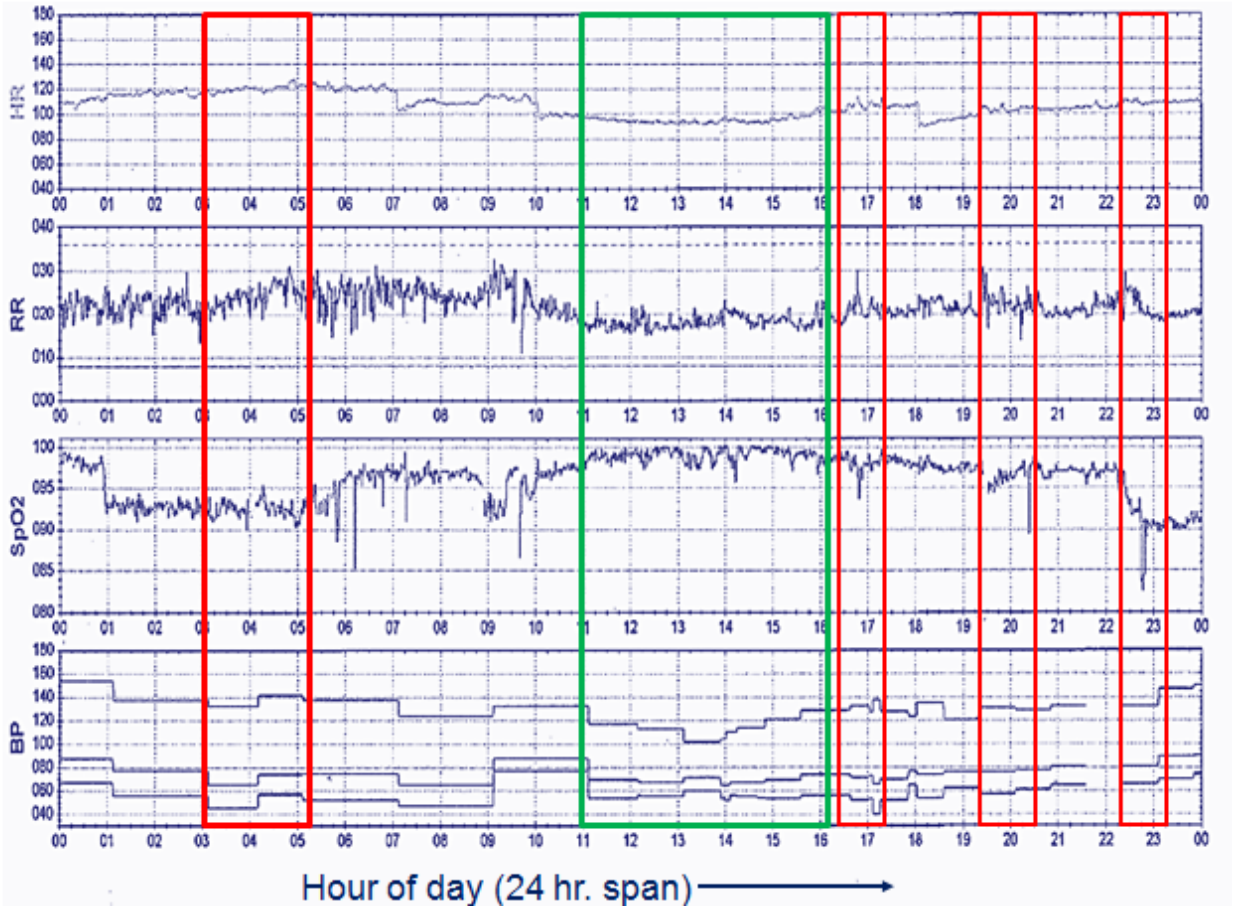

Figure 2. Graph to show the emerging constellation of subtle abnormality in one or more VS and that CRI is an evolving process in time as opposed to an event

1.2.8 The need for Time Series approaches to studying CRI retrospectively

However, the problem of recognizing evolving patterns in overt CRI, or the changes in VS leading up to CRI, requires an approach which accounts for identifying changes over real time. Therefore, time series analytic approaches are necessary.

A time series of HR for a particular patient is a sequence of HR values measured typically at successive points in time, and spaced at uniform time intervals. Time series models are increasingly being used in the field of medicine for analyses of beat-to-beat variability in HR in order to discriminate between survivors and non-survivors (Stein et al., 2008) and have been shown to be effective for retrospective analysis of physiological variables in the field of intensive care medicine (M Imhoff & Bauer, 1996; Michael Imhoff, Bauer, Gather, & Löhlein, 1998). A univariate analysis of HR, for instance, provides information about the range of heart rates and its distribution, and a multivariate analysis of HR as a predictor variable provides an understanding of how HR relates to RR or SpO_2. However, a time series analysis, with its associated properties of autoregression and moving average, provide an understanding of how HR changes over time. Time series data points are assumed to correlate to adjacent data points, providing information about how a variable relates to itself in time over a defined period (autocorrelation), thus providing a paradigm to evaluate the dynamic state of a variable over multiple points in time. Since time series are repeated measures of the same variable over time, it also allows the study of patterns, called trends. Furthermore, time series can be split into different window periods, or intervals, and allow for computations of the slopes, intercepts, means and variances so as to compare one interval with the next.

Time series analysis Autoregressive (AR) models are models in which the value of a variable in one period is related to its values in previous periods. AR (p) is an autoregressive model with p lags: $y_t = y_{t=} \mu + \sum_{i=1}^{p} \gamma iyt - i + \varepsilon_t$, where μ is a constant, and γ_p is the coefficient for the lagged variable in time t-p. An AR (1) process is expressed as:

$yt = \mu + \gamma yt\text{-}1 + Et = \mu + y(Lyt) + Et$ or $(1 - \gamma L)yt = \mu + Et$

Moving average (MA) models account for the possibility of a relationship between a variable and the residuals from previous periods. MA(q) is a moving average model with q lags is

$$yt = \mu + Et + \sum_{i=1}^{q} \theta i \, \varepsilon t - i$$

where θ q is the coefficient for the lagged error term in t-q. For instance, MA(1) model is expressed as: $yt = \mu + Et + \theta Et\text{-}1$. Autoregressive moving average (ARMA) models combine both *p* autoregressive terms and *q* moving average terms, also called ARMA(p,q).

$$yt = \mu + \sum_{i=1}^{p} Yi \, yt - 1 + \varepsilon t + \sum_{i=1}^{q} \theta i \varepsilon \text{t-i}$$

Since the development of CRI is a process and develops over a period of time, time series modeling approaches incorporating the AR and MA parts can be applied to retrospectively analyze patterns within the variables prior to the overt instance of CRI (CRI epoch).

Based on the properties of a continuously monitored signal's characteristics, instead of accounting for an instantaneous deviation from normal thresholds as being a case of CRI (when in actuality, it could be an artifact), two additional time series properties can be imposed, referred to as the duty cycle and tolerance. For a pre-defined window period (P) of monitoring, if (T) be the time the signal persists in a particular state, duty cycle is defined by the relationship $D(\%) = \frac{T}{P} X\ 100$.

1.2.9 Time series modeling approaches and the use of ARIMA and VAR

The AutoRegressive Integrated Moving Average (ARIMA) model uses the lag and shift of historical information (AR and MA) in order to develop a mathematical model on an existing

univariate time series to provide great detail and precision. First proposed in 1976 by Box and Jenkins (Box, Jenkins, & Reinsel, 2013), ARIMA time series intervention analysis has been used widely for prediction and early warning analysis of infectious diseases (Luz, Mendes, Codeço, Struchiner, & Galvani, 2008; Reichert et al., 2004; Yi, Du, Wang, & Liu, 2007). ARIMA (AR, D, MA) models make use of previous observations to make predictions of future values using lagged variable values. While the advantage of the ARIMA is that it can parsimoniously model a given variable, requiring only the prior data of the variable, building models to study CRI patterns has to be done individually on a patient-by-patient basis and mostly on a univariate basis. This makes the approach computationally inefficient to find the "best" generalizable model to study patterns among the variables in large datasets involving multiple patients and their corresponding time series variables. Furthermore, in preliminary study, we have tried to implement the use of the ARIMA model after applying a T4253 data smoothing procedure for artifacts on a small subset of this study's SDU patients. We were able to forecast univariately, after several iterations of deciding the parameter values and best fit, based on information criteria (AIC and BIC). However, we could not identify specific patterns common to this set of patients, owing to numerous individual differences in the time series of each of the variables from patient to patient. It remains unclear if this was due to the imputation procedure, the smoothing, the lack of uniformity of the time series, or the iterative nature of ARIMA modeling to arrive at a best fit model, without overfitting, to study signal patterns prior to CRI.

The Vector autoregression (VAR) model extends the univariate autoregressive model in order to describe not only how the values of a particular variable at time, t, depend linearly on the past values but also include the past values of the other variables as input for modeling (Wild et al., 2010). The general VAR (p) model is

$y_t = c + A_1 y_{t-1} + A_2 y_{t-2} + \ldots\ldots + A_p y_{t-p} + e_t$ where

$$\begin{bmatrix} y_{1,t} \\ y_{2,t} \\ \vdots \\ y_{k,t} \end{bmatrix} = \begin{bmatrix} c_1 \\ c_2 \\ \vdots \\ c_k \end{bmatrix} + \begin{bmatrix} a^1_{1,1} & a^1_{1,2} & \cdots & a^1_{1,k} \\ a^1_{2,1} & a^1_{2,2} & \cdots & a^1_{2,k} \\ \vdots & \vdots & \ddots & \vdots \\ a^1_{k,1} & a^1_{k,2} & \cdots & a^1_{k,k} \end{bmatrix} \begin{bmatrix} y_{1,t-1} \\ y_{2,t-1} \\ \vdots \\ y_{k,t-1} \end{bmatrix} + \cdots + \begin{bmatrix} a^p_{1,1} & a^p_{1,2} & \cdots & a^p_{1,k} \\ a^p_{2,1} & a^p_{2,2} & \cdots & a^p_{2,k} \\ \vdots & \vdots & \ddots & \vdots \\ a^p_{k,1} & a^p_{k,2} & \cdots & a^p_{k,k} \end{bmatrix} \begin{bmatrix} y_{1,t-p} \\ y_{2,t-p} \\ \vdots \\ y_{k,t-p} \end{bmatrix} + \begin{bmatrix} e_{1,t} \\ e_{2,t} \\ \vdots \\ e_{k,t} \end{bmatrix}$$

VAR models have been used in medicine receiving wide-spread acceptance. This is because they are not only capable of analyzing time series variables multivariately, but also provide an environment for testing Granger causality, a common method used for the investigation of dynamic interrelationships in multivariate time series (e,g. increase in HR, causes a decrease in RR within a particular period etc.) (Goebel, Roebroeck, Kim, & Formisano, 2003; Roebroeck, Formisano, & Goebel, 2005). Granger causality is based on the common-sense concept that causes precede their effects in time. Such temporal ordering implies that if there are two time series represented generally as X and Y, the past and present values of the series X should help to predict future values of series Y (Barnett & Seth, 2014).

The VAR framework allows all variables to be treated as if the variables have equal influence on each of the other variables--allowing for feedback relationships within the variables. In preliminary study, we have previously implemented the VAR model in a small subset of the data, multivariately, using HR, RR and SPO_2 to study the inter-relationships among the variables as well as the Granger causal dynamics among the variables leading up to CRI. For instance, in our cases as shown in Preliminary Study Section 13.5, SpO2 falling below threshold was the first indicator of CRI. However, SpO_2 itself was generally not the cause for changed RR or HR, but rather RR and HR tended to be the cause for the SpO_2, suggesting that SpO_2 is a later VS change, and is led by more subtle changes in other VS as causative. Our preliminary study also demonstrated that building a VAR model (being an iterative approach) to explain the causal

patterns among the variables, with the sheer number of coefficients (as high as 273) which needed to be estimated, led to greater room for modeling errors and over fitting and at times not being achieve a stable VAR model. The VAR model, if well implemented, is quite rich in capturing the temporal dynamics made possible by adjusting the model order (max lag), but has also been criticized in medical literature since it tends to be a simplified characterization of highly complex hemodynamic response (Gorrostieta, Ombao, Bédard, & Sanes, 2012) and is open to confounding from unmeasured relationships, as are most other statistical procedures (Thompson & Siegle, 2009). Thus, while CRI is a process with evolving patterns prior to overt CRI, better approaches besides ARIMA and VAR models to study inter-relationships among the variables and their patterns are needed.

1.2.10 Machine Learning

1.2.10.1 Definition and Benefits

Machine learning, the science of learning from data, automates mathematical and statistical analyses of time series datasets in order to learn from the data and extract important patterns and trends (Goodwin, VanDyne, Lin, & Talbert, 2003; Lucas, 2004). In a type of machine learning called unsupervised machine learning, the outcome is not specified or known, and the goal is to provide a training sample data in order to identify inter-relationships among the time series variables and to then detect emerging patterns. The resulting model may assume the form of a set of rules or descriptions that lead to the outcome (CRI) which can then be tested on a validation data set, not exposed to prior training. Small changes in multi-parameter time series of physiologic data (HR, RR, SpO_2) encompass subtle patterns that may seem random or of low

certainty upon visual monitoring of the time series, but could in fact be early signatures of impending CRI (Lynn & Curry, 2011) and as such, lend themselves to machine learning algorithms (Crump et al., 2009), which are better than standard time series approaches in terms of their performance of identifying patterns.

1.2.10.2 Unsupervised machine learning—clustering approach to pattern recognition

In machine learning, the problem of unsupervised learning is that of trying to find hidden structure in unlabeled data. Unsupervised learning methods have commonly been used in bioinformatics for sequence analysis and genetic clustering; in data mining for sequence and pattern mining; and in medical imaging for image segmentation (Gupta, Saul, & Gilbertson, 2004) Unsupervised learning algorithms try to find correlations without any external inputs (i.e. labeled data) other than the raw data itself. As such, the training data consists solely of a set of input vectors *X* without any corresponding target values. The goal in such unsupervised learning problems is to discover potential regions where there may be groups of similar kinds within the data. These advanced computational algorithms decide on how to group the sample into clusters which share similar properties. The most common unsupervised learning method is cluster analysis, which is used for exploratory data analysis to find hidden patterns or grouping in data. The clusters are modeled using a measure of similarity which is defined upon metrics such as Euclidean or probabilistic distance.

1.2.10.3 Clustering Approaches to pattern recognition

The clustering problem is defined as a problem of classifying a group of data points into a number of clusters without any prior knowledge about data structure, to produce a concise

representation of the data. It is a fundamental means for multivariate data analysis widely used in numerous applications, especially in pattern recognition. Clustering, as an unsupervised machine learning technique aims to explore the unknown nature of data through the separation of a defined dataset, with no ground truth, into a finite set of "natural" data structures (Jain & Dubes, 1988; Xu & Wunsch, 2008; Xu & Wunsch, 2005). Clustering algorithms have been employed extensively in biomedical research (Andreopoulos, An, Wang, & Schroeder, 2009) with particular focus in areas involving gene expression data analysis, genomic sequence analysis and MRI data analysis.

Given a set of data objects (entities, input patterns, instances, observances, units), the objective of clustering is to partition them into a certain number of clusters (groups or subsets) in order to explore the underlying structure and provide useful insights for further analyses. The operational definition of a cluster is that it is a set of data objects which are similar to each other, with data objects pertaining to different clusters different from one another (Everitt, Landau, & Leese, 2001). Two of the most commonly employed types of clustering procedures include—hierarchical and partitional (eg: K-means) clustering.

1.2.11 Hierarchical Clustering

Hierarchical clustering (HC) is an unsupervised machine learning method of cluster analysis which seeks to build a hierarchy of clusters. Common strategies for hierarchical clustering include agglomerative ("bottom up") approach where each observation starts within its own cluster and pairs of clusters merged moving up in the hierarchy (as shown in Figure 3). The

divisive (“top down”) approach starts with clumping all the observations into a single cluster and then performs a recursive splitting moving down in the hierarchy (as shown in Figure 4).

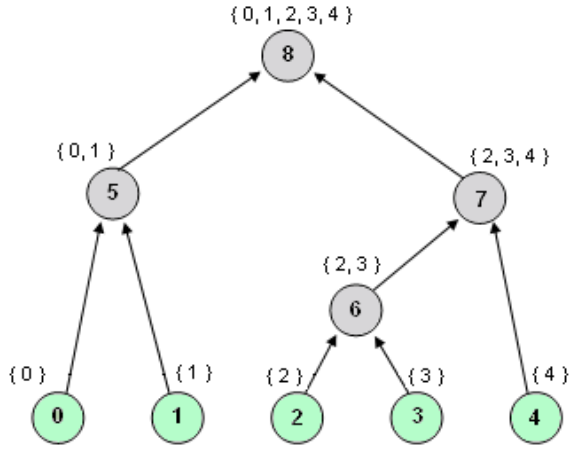

Figure 3. “Bottom up” clustering approach

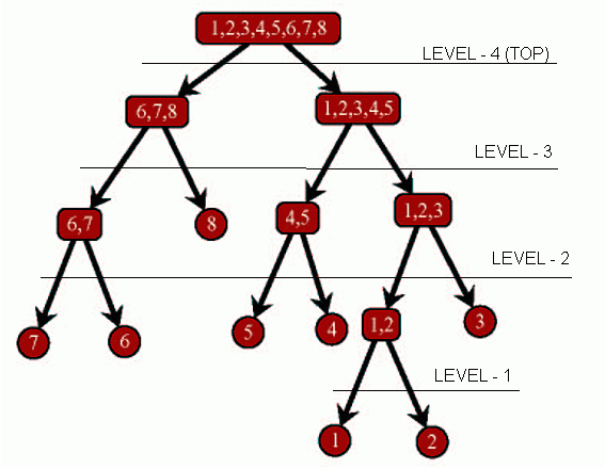

Figure 4. “Top down” clustering approach

Both agglomerative and divisive clustering algorithms organize data objects into a hierarchical structure based on the proximity matrix. The results of hierarchical clustering are usually depicted by a dendrogram as shown in Figure 5.

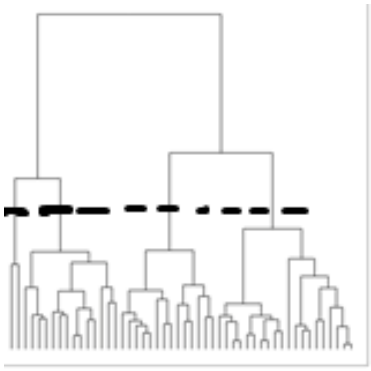

Figure 5. Dendrogram showing the implementation of hierarchical clustering on a dataset.

The root node of the dendrogram represents the entire data set, and each leaf node is regarded as a data object. The intermediate nodes describe the extent to which the objects are proximal to each other, and the height of the dendrogram expresses the distance between each pair of data objects or clusters, or a data object and a cluster. The ultimate clustering results can be obtained by cutting the dendrogram at different levels (the dashed line in Fig. 5).

This representation provides very informative descriptions and a visualization of the potential data clustering patterns, especially when real hierarchical relations exist in the data, such as the data in medicine, physiology and biology (Jain & Dubes, 1988; Kaufman & Rousseeuw, 2009; Theodoridis & Koutroumbas, 2008). Agglomerative clustering, which starts with exactly one data object, is often preferred as compared to the divisive approach which is computationally much more intensive (Kaufman & Rousseeuw, 2009).

Hierarchical clustering approaches have been employed for gene clustering providing useful insights into annotating functionally unknown genes through annotated genes which exhibit similar expression patterns (Iyer et al., 1999; Moreau, De Smet, Thijs, Marchal, & De Moor, 2002). It has been employed in gene profiles for fingerprinting diseases such as cancer, providing new approaches for diagnosis and drug development (Alon et al., 1999; Scherf et al.,

2000). Garber et al. applied hierarchical clustering to data from 67 different lung tumors from four different types—squamous, large cell, small cell and adenocarcinoma and identified that adenocarcinomas exhibited more heterogeneity in terms of its patterns while the others remained within their own clusters (Garber et al., 2001). Alizadeh et al. successfully implemented hierarchical clustering to distinguish between the patterns of two molecularly distinct subtypes of diffuse B-cell lymphomas, providing molecularly relevant criteria for therapy and drug selection (Alizadeh et al., 2000).

1.2.12 K-means clustering

The K-Means method is another type of unsupervised machine learning clustering approach which can be used to generate globular clusters—i.e. clusters with non-convoluted boundaries, bearing some resemblance to the mean of the cluster. Clusters produced in this manner are non-hierarchical and do not overlap. The general procedure of the K-means algorithmic approach begins by partitioning the data set into K clusters and the data points are randomly assigned to the clusters resulting in clusters that roughly have the same number of data points. For each and every data point, a distance measure is calculated from the data point to each cluster and if the data point is closest to its own cluster, it remains in the cluster it started with, but if not, then it is moved to the closest cluster. The process is repeated until a complete sweep through of all the existing data points, results in no data point moving from one cluster to another, thus ending the clustering process (Jain, 2010). An example of a graph derived after such a procedure is shown in Fig 6. K-means has commonly been employed in the medical literature because it has the advantage of being computationally faster than hierarchical clustering and produces tighter

globular clusters, especially with a large number of data points. Heuristic algorithms employed by K-means are efficient in converging quickly to a local optimum, so as to

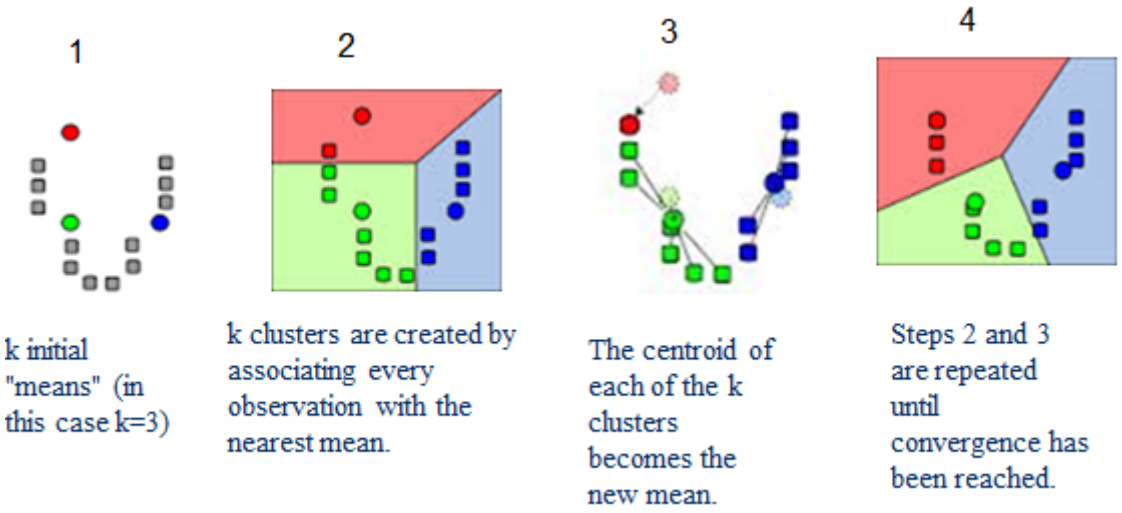

Figure 6. K-means clustering illustration.

terminate the process. However, automatically determining the final number of clusters has been a challenging problem in this type of clustering procedure, with the general procedure being to implement different values of K. Although there are a number of predefined criterion established (Figueiredo, Cheng, & Murino, 2007; Hansen & Yu, 2001), the commonly employed criteria include the AIC and BIC and minimal values of the sum of squares of error. The main assumption is that the division of the clusters will produce an optimum number of patterns with a type of partitioning that is resilient to random change in values within the system (Jain, 2010).

1.3 CONCEPTUAL FRAMEWORK

Physiologic alterations, in most hospitalized patients are preceded by changes in monitored parameters and a period of cardiorespiratory instability (CRI) that is either unrecognized or improperly detected. In clinical practice, vital sign monitoring and early detection of easily discernible physiological alterations are the key to detecting CRI, identifying it appropriately, and applying appropriate interventions to prevent negative patient outcomes that result in failure to rescue (FTR) or death of the patient. The proposed study, which aims to identify and compare the admission characteristics of patients who develop overt CRI (unstable) with patients who do not develop CRI, characterize the first vital sign (VS) over stability threshold and use clustering to study interaction among other VS within each cluster, and explore whether the various CRI patterns are linked to specific disease states was guided by the conceptual framework shown below.

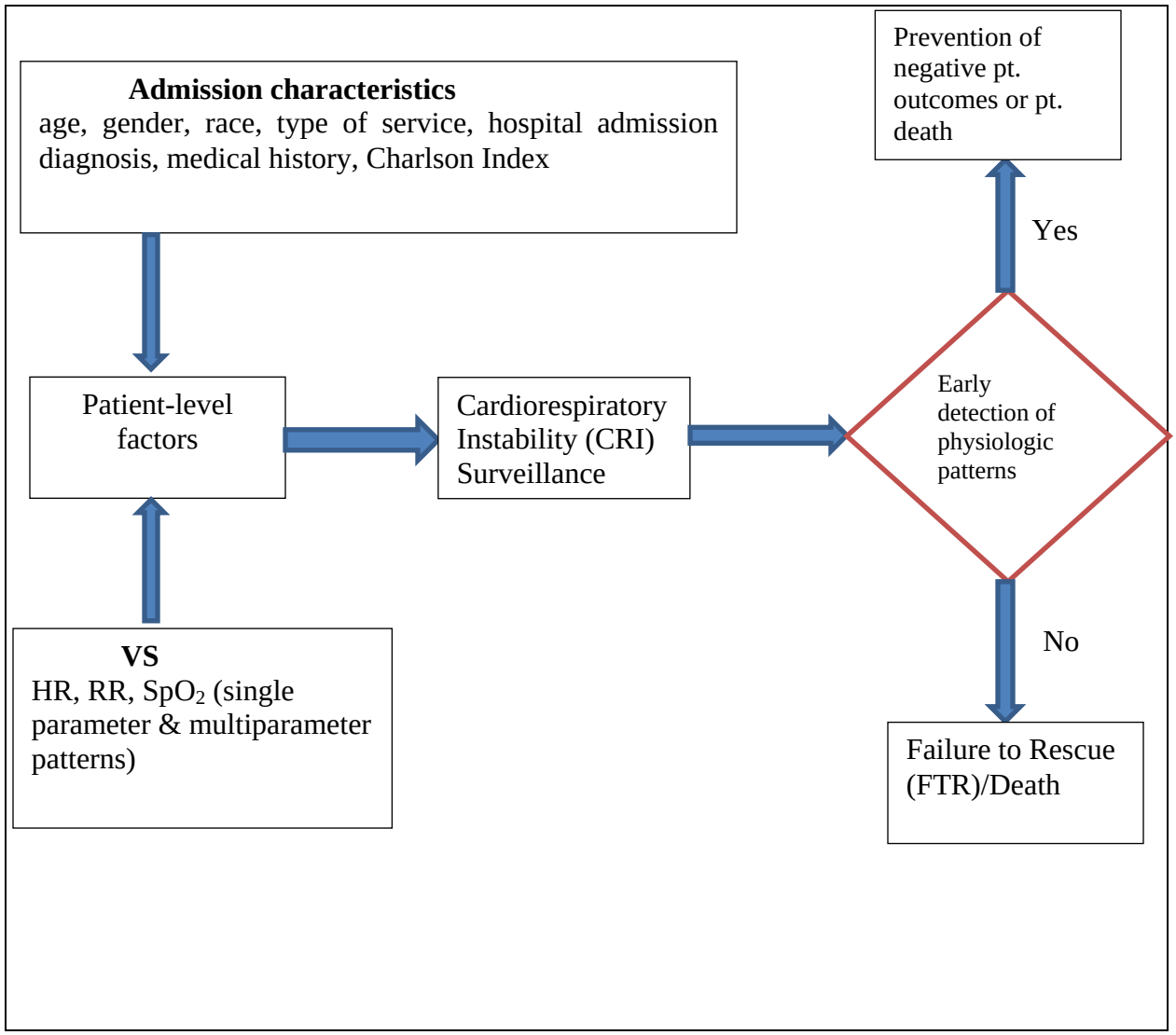

Figure 7. Theoretical/Conceptual Framework

There are both dynamic (continuously changing with time) and static patient-level factors that contribute to create CRI. Dynamic physiologic patient changes responsible for a patient's CRI include traditionally measured parameters, e.g., vital signs. For the purposes of the proposed study, heart rate (HR), respiratory rate (RR) and oxygen saturation (SpO_2) were used to identify dynamic patient changes. We analyzed both single parameter (i.e. each of the parameters individually) as well as multiparameter trends of change in these variables. Static patient-level factors long known to contribute to the mortality of hospitalized patients (generally incorporated

in a variety of acuity-scoring systems) were also analyzed for the purposes of our study. Examples include age, gender, race, type of service (medical/surgical), hospital admission diagnosis, medical history and Charlson Comorbidity Index (CCI) score for patients on whom physiological information was obtained. Although, these static characteristics cannot independently be used for CRI surveillance, they could be valuable when used in combination with dynamic patient changes for patterns of physiologic alterations. Thus, both dynamic patient changes and static patient characteristics were used for pattern analysis of CRI.

The proposed study was based on the belief that the earlier the physiological alterations are recognized and acted upon, the less negative impact that their occurrence will have on the patient's outcome. Hence, early detection of physiologic alterations could prevent negative patient outcomes or even death during hospitalization, while not doing so will lead to FTR or death. Since CRI does not happen without some alteration in either single parameter or multi-parameter trends of change, early detection of physiological alterations could be analyzed using unsupervised machine learning algorithms. If vital decision-making information obtained from these patterns can be used to guide therapeutic interventions, then hopefully negative consequences or death during hospitalization could be averted.

1.4 SIGNIFICANCE OF RESEACH STUDY FOR NURSING

Existing monitoring systems hold the promise of both detecting and predicting patient deterioration at the time of its occurrence. However, current monitoring tools in SDU patients do not characterize inter-temporal patterns in multiple VS during the time of overt CRI. Pattern

recognition of CRI even from its very first occurrence, prior to the occurrence of an adverse event carries with it the possibility of targeted interventions to avert an impending adverse event. Such studies will provide direction to augment existing monitoring efforts for improved and early prediction capabilities in order to shift nursing focus on CRI from a reactive approach to a preemptive one. Eventually, monitoring systems can be integrated to generate databases which will enable improved risk prediction models (DeVita et al., 2009). Such data can also be used for improved critical incident review and contribute to quality improvement thereby serving as better tools in avoiding negative patient outcomes or death, while being extremely beneficial for clinicians and bedside nurses.

Acuity of patients transferred from the intensive care units to step-down units (SDUs) or wards is increasing, making cardiorespiratory instability (CRI) an increasingly common occurrence on these units. Although multiple vital signs (VS) are continuously monitored, alerts are provided to staff only when individual parameters exceed presumed thresholds of stability, without relationship to each other. To better inform clinical decision-making, it would be helpful to know if VS changes manifest in unique clusters, and are related to certain patient characteristics or pathophysiologic etiologies.

Initial exploration of the potential of grouping patient deterioration according to VS change patterns was motivated by the emergence of medical emergency teams (MET).(Buist et al., 2002) The emergence of MET prompted evaluation of their benefit in improving patient outcomes(Bellomo et al., 2003; Bristow et al., 2000; Buist et al., 2002; DeVita et al., 2004; Hillman et al., 2005), and critical analysis of events preceding a MET call for help(Downey et al., 2008; Jones, Bates, et al., 2006; Jones, Duke, et al., 2006). Jones et al.(Jones, Duke, et al., 2006) studied 400 MET calls in intensive care unit (ICU) settings and found the underlying

reasons for initiating calls were hypoxia (41%), hypotension (28%), altered consciousness (23%), tachycardia (19%), tachypnea (14%) and oliguria. They termed these etiologies “MET syndromes.” In their study, infections (especially pneumonia), cardiogenic shock or pulmonary edema and arrhythmias were responsible for 53% of all MET calls. Jones et al. were the first to suggest that, if there are differing causes for MET calls, there must be differing patterns in monitored variables that precede the unstable state. If so, they suggested there might be different approaches to managing CRI based on MET syndrome. We were unable to identify any studies that attempted to analyze patterns of CRI using commonly monitored variables, e.g., heart rate (HR), respiratory rate (RR) and peripheral oxygen saturation (SpO2) prior to instability that was sufficiently severe to prompt MET activation. Having such information prior to a MET need might help clinicians recognize the syndrome, or instability pattern, earlier in its course and provide more targeted supportive or preventative measures to avert the crisis.

1.5 PRELIMINARY STUDIES

The following sections demonstrate the candidate’s development of knowledge and skills to support doctoral work.

1.5.1 Understanding of the Pathophysiologic Underpinnings of Hemodynamics, CRI and Patterns of Shock

The candidate developed two manuscripts, now published, to demonstrate his evolving understanding of the pathophysiologic underpinnings of hemodynamics, CRI, and shock evolution.

The first paper (Appendix A) described the physiology of cardiac output, and the various parameters and technologies used to assess volume status and cardiac output, The candidate was first author on this paper published in the Oxford Textbook of Cardiology, Fall 2012. In summary, this paper demonstrated that there was no such thing as a "normal" cardiac output but rather the question was whether cardiac output is either adequate or inadequate to meet the metabolic needs of the body. As such, choices for hemodynamic monitoring should always reflect the necessity for information that might alter patient management based on preload responsiveness. This paper demonstrated theoretically that the diagnostic accuracy of preload responsiveness is markedly improved by the use of arterial pulse pressure or stroke volume variation, within the context of their physiological limitations. Most importantly, the paper showed that the accuracy of absolute values may be less important at a given point in time, rather it is important to follow the trends of monitored variables to track the short-term effects of therapies, such as fluid loading, for improvements in cardiac output. Finally, the authors pointed out that it is not monitoring of hemodynamic variables that can improve outcomes, instead it is the changes in therapy guided by the patterns of the data and appropriate treatments based on that data that can improve patient outcomes.

The second paper (Appendix B) has been published as a refereed book chapter in Monitoring Technologies in Acute Care, Spring 2014 where the candidate was the first author. This paper focuses on the interface between monitoring and physiology at the bedside. In summary, the authors showed that hemodynamic instability (used instead of CRI, since it was described from a pathophysiological perspective instead of thresholds) as a clinical state represents either a perfusion failure with clinical manifestations of circulatory shock and/or heart failure. Different types of circulatory shock etiologies—hypovolemic, cardiogenic, obstructive and distributive shock-- require different types of treatment modalities making distinctions among them important. Diagnostic approaches or therapies based on data derived from hemodynamic monitoring assume that specific patterns of derangements reflect specific disease processes, which will respond to appropriate interventions. This paper further described the physiologic underpinnings of various forms of shock (hypovolemic, obstructive, distributive, cardiogenic) and demonstrated how shock patterns can be recognized based upon manifestation of monitored parameters. Finally, this paper pointed out that hemodynamic monitoring at the bedside improves patient outcomes, however treatment decisions and pharmacological management should be directed at the right time, ensuring that the patterns are monitored for patients experiencing hemodynamic instability.

These two papers above demonstrate the development of the candidates understanding of the physiologic and pathophysiologic underpinnings of CRI and its assessment, and the ability to describe and disseminate this information.

1.5.2 Baseline Characteristics Contributing to CRI Propensity

The candidate also examined mechanisms to evaluate characteristics other than VS as they contribute to CRI, specifically co-morbid conditions. The first study was a psychometric analysis of the Charlson Comorbidity Index (CCI) Deyo Method (an indicator of comorbidity extracted from administrative databases, and a variable in the parent study Appendix C. This work was presented as a poster at the Society of Critical Care Medicine Scientific Congress, Spring 2013. Since CCI items were originally empirically derived, this study sought to provide psychometric information about the CCI Deyo through exploratory factor analysis (EFA) to expose factor structure of the items and construct validity. This study used the entire sample of patients who will be used for dissertation purposes, but used their admission characteristics of age, gender, race and CCI to apply EFA. In summary, EFA revealed multiple comorbidity groupings within the list of CCI disease states. However, this abstract also showed that the CCI as a scoring mechanism had a poor construct validity.

In addition, the candidate conducted a study to examine the internal structure of the CCI Appendix D. In this study, principal component analysis (PCA) was utilized to investigate the internal structure and identify subscales. In summary, this manuscript submitted to the Journal of Nursing Measurement, Spring 2015, using PCA revealed co-occurrence of certain disease items, indicating common underlying pathologic mechanisms, as well as propensity of multiple comorbidity groupings. The study findings of a multidimensional internal structure of the CCI implied that subscale scores could provide more detailed information on patient comorbidities than an overall index.

These two (a poster and a paper) demonstrated the candidate's development of skills in implementing a modified version of a type of dimensionality reduction approach called PCA. Some studies (Honda, Notsu, & Ichihashi, 2010; Su & Dy, 2004) have shown that PCA could be used initially prior to the implementation of other clustering approaches such as K-means as a way of reducing computations for K-means. Performing PCA before implementing clustering procedures is done sometimes as an optional step for efficiency purposes. The skills acquired by the candidate in implementing PCA approach were useful for decisions to be made during K-means clustering for finding optimal solutions.

1.5.3 Dissertation Topic Evolution

The candidate developed a doctoral dissertation approach abstract which was accepted for presentation of a poster at the Eastern Nursing Research Society, Boston, MA, Summer 2012. This poster outlined the initial background, purpose and aims for the current study, which has since been further refined. This poster is in Appendix E.

This poster demonstrated the candidate's progress in developing an initial research proposal, formulating preliminary studies and necessary course work required in planning to accomplish its aims and mathematical, statistical and computer skills required to implement machine learning approaches. It also demonstrated the change in the nature of the methodological approaches which must be implemented, based on actually working with the dataset.

1.5.4 Temporal Variation in CRI

The candidate also conducted a study examining temporal variation in CRI onset. He reported this study in a poster for presentation at the Rapid Response Systems International Society Conference in Spring 2014 (Appendix F). In summary, hypothesizing that real VS variations indicating CRI occur throughout the clock, unlike MET calls which are made more frequently during mid-day hours, we proceeded to test our hypothesis. We discovered that patients became unstable throughout the clock without specific clustering relative to time of day thus concluding that better methods to improve clinician's detection of patient instability were needed.

This poster demonstrated skills learned in using a count/tallying approach of the number of alerts based on each hour of the day for the entire group of patients within a 24 hour period. It also demonstrated the ability to calculate the probability values of the alerts per hour for the entire day. The project also clearly demonstrated the propensity of patient's developing CRI throughout the clock, thus highlighting the importance of our future dissertation in that that, just as CRI develops around the clock, patterns of CRI develop prior to overt CRI also develop and are evolving in time. Thus, approaches to preemptively recognize the patterns are needed.

1.5.5 Time-Series Analysis using Vector Autoregressive (VAR) model

The candidate also examined the use of a time-series modeling approach called VAR to study Granger causal dynamics among the variables of HR, RR and SpO2. The first study was VAR model for studying causal dynamics of CRI (Appendix G). This work was submitted to the upcoming Society of Critical Care Medicine conference, Spring 2015. Since vital signs of HR,

RR and SpO2 undergo inter-related changes in situations of stress, from a physiologic perspective, we hypothesized that VAR model could explore the inter-related Granger causal dynamics among the variables prior to CRI. In summary, VAR modeling indicated that, HR changes seemed to occur before those in RR, within the examined sample of patients.

In addition, the candidate also worked on a paper, Vector Autoregressive (VAR) Environment For Assessing Granger Causal Dynamics Of Vital Sign Time-Series In Step-Down Unit (SDU) Patients With Cardiorespiratory Instability, which was submitted to Nursing Research, a publication of the Eastern Nursing Research Society, in Summer 2015 (Appendix H). This study was the first of its kind in the literature to use VAR modeling approach with HR, RR and SpO2 in order to apply Granger causality in SDU patients. We found out that within the study sample, SpO2 itself was generally not the cause for changed RR or HR, but rather RR and HR tended to be the cause for the SpO2. This suggested that SpO2 was a later VS change, and was led by more subtle changes in other VS as causative. In summary, even though it was an iterative and lengthy computational procedure to build patient-specific VAR models, these models in certain cases could reveal Granger causal inter-relationships among the three variables of HR, RR and SpO2.

These two (an abstract and a paper) demonstrate the candidate's development of skills in implementing time-series modeling approaches as well as a working knowledge of time-series related concepts such as lags, autocorrelation etc. and other time-series related concepts. We were able to build a few stable patient-specific VAR models to study Granger causality. However, there were instances where a stable VAR model could never be developed and as such causal dynamics could not be examined. We also discovered that in certain cases, VAR models were prone to much over-fitting of the data and as such, with the sheer number of coefficients to

be estimated, were erratic and unreliable. With the absence of continuous streaming data for the window-period examined, there were instances where, after rendering the time series uniform, we had to impute missing values. It was unclear if the models were erratic due to imputation procedures, artifacts or both. Accordingly, we decided to switch to better approaches to study patterns. However, basic skills of working with time-series data were acquired.

1.5.6 Monitoring Cardiorespiratory Instability-Current status and implications for nursing practice

The candidate developed a manuscript which was submitted to Intensive and Critical Care Nursing in Summer 2015 and is currently under review. This manuscript was a literature review on other existing options to identify in-hospital patient instability such as telemedicine, rapid response teams and technology-enabled early warning scores. Although existing monitoring systems hold the promise of better detection and recognition of CRI, nursing surveillance still remains the key to reliable early detection. Research directed towards improving nursing surveillance and facilitating decision-making is needed to ensure safe patient outcomes and prevent CRI.

This manuscript in Appendix I demonstrated the development of the candidates broad understanding of the various approaches currently being extensively studied and implemented to better detect CRI, along with their strengths and shortcomings.

2.0 RESEARCH DESIGN AND METHODS

2.1 STUDY DESIGN

This study was conducted under the domain of the ongoing NIH R01-NR013912. The study design was descriptive and utilized a convenience sample of non-randomized self-controlled cohorts to identify and compare the characteristics of step-down unit (SDU) patients who develop true cardiorespiratory instability (CRI) (unstable) with patients who never develop CRI (stable), identify inter-relatedness of the other VS within and prior to the CRI_1 epoch, and explore whether CRI_1 patterns are linked to specific disease states.

2.2 SAMPLE AND SETTING

The study was approved by the University of Pittsburgh Institutional Review Board (IRB) (PRO13030536). This research study utilized data from patients between 11/06-8/07 who have been discharged in the 7-8 years since, using only archived medical records and physiologic data of patients. The sample for the study was recruited from a 24-bed trauma step-down unit (SDU), located in a tertiary academic medical center. For the proposed study, data were extracted from the input obtained from beside monitors (model M1204, Philips Medical, Bothell, WA). The

standard of monitoring care on the SDU is that all patients undergo physiologic noninvasive monitoring of continuous HR (3-lead ECG), RR (bioimpedance signal), and peripheral blood oxygen saturation (SpO2) plethysmographic signal (model M1191B, Phillips Medical Systems). Nurse to patient ratios in this SDU ranged from 1:4 to 1:6 during the study period and depended on the number of patients in the unit and the acuity of the patients' conditions. Data were collected during a sequential 8-week time period. There were 307 admissions with 22,588 total patient-hours of monitoring data (81 mean monitoring hours/patient).

2.3 ENTRY/EXCLUSION CRITERIA

Patient entry criteria for the study were : 1) admitted to a monitored bed on Unit 9G, and 2) age >21 years during the study period (11/06-8/07; 8 weeks). All patients were admitted to the study unit according to the usual standard of care for monitored bed admission and utilization. There were no special efforts to direct patient admissions to the SDU. Patients remained in the study sample until their discharge to another unit or from the hospital. If they were readmitted to the SDU, they were treated as another admission. These criteria yielded a convenience sample of 307 patients during the study time period. The total census of patients on the study unit was included in the sample, with only patients ≤ 21 years of age excluded.

2.4 DEFINITION OF CARDIORESPIRATORY INSTABILITY AND COHORT ASSIGNMENT

During the study continuously monitored vital signs were recorded and then the data were downloaded from the bedside monitors (See 2.7 for data frequency, format, and storage). Data streams were then analyzed to determine if any of the VS variables measured violated the thresholds deemed to constitute normality, and thereby defined as CRI: HR between 40-140 beats per minute, RR between 8 and 36 breaths per minute, and SpO2 > 85%, with additional persistence requirements and artifact elimination as in 2.7. Patients' status was classified as unstable if their continuously monitored and recorded vital signs had even once exceeded any of the normality thresholds during their SDU stay, and as stable if their continuously recorded vital signs had never exceeded any of the thresholds (excluding artifact). A CRI epoch is defined as the first time a VS exceeded normality thresholds, and continues until the time at which all VS return to normality. The patient's first instance of CRI not caused by artifactual VS cross of threshold is assigned as CRI_1. The CRI driver is defined as the VS first to cross the CRI stability thresholds in the CRI_1 epoch.

2.5 SAMPLE SIZE

The sample size is limited to that of the parent study. For this proposed study, 307 patients were included and yielded 22,588 hours of continuous VS monitoring data.

2.6 SAMPLE SIZE JUSTIFICATION

The sample size is a subset of the data obtained in the parent study. Based on our previous studies which indicate CRI prevalence of about 25%, we projected that our total sample of 307 patients would yield 25% unstable (~77 patients) and 75% stable patients. However, there were more unstable patients (n=133) than were initially anticipated. Since Aim 1 of our study was to only provide a baseline assessment of identifying whether any of the admission characteristics differ between CRI and no CRI patients (a dichotomous outcome), our sample size of 307 patients was sufficient for exploration purposes. Specific aim 2 of our study related to the use of unsupervised learning techniques of hierarchical and K-means clustering on the sample to identify potential patterns in CRI manifestation. These procedures were employed only on unstable patients (n=133). There are no generally accepted rules regarding minimum sample sizes or the relationships between the clustering objects and the number of cluster variables. The choice of clustering variables is dependent on the context of the study (CRI from VSTS) with clustering algorithms capable of implementing the procedure with any sample sizes. However, empirically, studies have shown that hierarchical clustering works best with small sample sizes while K-means works best with sample sizes > 100—which was satisfied by the current sample.

2.7 SDU ADMISSION CHARACTERISTICS

Clinical and demographic variables present at the time patients were admitted to the SDU were collected from the patients' clinical records and the hospital's electronic databases. The

following are the admission characteristics that were used—age (continuous), gender (dichotomous M/F), race (categorical), type of medical care service (categorical), hospital admission diagnosis (categorical), medical history (categorical), SDU intake admission source and Charlson comorbidity index (CCI) Deyo Method (cumulative score, 0,1, $\geq$2, categorical). Outcome variables included hospital length of stay (LOS; continuous), SDU LOS (continuous) and transfer from SDU to either a higher intensity monitoring unit or lower intensity monitoring unit. Lower intensity unit collectively included patients transferred either to a rehabilitation center, a long-term hospital, a skilled nursing facility, a home health agency or directly to home. These data collected for the purpose of this research study were assigned a research code number and any obvious patient identifiers (name, SSN, hospital record number) were removed from this information using De-ID software ™ (Gupta et al., 2004) prior to entry into the study database. De-ID™ is recognized as being appropriate for this use by the University of Pittsburgh IRB. These data were extracted for the entire 307 patient dataset and placed in a .csv file for study purposes. All dates in this file (admission time and date, LOS, etc.) have been converted to Coordinated Universal Time (UTC) to ensure congruence of time stamps across years and seasonal time changes.

2.7.1 Continuous vital sign monitoring data

The time stamped analog data for HR, RR and SpO2 (at 1/20 Hz freq.) was downloaded from every bedside onto external drives during the retrospective study interval. All time stamps of the VS data were also converted to UTC time. These time-stamped data were stored as continuous data streams and were identified only according to the bed space monitoring device from which

they were obtained, with no patient identifiers. These data were then placed on the study secure server in .csv file format. To parse the bedside VS data streams in order to assign them to specific patients, an IRB honest broker, Ms. Saul, provided the research team with the patient Study IDs (no identifiers) and their associated times of admission and discharge from each Unit 9G bed space. Each bed space was then correlated to individual patients by using the Study ID only. Once collected, these data were entered into a research database containing no protected health information (PHI) and only included a study-ID to uniquely identify each patient and his/her data stream. The linkage file which was automatically generated by the De-ID software was in an encrypted format and was retained only by Ms. Saul.

3.0 STATISTICAL MANAGEMENT PLAN

3.1 SPECIFIC AIM 1

Hospital admission characteristics consisted of age, gender, race, type of service, medical history, type of service, and Charlson-Deyo comorbidity Index (0,1,> 2).(Deyo, Cherkin, & Ciol, 1992) “Type of Service” was classified as surgical if patients were assigned to the general surgery service on admission to the hospital, irrespective of whether their hospital course warranted a surgical procedure or not. Medical patients were assigned to services such as cardiology, critical care medicine, family medicine, internal medicine, haematology, orthopaedics, otorhinolaryngology, pulmonary and vascular. We also recorded the admission diagnosis as based on the ICD-9 classification code assigned at hospital admission. ICD-9 codes were grouped into 14 categories according to the classification system reported by Brown et al.(Brown, Terrence, Vasquez, Bates, & Zimlichman, 2014) and then reduced to 4 categories based on the majority of codes. The resulting 4 categories were: trauma, diseases of circulatory system, diseases of digestive system and all other diagnoses. We also recorded SDU admission intake source (transfer from higher intensity monitoring, direct SDU admission or transfer from lower intensity unit). Outcomes were total hospital length of stay (LOS) in days, SDU LOS, and discharge disposition from the SDU (transfer to a higher or lower intensity monitoring unit) and mortality.

3.1.1 CRI determination.

Physiologic monitoring data for the 307 patient admissions were available for a mean of 80 hours and median of 60 hours each. HR, RR, and SpO2 data were recorded at 1/20 Hz frequency while systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded less frequently. VS excursions beyond our local criteria for instability concern (HR< 40 or > 140, RR< 8 or > 36, SpO2< 85%, SBP < 80 or > 200, DBP>110) were defined as "CRI events" and occurred 271,288 times. Owing to a high incidence of artifacts with pure threshold deviations, we additionally required that "events" had to persist for a minimum duration of 3 minutes, either continuously or sporadically, for 4 minutes out of a 5-minute moving window (80% duty cycle) with or without changes in other VS, to be initially classified as CRI. Events that did not meet persistence criteria were termed artifact.

Of 307 patients, 113 never developed CRI, leaving 194 patients to be considered who demonstrated 1582 events (Figure 8). We annotated these events as real CRI (1137 events) or artifact (445 events). We created a Gantt chart per patient to record the occurrence of real and artifact events in the order that they occurred during a patient's SDU stay. From that analysis, 61 patients only had artifact alerts, so they were included in the group who never developed CRI. This left a total of 133 (43%) patients who experienced CRI and 174 (57%) who did not.

The driver of CRI was defined as the first VS to cross a threshold and meet persistence criteria. Time to onset of first CRI (CRI1) was the time in days from initial admission to the SDU to CRI1, and duration was length of the CRI1 epoch in minutes.

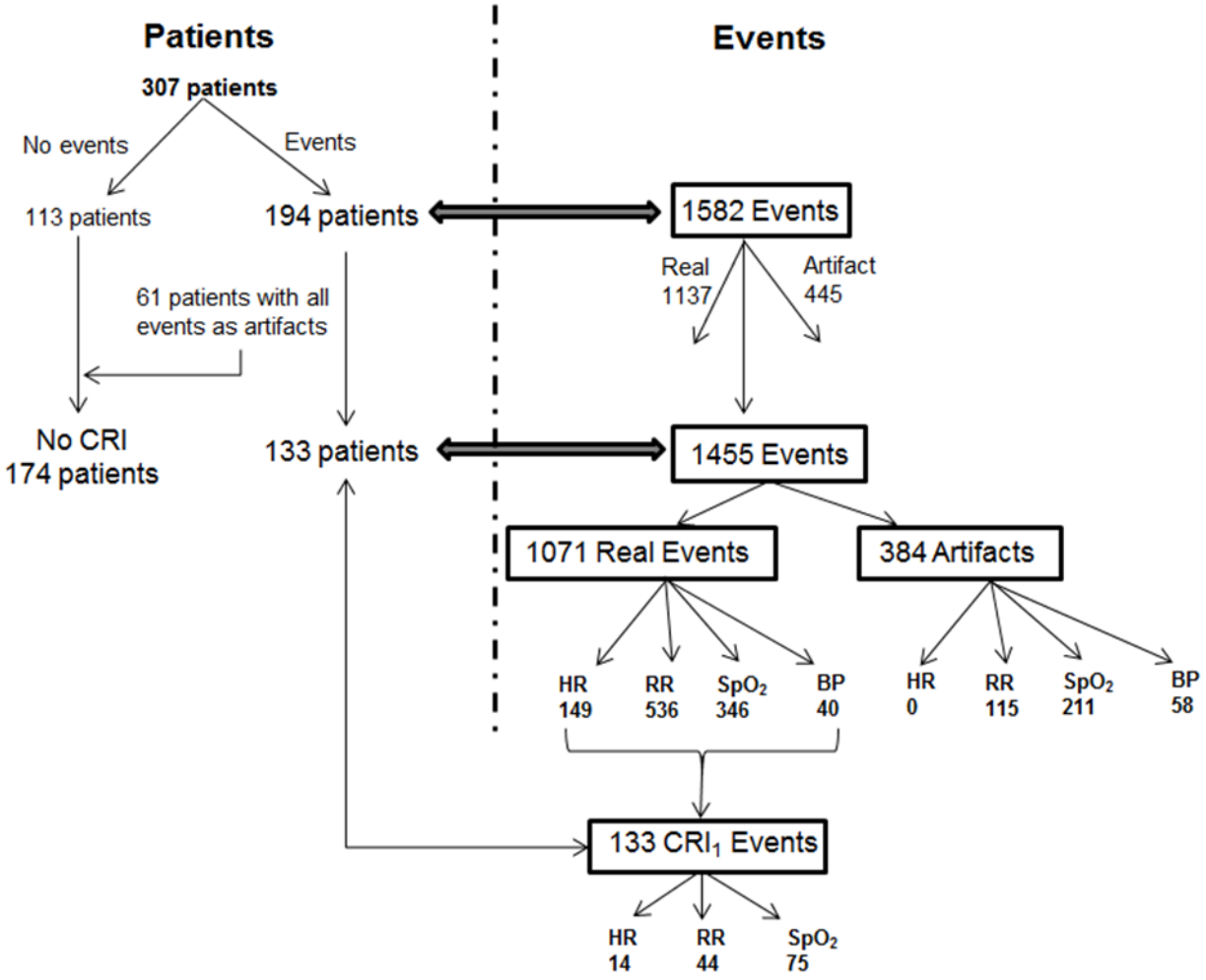

Figure 8. Schematic diagram of patients and events**.**

The schematic details the process of deriving initial cardiorespiratory instability (CRI_1) events and the distribution of events due to cardiorespiratory instability drivers - heart rate (HR), respiratory rate (RR), pulse oximetry (SpO_2) and blood pressure (BP). The resulting sample included 133 patients with initial cardiorespiratory instability (CRI_1) due to HR, RR or SpO_2 which accounted for 133 CRI_1 events.

3.1.2 Statistical Analysis

Data were analyzed using IBM SPSS v22 for descriptive analysis and exploration. The Mann-Whitney U-test was used to analyze non-parametric differences between groups for continuous variables and Chi-square to compare categorical variables. A $p < .05$ was considered significant.

3.2 SPECIFIC AIM 2 & 3

3.2.1 Event Identification (CRI_1 determination)

Continuous bedside physiologic monitoring data were available for a mean of 80 hours per patient. HR, RR, and SpO2 data were recorded at 1/20 Hz frequency. VS excursions beyond our local criteria for instability concern (HR< 40 or > 140, RR< 8 or > 36, SpO2< 85%) not due to artifact were defined as CRI if they persisted for a minimum duration of 3 minutes, or for 4 minutes out of a 5-minute moving window (80% duty cycle) with or without changes in other VS. Of the 307 patients, 133 (43%) experienced CRI and 174 (57%) did not. For this aim, analysis of data was restricted to the first CRI event (CRI_1). The first vital sign to exceed the previously identified thresholds was termed the CRI_1 driver.

3.2.2 Cluster identification

Steps in preprocessing were feature extraction, standardization, and outlier removal. A combination plot of the feature space of all variables was created to facilitate visualization of all

possible combinations between VS for each of the features. Hierarchical and k-means clustering were then used to complete analysis of the data.

3.2.2.1 Feature extraction, standardization and outlier removal

We extracted statistical features (mean, median, mode, minimum, maximum, range, variance and standard error of mean) for HR, RR, and SpO2. Since measurement of each VS used a different scale, we standardized the variables, thus rendering them scale free. Clustering techniques and k-means in particular are sensitive to outliers, causing outliers to be selected as initial clusters. Two patients with this characteristic were eliminated ($|z| > 3.29$), leaving 131 patients.

3.2.2.2 Combination plot of feature space

Figure 9 shows the combination plot. In this analysis, if a feature for HR exists but RR does not exist, it is dark grey colored, indicating missingness. We discovered 13 patients with only HR and RR, 7 patients with only HR and SpO2, 5 patients with missing data for HR or SpO2 and 3 patients with only SpO2. These 28 patients were omitted, leaving 103 patients with complete data for cluster analysis.

3.2.3 Hierarchical clustering—Ward's linkage procedure

We next implemented agglomerative hierarchical clustering on the remaining sample. In order to form clusters, there must be a criterion for similarity or distance between patients and a criterion for determining which clusters are to be linked at successive steps. We used squared Euclidean distance, since all variables were continuous, and Ward's linkage method for determining

linkage of clusters. The algorithm began by merging similar clusters, two at a time, at successive steps until all cases were complete. Additional cases were then added to the cluster using the linkage procedure.

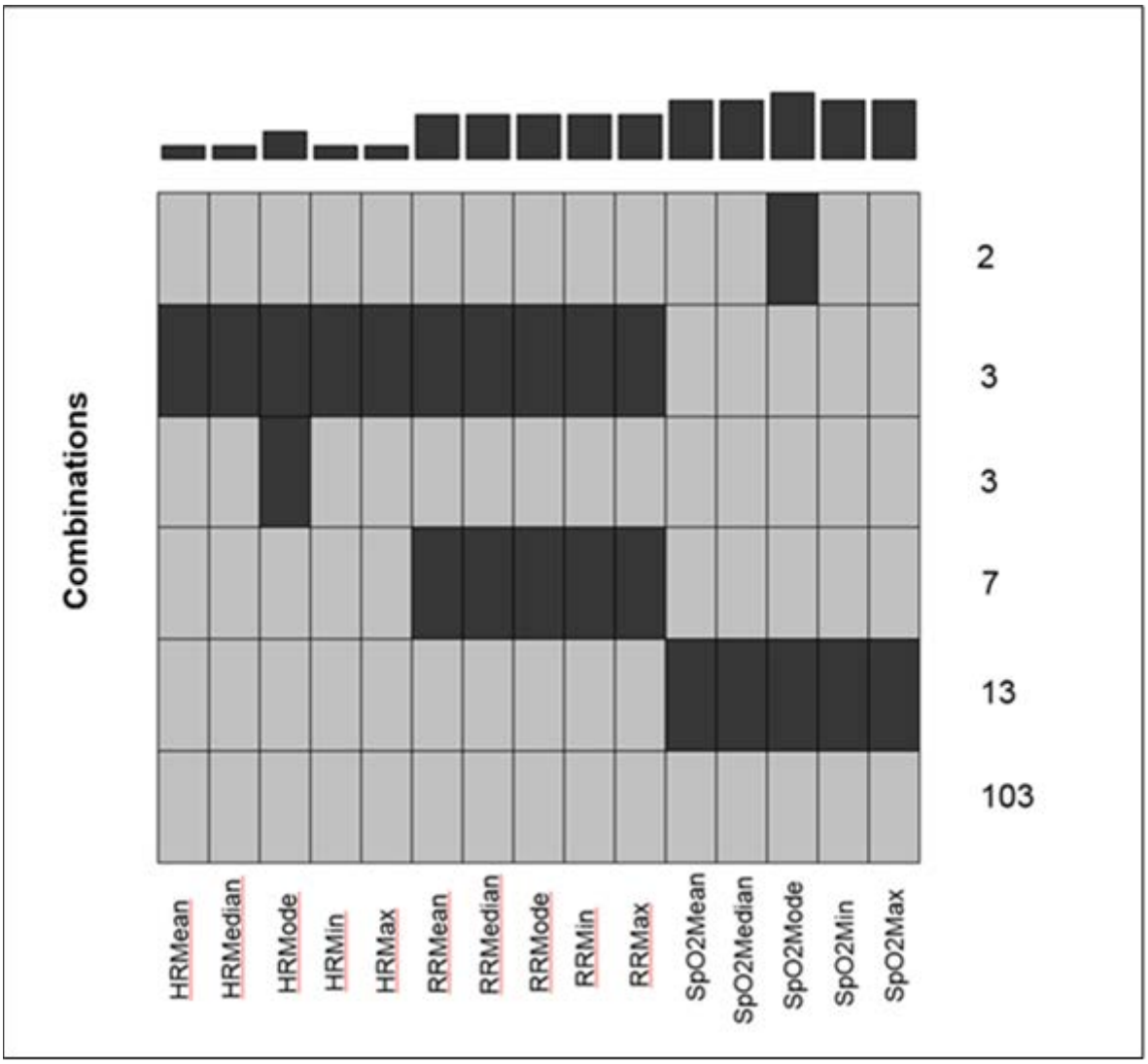

Figure 9. Combination plot of the feature space.

A combination plot is a visualization of all possible combinations between the feature space and the combination of each feature to the next, for all the available patients. The dark grey color indicates missingness. There were 13 patients with only heart rate (HR) and respiratory rate

(RR), 7 patients with only HR and peripheral pulse oximetry (SpO2), 5 patients with missing modes in either HR or SpO2 and 3 patients with only SpO2.

The algorithm developed a proximity matrix to calculate the squared Euclidean distance between the standardized features for all patients (Jain et al., 1999). Clustering began with each case being a cluster unto itself. Next, cases with smaller distances from each other were linked until all clusters were completed and means for all variables were calculated for each cluster. The squared Euclidean distance to cluster means was calculated and distances summed for all cases. At each stage, the two clusters that merged were those that resulted in the smallest increase in the overall sum of squares within-cluster distances. A visual representation of the distance at which clusters combined was represented by a dendrogram.

3.2.4 K-means clustering

The major difference in k-means involves pre-specifying k, which is the number of clusters. By visualizing potential cluster solutions from the dendrogram, we chose an initial starting value for k at 3. The first step in k-means clustering involved finding k centers. The algorithm started with an initial set of means and classified patients based on their distances to the centers. Next, it re-computed the cluster means using patients that were assigned to the cluster and then reclassified all patients based on a new set of means. The steps were then repeated until cluster means changed minimally between successive steps. Finally, the algorithm calculated the means of the clusters again and assigned patients to their permanent clusters. We tested several clustering solutions that entailed using 3 to 5 clusters after visualizing the dendrogram obtained from hierarchical clustering.

3.2.5 Feature selection

Following initial identification of clusters, an ANOVA table was constructed to describe F ratios per feature within the clusters for a particular solution. If non-significance was observed, it indicated that that feature contributed minimally to separation of clusters. From this analysis, we discovered that VS range, variance and standard error of mean value were mostly non-significant whereas features of mean, median, mode, maximum and minimum always contributed significantly to differences between clusters. Hence, we used the latter 5 features per VS for further clustering analyses.

3.2.6 Cross Validation of Cluster Solution

As the final step, we implemented cross-validation (CV) of each of the cluster solutions. To determine the best solution, we performed a commonly used process(McLachlan, Do, & Ambroise, 2005) termed a stratified 10-fold CV to each solution. For this analysis, the original sample was partitioned into 10 equal sized subsamples. A single subsample was retained as validation set for testing the cluster solution with the remaining 9 subsamples used as training data and the process repeated 10 times. The advantage of this method is that all observations are used for both training and validation, and each observation is used for validation exactly once. The performance of a particular clustering solution was assessed by its accuracy, which is the number of correctly classified instances.

3.2.7 ANOVA Posthoc Bonferroni Test

To test if there were significant differences between per feature between various clustering solutions, we implemented ANOVA posthoc bonferroni test with the dependent variable as the feature (eg: HRMedian, HRMode etc), with the fixed factor being the cluster grouping (eg: C3-1, C3-2 etc).

3.2.8 CRI_1 driver within each cluster of patients

Once we identified the best cluster solution, we labeled each cluster based on the general pattern of each VS within that particular cluster. We also examined the interaction among VS within that cluster and its relationship with the other two VS per patient, using cross correlations of HR with RR, HR with SpO2 and RR with SpO2 per patient within each cluster.

3.2.9 Admission characteristics and outcomes

Admission characteristics were age, gender, race, type of service (admitted to a medical or surgical service, irrespective of whether they had a later surgery or not), medical history, and Charlson-Deyo comorbidity Index (0,1,> 2).(Deyo, Cherkin, & Ciol, 1992) We recorded admission diagnosis based on the ICD-9 classification code assigned at hospital admission, which we first grouped into 14 categories according to the classification system reported by Brown et al.(Brown, Terrence, Vasquez, Bates, & Zimlichman, 2014), and further reduced into 4 categories based on code frequency. The resulting 4 diagnosis categories were: trauma, diseases

of circulatory system, diseases of digestive system, and all others. We also recorded SDU admission intake source (transfer from a higher intensity monitoring unit, or direct SDU admission or transfer from lower intensity unit). Outcomes were hospital length of stay (HLOS) in days, SDU length of stay (SDU LOS), and discharge disposition from the SDU (transfer to a higher or lower intensity unit). Lower intensity unit collectively included patients transferred either to a rehabilitation center, a long-term hospital, a skilled nursing facility, a home health agency or directly to home. In our sample, there were no reported deaths for any of the patients.

3.2.10 Medications per cluster and a control group

We reviewed the list of medications given 24 hours prior to and after CRI_1 epoch, per patient within each cluster. Since patients received several types of medications, based on critical care expert physician reviews, we pooled medications into seven different categories. The categories were AntiInfectives (which included antibacterial, antifungal and antivirals), Cardiovascular Drugs, Vitamins/Electrolytes/Hematinics, Fluids, Respiratory Drugs, Narcotics and Sedatives and Other (all other drugs besides the other 6 categories).

The choice for the control group (patients who never developed CRI) was based on the following stratified random sampling approach. Within the set of patients used for clustering, the breakdown by hospital admission diagnosis was—52.4% Trauma, 15.5% diseases of circulatory system, 14.6% diseases of digestive system and 17.5% all other diagnoses. Further, based on the driver of CRI_1, most CRI_1 events occurred on Day 2 of SDU admission. The selection process for the control group therefore used Day 2 of the SDU admission for No CRI patients. Medications administered on Day 1 (24 hours prior) and Day 3 (24 hours after). Similar to

patients with CRI, their medications were also grouped into the same 7 different categories. We randomly chose 50 patients from the 174 patients who never developed CRI. However, the choice for these 50 patients was based on a stratified random sampling approach of using

52.4 % of 50 = 26 Trauma patients

15.5% of 50 = 8 disease of circulatory system patients

14.6% of 50 = 7 disease of digestive system patients and

17.5% of 50 = 9 All other diagnoses patients.

3.2.11 Statistical Analysis

Data were analyzed using IBM SPSS v22 for descriptive analysis and exploration, WEKA and MATLAB R2015a for clustering and cross validation. We also examined the interaction among VS within that cluster and its relationship with the other two VS per patient, using cross correlations of HR with RR, HR with SpO2 and RR with SpO2 per patient within each cluster. One way ANOVA was used to verify if there were inter-cluster differences between age (continuous variable), while a Chi-square test was used to verify if there were inter-cluster differences based on other categorical variables (gender, race, type of service, hospital admission diagnosis, SDU admission source and Charlson Comorbidity Index). A chi-square test was also used to verify whether there were differences in the proportion of medications received between each of the clusters (1,2,3 and 4) and the control group (Cluster 0) by each medication category.

4.0 HUMAN SUBJECTS RESEARCH

4.1 RESPONSIBLE CONDUCT OF RESEARCH

All doctoral students are required to complete the University of Pittsburgh Education and Certification Program in Research and Practice Fundamentals, an online educational series designed to provide training to individuals employed by the University of Pittsburgh, and its affiliated institutions. The program consists of both required and optional modules, depending on one's research focus. There are four required modules:

Module 1—Research Integrity

Module 2—Human Subjects Research

Module 6—HIPPA Researchers Privacy Requirements

Module 14—UPMC HIPPA Staff Security Awareness Training

Upon completion of this program, a certification is stored in a database and the examinee is able to print out a hard copy of this certificate for their records and submission to the Public Health Service granting agencies. The PI successfully completed modules 1, 2, 6 and 14. Certificates of successful completion are on file.

Ethical issues related to human subjects' research are incorporated in doctoral courses including Nursing Theory and Research, Research Methods, Qualitative Research, Pilot study, Grant writing Practicum, Research Development and others. Areas covered in these courses include

ethical issues related to obtaining informed consent, participant confidentiality, conflict of interest, research integrity, protection of vulnerable subjects, internal audit procedures, seeking IRB approval, and adverse event monitoring. Further instruction was received through the various research seminars the PI attended including the Surviving Skills Workshop, Research Methodology Series, and Research Progress Update Series available through the School of Nursing and the University.

4.2 PROTECTION OF HUMAN SUBJECTS

All the data were deidentified and retrieved from a retrospective chart review of existing databases and the data will be linked to specific patient identifiers once all the data has been collected from the data sources. The University of Pittsburgh Institutional Review Board reviewed and approved the study by the expedited review procedure authorized under 45 CFR46.110 and 21 CFR 56.110. All study data were stored in a locked filing cabinet in the School of Nursing. All study data were managed in a secure password protected and encrypted database. Research records were maintained for as long (indefinite) as it took to complete this research study, as well as the parent study. Research subjects were never identified by name.

4.3 WOMEN, MINORITY AND CHILDREN INCLUSION IN RESEARCH

4.3.1 Inclusion of women and minorities

The study enrolled both men and women who experienced CRI during the study time frame. The current UPMC patient demographic composition by gender, race and ethnicity is 49% female, 51% male, 1% Hispanic, 99% Non-Hispanic with the non-Hispanic population of 0% American Indian/ Alaskan native and Native Hawaiian/Pacific Islander, 5% Asian, 20% African American and 75% Caucasian. We anticipated that prevalence of the gender and race of the patients who experienced CRI will be consistent with these UPMC—wide patient demographics and noticed this to be true in the results. No one was excluded from participation in this study based on race, ethnicity or gender.

4.3.2 Inclusion of Children

The study setting was an adult tertiary care hospital where the care of children is a rare occurrence, however children under 18 years of age who may experience a MET activation were excluded from this study due to the unique patterns of instability and surveillance required and special training necessary for pediatric care.

4.4 DATA SAFETY AND MONITORING PLAN

Data and safety monitoring was conducted during monthly meetings with the dissertation committee. During these meetings any change in exempt status for human research were discussed and addressed. We were prepared to report any change of status immediately to the IRB, but this was never needed. A summary of these reviews was provided to the IRB at the time of the yearly renewal. There was no change in exempt status.

5.0 RESEARCH RESULTS AND DISCUSSION: SPECIFIC AIM 1

5.1 RESULTS FOR SPECIFIC AIM 1

Hospital admission characteristics of the 307 patients (174 with no CRI and 133 with CRI) are related in Table 1. There were no significant differences between CRI and no CRI patients in regard to age, gender, race, or admission service. Chronic obstructive pulmonary disease was the most common comorbidity (16.6%), but there were no significant differences in comorbidities between groups. Slightly more than half (52.1%) had a Charlson Comorbidity index of 0, indicating a relatively healthy population; however there were no significant differences between CRI and no CRI groups.

There were significant differences between groups based on SDU intake admission source (p=.042) (Table 2). Almost half of CRI patients were admitted to the SDU from an intensive care unit (ICU) (44.4%), whereas less than a third (31%) of no-CRI patents were admitted from an ICU. CRI patients had a longer hospital LOS (11.3 days [95% CI = 9.6-13.0]) than the no-CRI patients (7.8 days [95% CI = 6.4-9.20], p=.001). The mean SDU LOS was also longer for CRI patients (6.1 days [95% CI = 5.3-6.9]) than the no-CRI patients (3.5 days [95% CI = 3.1-3.9], p<.001). There was no significant difference between groups in terms of discharge destination or mortality.

Table 1. Hospital admission characteristics in patients with and without one cardiorespiratory instability (CRI) event during step-down unit length of stay

Variable	Total (N=307) No. (%)	No CRI (n = 174) No. (%)	CRI (n = 133) No. (%)	p-value
Age, mean, SD	57.4 ± 20.2	55.9 ± 20.4	59.28 ± 19.9	.146
Gender, n (%)				.55
Male	179 (58.3)	104 (59.8)	75 (56.4)	
Female	128 (41.7)	70 (40.2)	58 (43.6)	
Race, n (%)				.136
White	220 (71.7)	117 (67.2)	103 (77.4)	
Black	43 (14)	29 (16.7)	14 (10.5)	
Other	44 (14.3)	28 (16.1)	16 (12.0)	
Type of Service, n (%)				.54
Surgical	167 (54.4)	92 (52.9)	75 (56.4)	
Medical	140 (45.6)	82 (47.1)	58 (43.6)	
Hospital Admission Diagnosis				.124
Trauma	176 (57.3)	106 (60.9)	70 (52.6)	
Diseases of Circulatory System	46 (15)	27 (15.5)	19 (14.3)	
Diseases of Digestive System	34 (11.1)	13 (7.5)	21 (15.8)	
All other diagnoses	51 (16.6)	28 (16.1)	23 (17.3)	
Medical History				.278
Chronic Obstructive Pulmonary Disease	51 (16.6)	25 (14.4)	26 (19.5)	
Diabetes	50 (16.3)	25 (14.4)	25 (18.8)	
Myocardial Infarction	25 (8.1)	11 (6.3)	14 (10.5)	
Congestive Heart Failure	24 (7.8)	9 (5.2)	15 (11.3)	
Cerebral Vascular Disease	20 (6.5)	12 (6.9)	8 (6)	
Charlson-Deyo Comorbidity Index				.507
0	160 (52.1)	94 (54)	66 (49.6)	
1	76 (24.8)	44 (25.3)	32 (24.1)	
≥ 2	71 (23.1)	36 (20.7)	35 (26.3)	

Table 2. Intake admission source to the step-down unit (SDU), and outcomes in patients with and without one cardiorespiratory instability (CRI) event during step-down unit (SDU) length of stay

Variable	Total N = 307	No CRI (n=174) No. (%)	CRI (n=133) No. (%)	p-value
SDU Intake Admission Source				**.042**
Higher intensity monitoring unit	113 (36.8)	54 (31)	59 (44.4)	
Direct Admission, or lower intensity monitoring unit	182 (59.3)	109 (62.6)	73 (54.8)	
Unknown	12 (3.9)	11 (6.3)	1 (0.8)	
Outcomes				
Hospital LOS, mean days, SD	9.2 ± 9.8	7.8 ± 9.2	11.3 ± 10.2	**.001**
SDU LOS, mean, SD	4.7 ± 4.2	3.5 ± 2.9	6.1 ± 4.9	**<.001**
Transfer from SDU to a higher intensity unit, n (%)	31 (10.1)	15 (8.6)	16 (12.0)	.449
Died, n (%)	5 (1.6)	5 (2.9)	0	

Key: LOS = length of stay

5.1.1 Drivers of CRI

Of the 133 patients with CRI they had collectively 1071 CRI events (Figure 8), the CRI driver for 536 (50%) of these events was RR. SpO2 was the driver for 346 (32%) events, HR for 149 (14%) and BP for 40 (4%). Although RR was the most common initial cause of CRI events overall, for the first 133 CRI events (CRI_1), SpO2 was most common (56%), followed by RR (33%) and HR (11%) (Figure 10).

5.1.2 Onset of initial and subsequent CRI Events

We computed the number of days from SDU admission to the development of CRI_1 by driver. As shown in Figure 11, CRI_1 driven by HR tended to occur between days 1 and 6. CRI_1 driven by RR varied in presentation between the first 10 days of SDU admission, with 34% developing CRI_1 on days 1-2. CRI_1 driven by SpO2 tended to occur between day 0 and day 6, with 47% occurring between days 0 and day 2. As shown in Figure 12, a minority (23%) of patients with one CRI_1 event never developed a second CRI event, while the remaining 77% of patients exhibited an average of 2-5 events each.

5.1.3 Duration of CRI_1 Epoch

For HR, CRI1 duration lasted between 3-8 minutes, with most lasting 4 minutes. For RR, CRI1 duration ranged from 3-20 minutes, with 48% of patients having duration of 3 minutes. For SpO2, CRI1 duration ranged from 3-56 minutes, with 76% lasting between 3 and 6 minutes.

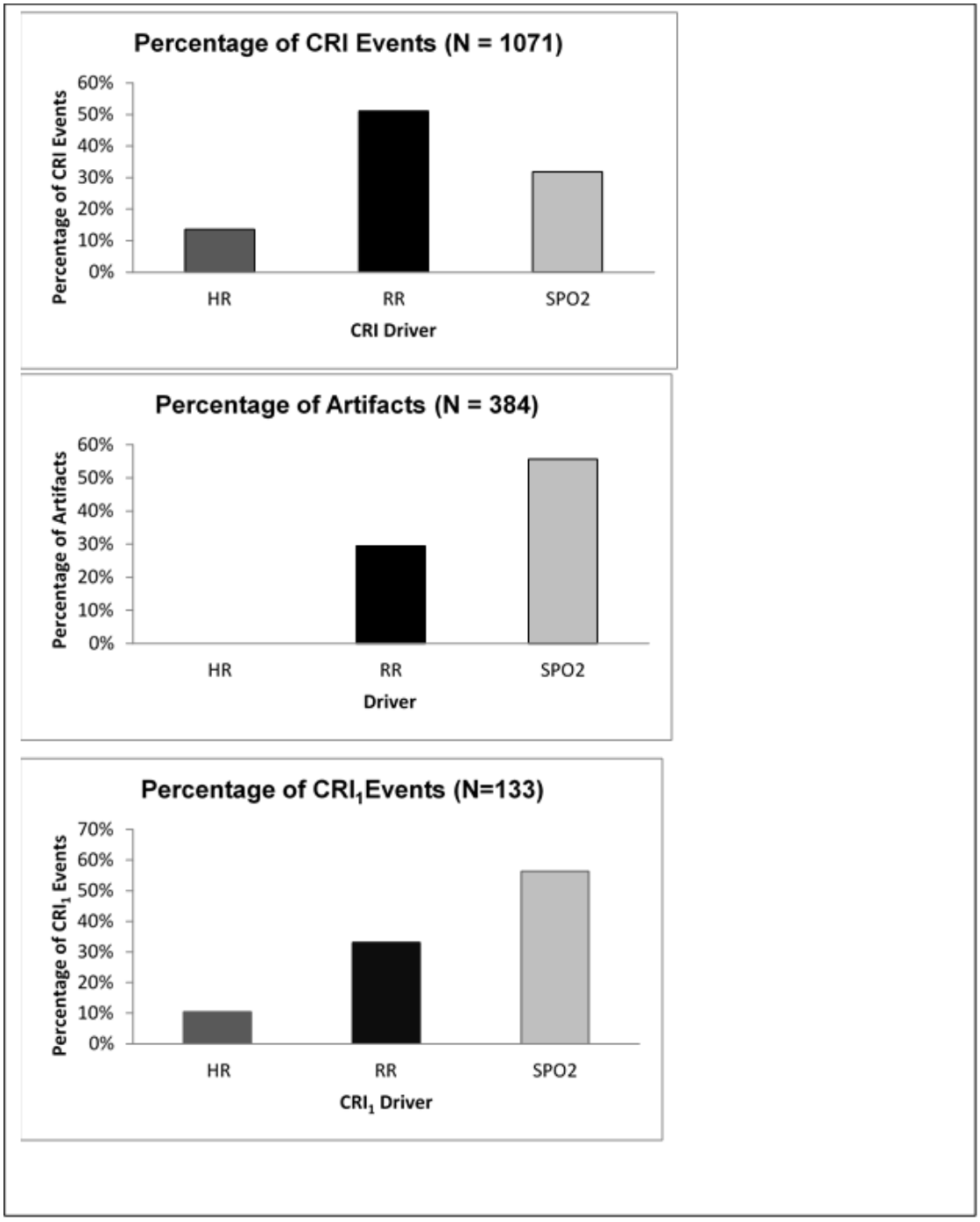

Figure 10. Percentage of cardiorespiratory instability (CRI) events and artifacts in 133 patients.

The CRI driver was most commonly respiratory rate (RR) while arterial oxygen saturation (SpO2) was the cause of most artifacts. SpO2 was also the most common cause of the first cardiorespiratory instability event (CRI_1). Heart rate (HR) was a relatively infrequent cause.

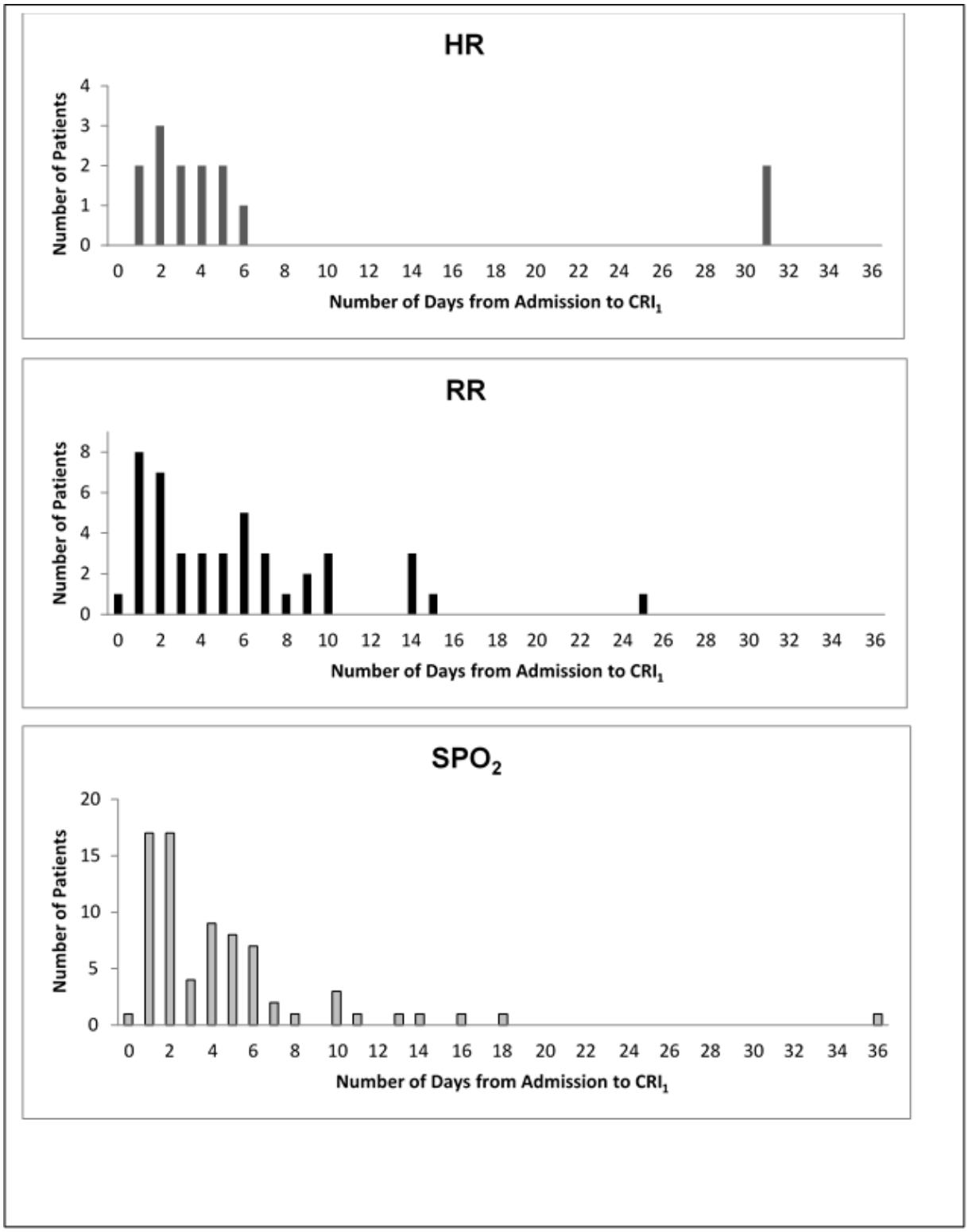

Figure 11. Number of days from admission to development of the first cardiorespiratory instability event (CRI_1).

CRI_1 events most commonly occurred in the initial days following step-down unit admission.

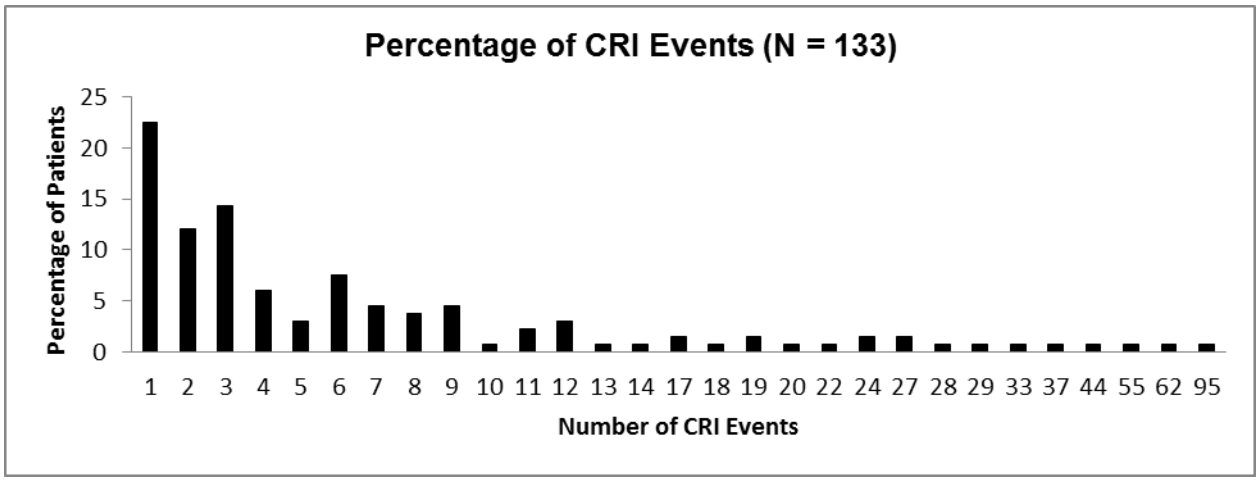

Figure 12. Frequency of further cardiorespiratory instability (CRI) events in patients who developed at least one instance of CRI.

Most events occurred on the first days of step-down unit admission with a progressive decline over time.

5.2 DISCUSSION FOR SPECIFIC AIM 1

The major findings from this study are: 1) There were no demographic differences between patients who did and did not develop CRI, except that patients who were admitted from an ICU were more likely to become unstable; 2) patients who developed at least one instance of CRI had longer lengths of SDU and hospital stays; 3) the driver for most CRI events was RR; and 4) onset

of CRI1 differed between drivers, whereas SpO2 was the most common CRI1 driver. While CRI1 due to HR and SpO2 tended to occur between the 1st and 6th day, CRI1 due to RR occurred later in hospitalization (up to the 10th day); 5) duration of CRI1 due to SpO2 tended to last longer, while duration of CRI1 due to HR was short-lived.

Patients are admitted to a SDU because they are viewed as potentially unstable and in need of closer monitoring for CRI, but knowing which VS to observe more carefully would be helpful. Respiratory rate, which has been termed the "neglected sign",(Cretikos et al., 2008) caused more events within our sample than HR or SpO2. Our findings suggest that RR should receive greater emphasis as an important component of clinical monitoring. The importance of this finding is reinforced by the criteria we used to define RR as a driver of CRI, e.g., a rate that was clearly abnormal (<6 and >36 min-1). It is therefore likely that RR is more sensitive and may be abnormal before reaching these threshold values. Respiratory rate is altered by numerous clinical states commonly seen in SDU patients, such as pain, pre-existing lung disease, infection, and opioid use. An increase in RR signals increased work of breathing, which places additional stress on the cardiovascular system. Consequently an increase in RR is an important predictor of cardiopulmonary arrest.(Hodgetts, Kenward, Vlachonikolis, Payne, & Castle, 2002) Findings of our study can be best paired with those of Nurmi et al.(Nurmi, Harjola, Nolan, & Castren, 2005) who found the most common medical emergency team trigger criteria was respiratory distress. Goldhill et al.(Goldhill & McNarry, 2004) identified RR and HR as the VS most often abnormal prior to unexpected death. Despite these known associations, RR is too commonly dismissed as an indicator of distress and recorded as an approximate value or consistently recorded as either 16 or 18(Cooper, Cant, & Sparkes, 2014). Education regarding the importance of proper

monitoring and reporting of values which exceed expected norms should become an integral part of staff orientation and continuing education.

We also found that patients admitted from a higher intensity monitoring unit were more likely to develop CRI, a finding that also has implications for practice. Although objective criteria exist for determining optimal time for transfer out of the ICU, the decision is often driven by a variety of factors, including subjective judgment. (Garland & Connors, 2013) In addition, bed availability, both in the ICU and SDU, can influence timing of transfer. (Truog et al., 2006) The process of transfer, itself, can lead to increased stress and the potential for instability. Our findings suggest that close observation is indicated in the initial hours following transfer and for the next several days. In our sample, CRI tended to occur early following SDU admission. Notably, 77% of patients who developed one CRI event subsequently developed additional events. This suggests the need to monitor patients more closely following SDU admission and monitor patients who experience CRI even more closely. Conversely, more than half of our sample never became unstable. If models could be developed that could predict patients who never become unstable, the ability to predict instability would have implications for patient triage and enable clinicians to focus attention on those with greater instability likelihood.(Chen, Dubrawski, Hravnak, Clermont, & Pinsky, 2014)

Patients who developed CRI had increased SDU and hospital length of stay, similar to the findings obtained by Fuhrmann et al.(Fuhrmann, Lippert, Perner, & Østergaard, 2008) Lighthall et al.(Lighthall et al., 2009) showed that patients with abnormal VS had a LOS twice that of “normal”. We also demonstrated that patients with CRI had both hospital LOS and SDU LOS that were twice that of the no-CRI patients. The literature reports increased 30-day mortality in patients with abnormal VS, (Bell et al., 2006; Fuhrmann et al., 2008; Goldhill & McNarry, 2004)

with the greater the number of abnormal VS, the greater the risk of mortality. While it is likely that mortality increases with increasing numbers of abnormal VS, in our study mortality between patients with and without CRI was not statistically significant, likely due to our small sample size.

5.3 LIMITATION FOR SPECIFIC AIM 1

The study has several limitations. The sample size was small and our thresholds for abnormality were externally set independent of prior physiologic analysis. However, these are the threshold values commonly used as medical emergency team trigger criteria. (Hravnak et al., 2011; Hravnak et al., 2008; Smith, Prytherch, Schmidt, Featherstone, & Higgins, 2008) Use of lower thresholds might have altered our results. Our data apply to the SDU of one Level-1 Trauma Center and may not be reflective of other settings or patient populations. Finally, our process of identifying events as “real” versus artifact may have misclassified events.

5.4 CONCLUSION FOR SPECIFIC AIM 1

Our retrospective analysis of CRI in monitored SDU, shows that patients admitted from a higher intensity monitoring setting were more likely to become unstable than those from elsewhere. Furthermore, patients who experienced one CRI event were more likely to have additional CRI events during their SDU stay and to remain longer in both SDU and hospital. The driver for most CRI events was RR although the initial CRI event was more often SpO2. Finally most CRI1

occur within the first 72 hours of SDU admission. Interestingly, there were no other demographic differences in patients who did and did not develop CRI. Findings suggest the need to more closely monitor SDU patients transferred from an ICU and accurately monitor for respiratory insufficiency.

6.0 RESEARCH RESULTS AND DISCUSSION: SPECIFIC AIMS 2 &3

6.1 RESULTS SPECIFIC AIM 2

Of 307 patients, 133 (43.3%) developed CRI1 due to HR, RR or SpO2. In 14 (11%) HR was the driver, in 44 (33%) RR was the driver and in 75 (56%) SpO2 was the driver, making SpO2 the most prevalent driver. A summary of features extracted from CRI_1 epochs per VS is provided in Table 3.

Table 3. Numeric features extracted from initial cardiorespiratory instability (CRI_1) epoch by vital signs of heart rate (HR), respiratory rate (RR) and arterial pulse oxygenation (SpO2) in N=133 patients.

Feature	**HR** **Mean ± SD**	**RR** **Mean ± SD**	**SpO_2** **Mean ± SD**
Mean	88.79 ± 25.52	17.42 ± 8.77	87.17 ± 7.39
Median	88.75 ± 25.83	17.46 ± 8.9	87.25 ± 7.35
Mode	88.85 ± 26.85	17.38 ± 8.93	87.28 ± 7.59
Maximum	95.19 ± 29.82	21.24 ± 10.01	90.07 ± 5.99
Minimum	83.02 ± 22.02	13.37 ± 7.91	84.18 ± 9.41
Range	12.35 ± 15.85	7.87 ± 5.53	5.89 ± 5.33
Variance	34.32 ± 134.69	7.98 ± 11.78	5.48 ± 12.09
Std. error of mean	0.98 ± 1.43	0.60 ± 0.45	0.45 ± 2.63

6.1.1 Hierarchical and K-means Clustering

Results of hierarchical clustering and distribution of the 133 patients into clusters (C) are shown for the 3 cluster solution (Figure 13), 4-cluster solution (Figure 14) and 5-cluster solution (Figure 15). For a 4-cluster solution, results were: C1 24%, C2 61%, C3 8%, and C4 7%. Using this information, we tested k-means clustering with k-values set between 3 and 5. The result of a 3-cluster solution is shown in Figure 16. Since k-means uses a different algorithm compared to hierarchical clustering, for k=4 the results were: C1 9%, C2 59%, C3 24% and C4 8% (Figure 17). With k=5 the results were: C1 24%, C2 7%, C3 31%, C4 8% and C5 30%.(Figure 18).

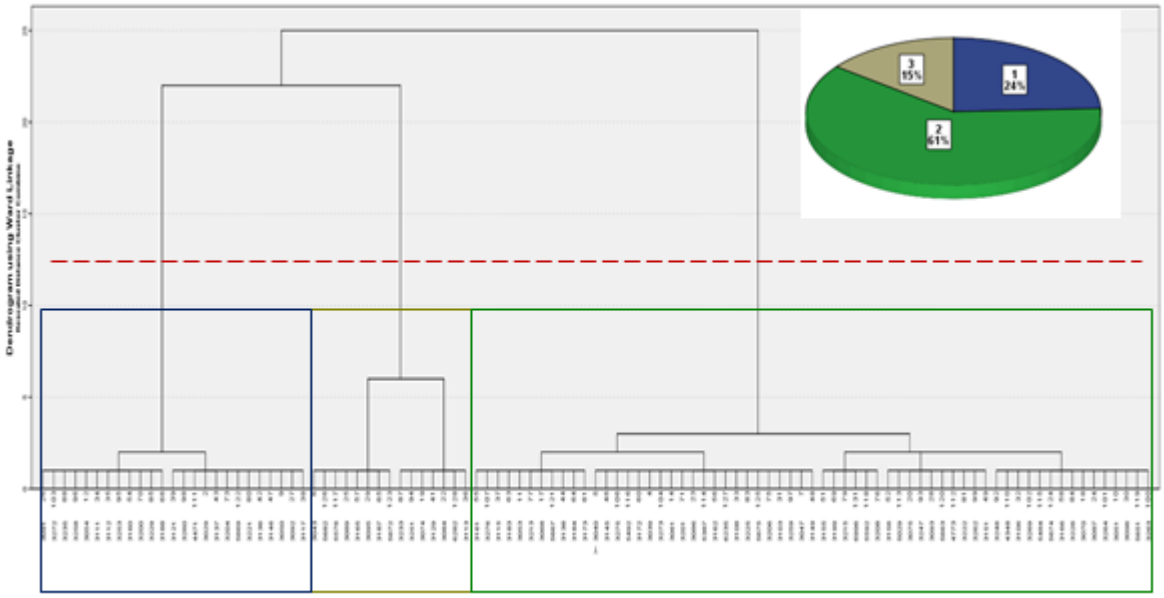

Figure 13. Dendrogram for 3 cluster solution

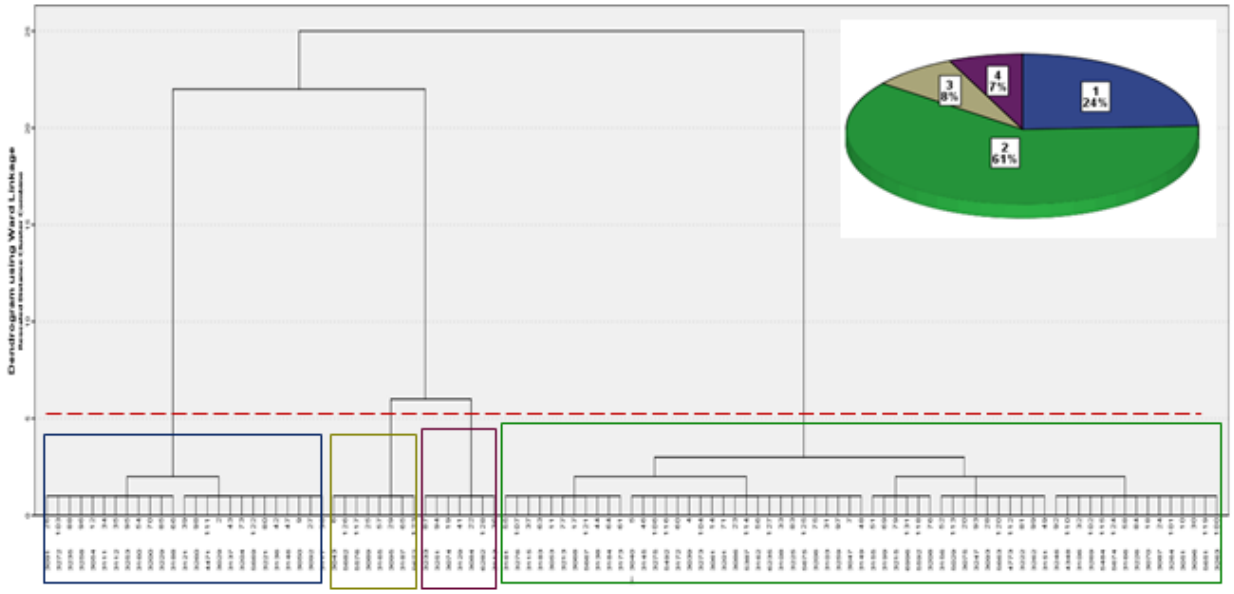

Figure 14. Dendrogram for 4-cluster solution

The dendrogram is read from bottom to top, with the vertical lines showing joined clusters. The bottom most row contains all N=103 patients. Hierarchical clustering and Ward linkage method joined the cases. The figure shows the cut dendrogram to obtain a 4-cluster solution along with the breakdown of the cases pie chart. The majority (61%) of cases were in cluster 2. Cluster distances are plotted with the dendrogram which is read from bottom to top with the vertical lines showing joined clusters. The plot is rescaled to fall within the range of 1 to 25; however the ratio of the rescaled distances within the dendrogram is the same as the ratio of the original distances.

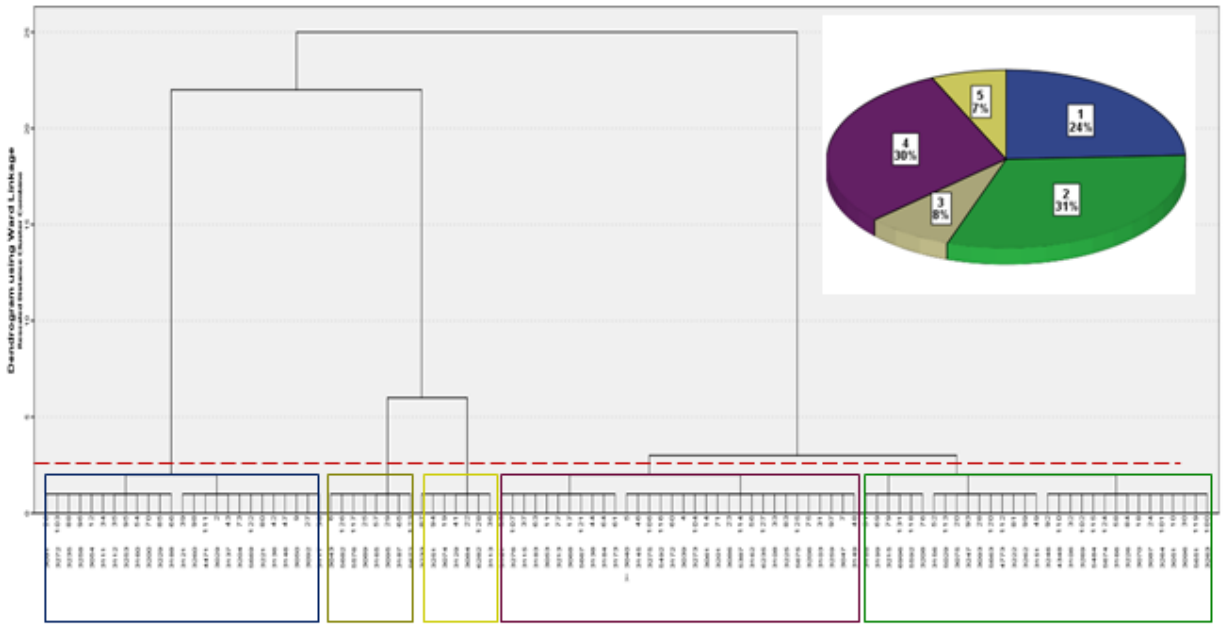

Figure 15. Dendrogram for 5-cluster solution

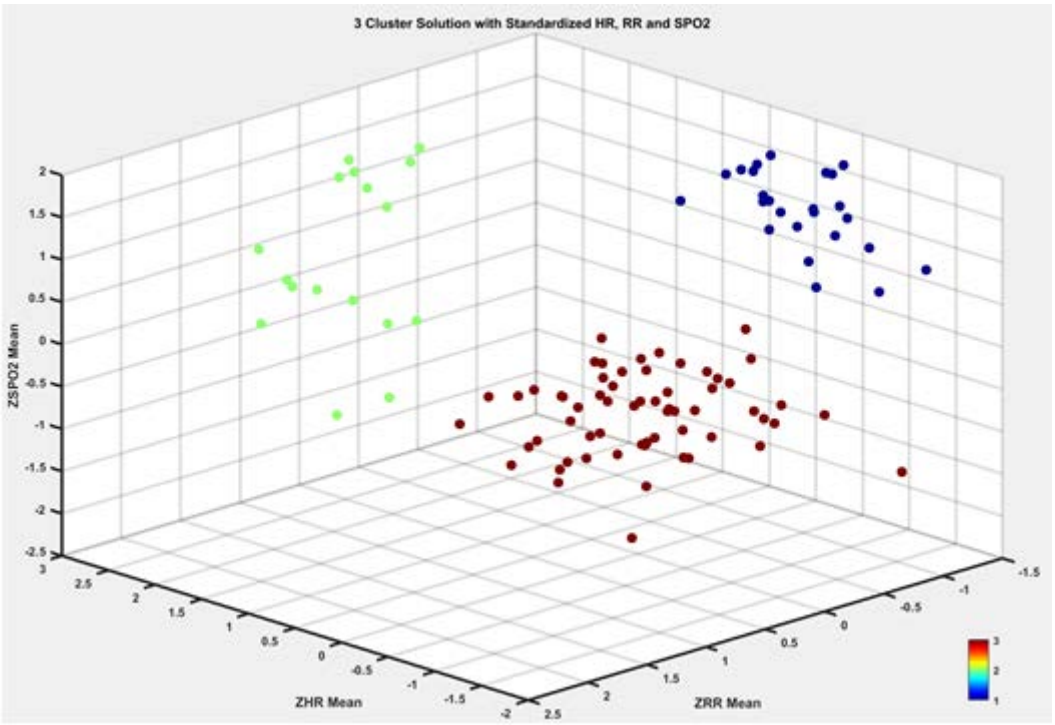

Figure 16. K-Means 3 cluster solution

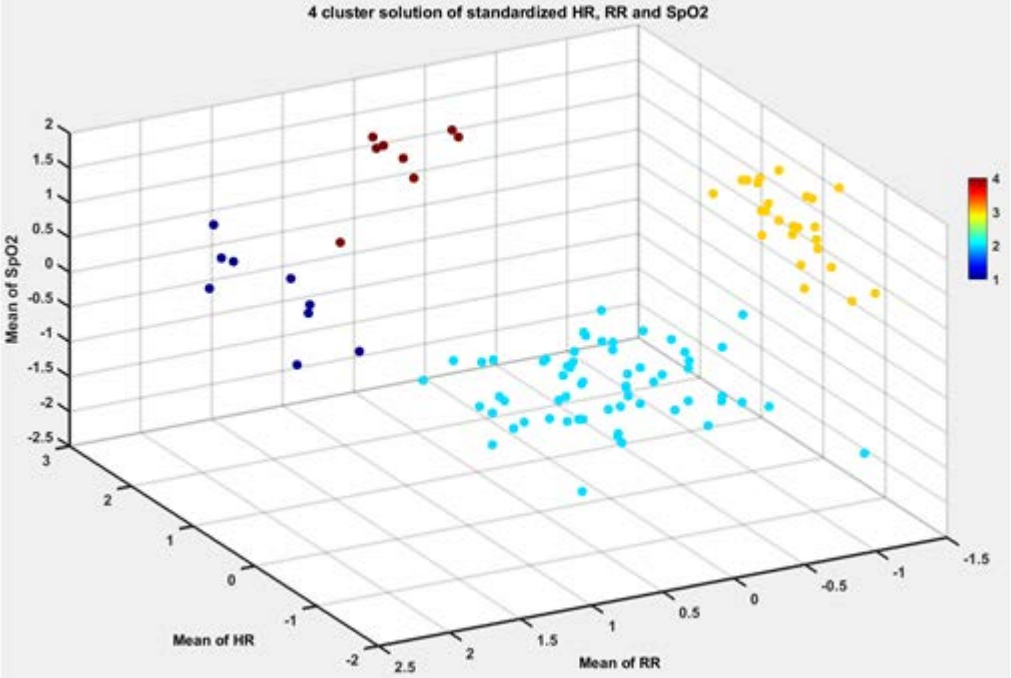

Figure 17. K-Means 4 cluster solution

For a 4-cluster solution, with k=4, there were 9 patients in cluster 1, 61patients in cluster 2, 25 patients in cluster 3 and 8 patients in cluster 4. The axis contains the standardized values of the mean for heart rate (HR), respiratory rate (RR) and arterial pulse oximetry (SpO2). The largest cluster is on the bottom of the 3D-graph. The pattern for this group is normal HR, low/normal RR and low SpO2.

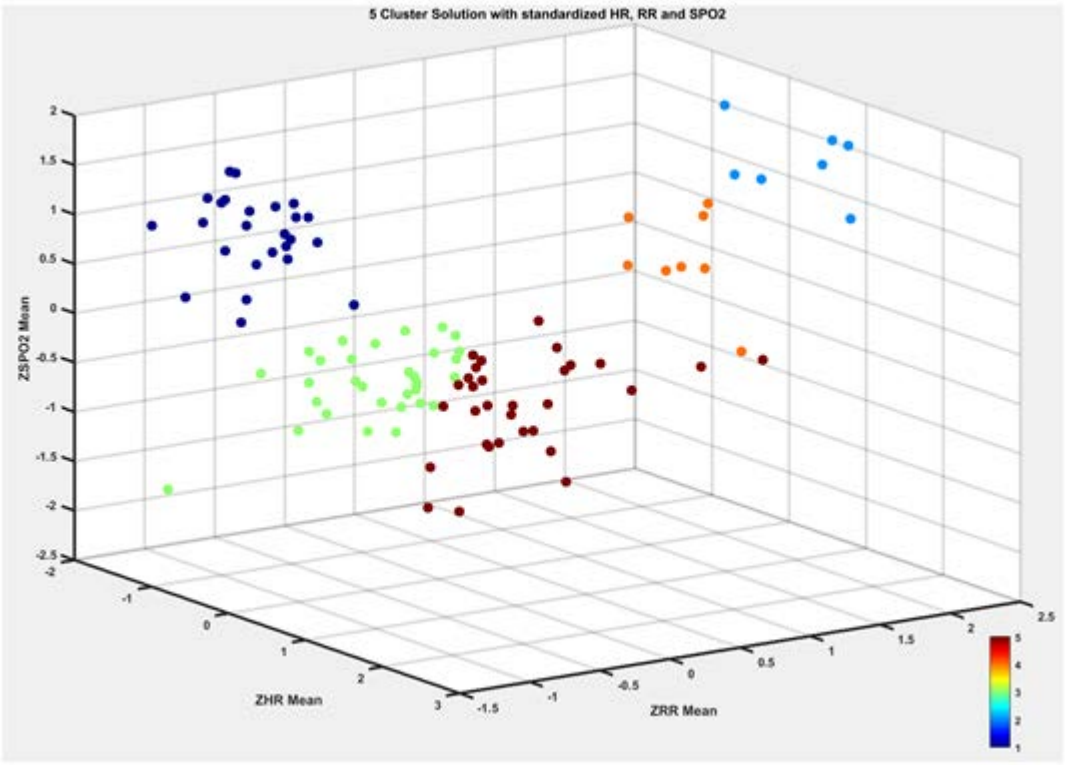

Figure 18. K-Means 5 cluster solution

6.1.2 Summary of vital signs with clustering solutions

A summary of the vital signs for the 3-cluster solution is as shown in Figure 19. While the CRI_1 driver for C3-1 (3 cluster solution, cluster 1) was exactly the same for all the patients in C3-1 and C3-3, the driver was unevenly split in C3-2 with HR 47%, RR 41%, SpO_2 12%.

	Cluster 1 (n = 25)		Cluster 2 (n = 17)		Cluster 3 (n = 61)	
	Min	Max	Min	Max	Min	Max
HR Median	48	116	70	158	55	114
RR Median	5	8	17	39	3	28
SpO_2 Median	89	100	84	100	73	85
CRI_1 Driver (1st VS to cross threshold in the epoch)	RR 100%		HR 47% RR 41% SpO_2 12%		SpO_2 100%	
Summary	Normal HR Low RR Normal SpO2		Normal-High HR Normal-High RR Low-Normal SpO2		Normal HR Low-Normal RR Low SpO2	

Figure 19. Summary of VS with 3 cluster solution

A summary of vital signs for the 4 cluster solution is in Figure 20, while for a 5 cluster solution is in Figure 21.

	Cluster 1 (n = 9)		Cluster 2 (n = 61)		Cluster 3 (n = 25)		Cluster 4 (n = 8)	
HR Median	70	119	55	114	48	116	142	158
RR Median	32	39	9	28	5	8	17	25
SpO_2 Median	84	100	73	85	89	100	95	100
CRI_1 Driver (1st VS to cross threshold in the epoch)	RR 78% SpO_2 22%		SpO_2 100%		RR 100%		HR 100%	
Summary	Normal HR High RR Normal SpO2		Normal HR Low-Normal RR Low SpO2		Normal HR Low RR Normal SpO2		High HR Normal RR Normal SpO2	

Figure 20. Summary of VS 4 cluster solution

	Cluster 1 (n = 23)		Cluster 2 (n = 37)		Cluster 3 (n = 24)		Cluster 4 (n = 7)		Cluster 5 (n = 6)	
	Min	Max	Min	Min	Min	Max	Min	Max	Min	Max
HR Median	60	102	55	95	78	114	142	158	89	119
RR Median	5	8	12	26	15	35	17	25	36	39
SpO_2 Median	89	100	71	85	76	85	95	100	94	100
CRI_1 Driver (1st VS to cross threshold in the epoch)	RR 100%		SpO_2 100%		SpO_2 100%		HR 100%		RR 100%	
Summary	Normal HR Low RR Normal SpO2		Normal HR Normal RR Low SpO2		Normal HR Normal RR Low SpO2		High HR Normal RR Normal SpO2		Normal HR High RR Normal SpO2	

Figure 21. Summary of VS 5 cluster solution

6.1.3 Cross Validation

For the 3 cluster solution, 93.2% of instances were correctly classified (Figure 22). For the 4 cluster solution, 89.3% of instances were correctly classified (Figure 23). The precision and recall values for each cluster was 1,0.97,0.46,0, while recall was 1,1,0.75,0. We noticed that for C1 and C2, recall was accurate. However, the confusion matrix showed that for C3, 2 patients were placed into C4, thus causing an error. For C4, the algorithm was performing extremely poorly by placing 2 patients in C2 and 7 patients in C3. However, a 5-cluster solution cross-validation performed more poorly, with only 68.9% of correctly classified instances (Figure 24). The precision values for each cluster were (1,0.85,0.77,0.58,0.27) and recall was (1,0.65,0.87,0.88,0.25). Thus, a 4-cluster solution performed better than a 5-cluster solution.

```
Time taken to build model: 0.01 seconds

=== Stratified cross-validation ===
=== Summary ===

Correctly Classified Instances          96               93.2039 %
Incorrectly Classified Instances         7                6.7961 %
Kappa statistic                          0.8806
Mean absolute error                      0.0453
Root mean squared error                  0.2129
Relative absolute error                 11.9889 %
Root relative squared error             49.0728 %
Total Number of Instances              103

=== Detailed Accuracy By Class ===

               TP Rate   FP Rate   Precision   Recall  F-Measure   ROC Area  Class
                 0.96      0.051       0.857     0.96      0.906      0.954    cluster1
                 0.882     0.012       0.938     0.882     0.909      0.935    cluster2
                 0.934     0.048       0.966     0.934     0.95       0.943    cluster3
Weighted Avg.    0.932     0.043       0.935     0.932     0.932      0.945

=== Confusion Matrix ===

  a  b  c   <-- classified as
 24  1  0 |  a = cluster1
  0 15  2 |  b = cluster2
  4  0 57 |  c = cluster3
```

Figure 22. 10-fold crossvalidation of 3 cluster solution

```
=== Stratified cross-validation ===
=== Summary ===

Correctly Classified Instances          92               89.3204 %
Incorrectly Classified Instances        11               10.6796 %
Kappa statistic                          0.8118
Mean absolute error                      0.0534
Root mean squared error                  0.2311
Relative absolute error                 18.2743 %
Root relative squared error             60.7743 %
Total Number of Instances              103

=== Detailed Accuracy By Class ===

               TP Rate   FP Rate   Precision   Recall  F-Measure   ROC Area  Class
                 1         0          1         1         1          1        cluster1
                 1         0.048      0.968     1         0.984      0.976    cluster2
                 0.75      0.074      0.462     0.75      0.571      0.838    cluster3
                 0         0.021      0         0         0          0.489    cluster4
Weighted Avg.    0.893     0.036      0.852     0.893     0.87       0.929

=== Confusion Matrix ===

  a  b  c  d   <-- classified as
 25  0  0  0 |  a = cluster1
  0 61  0  0 |  b = cluster2
  0  0  6  2 |  c = cluster3
  0  2  7  0 |  d = cluster4
```

Figure 23. 10-fold cross-validation of 4 cluster solution

The confusion matrix shows that for cluster 1 and cluster 2, the recall was accurate. For cluster 3, 2 patients were placed into cluster 4, thus causing a slight error. For cluster 4, the algorithm was performing extremely poorly by placing 2 patients in cluster 2 and 7 patients in cluster 3. However, the overall number of correctly classified instances was the highest at 89.32%.

```
=== Stratified cross-validation ===
=== Summary ===

Correctly Classified Instances          71               68.932  %
Incorrectly Classified Instances        19               18.4466 %
Kappa statistic                          0.7244
Mean absolute error                      0.0844
Root mean squared error                  0.2906
Relative absolute error                 31.8161 %
Root relative squared error             79.5834 %
UnClassified Instances                  13               12.6214 %
Total Number of Instances              103

=== Detailed Accuracy By Class ===

               TP Rate   FP Rate   Precision   Recall  F-Measure   ROC Area  Class
                 1         0          1         1         1          1        cluster1
                 0.654     0.047      0.85      0.654     0.739      0.736    cluster2
                 0.87      0.09       0.769     0.87      0.816      0.817    cluster3
                 0.875     0.061      0.583     0.875     0.7        0.911    cluster4
                 0.25      0.061      0.286     0.25      0.267      0.585    cluster5
Weighted Avg.    0.789     0.047      0.797     0.789     0.786      0.832

=== Confusion Matrix ===

  a  b  c  d  e   <-- classified as
 25  0  0  0  0 |  a = cluster1
  0 17  6  0  3 |  b = cluster2
  0  2 20  0  1 |  c = cluster3
  0  0  0  7  1 |  d = cluster4
  0  1  0  5  2 |  e = cluster5
```

Figure 24. 10-fold cross-validation of 5 cluster solution

6.1.4 ANOVA Posthoc Bonferroni Test

As shown in Figure 25, there were more slightly more significant differences (higher percentage) between the clusters of a 4 cluster solution (eg: C4-1 vs. C4-2 of a 4 cluster solution) and given that with 10-fold cross-validation, a 4-cluster solution achieved higher accuracy, we decided that the 4-cluster solution was the best cluster solution.

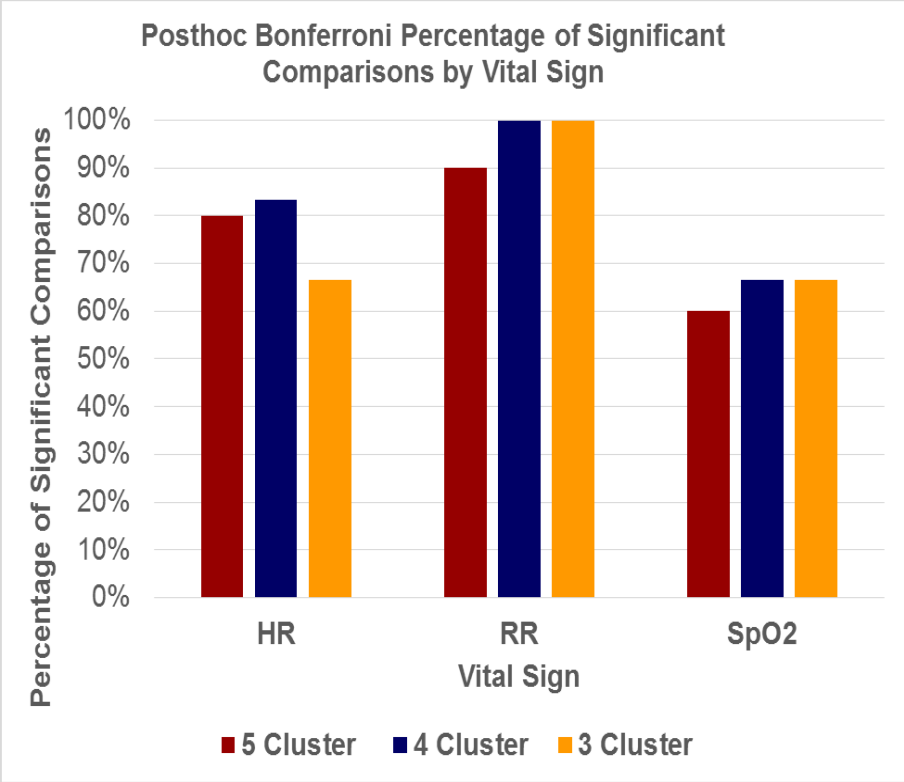

Figure 25. ANOVA Posthoc Bonferroni test percentage of significant comparisons

6.1.5 VS groupings in 4-cluster solution

In C1, there were 9 patients whose VS grouped into normal HR (70-119 bpm), high RR (32-39 breaths/min) and normal SpO2 (85-100%) with the driver being either RR or SpO2. In C2 there were 61 patients, whose VS grouped into normal HR (55-114 bpm), low to normal RR (3-28 breaths/min), and low SpO2 (73-85%). Every patient within C2 had SpO2 as the driver. In C3, there were 25 patients, and VS grouped as normal HR (48-116 bpm), low RR (5-8 breaths/min), and normal SpO2 (89-100%), with the driver for all patients being RR. In C4, there were 8 patients, whose VS grouped as high HR (142-158 bpm), normal RR (17-25 breaths/min) and normal SpO2 (95-100%), while the driver for all patients was HR. Significant cross-correlations ($p<.05$) were observed only between HR with RR. A box plot of the cross-correlations between the 4-cluster for HR with RR is shown in Figure 15. In C2 (the majority group), HR and RR had a positive cross-correlation indicating synergistic effect—either increasing or decreasing simultaneously. For C4, HR and RR had a negative cross-correlation indicating that while that HR increased RR decreased, and while RR increased, HR decreased.

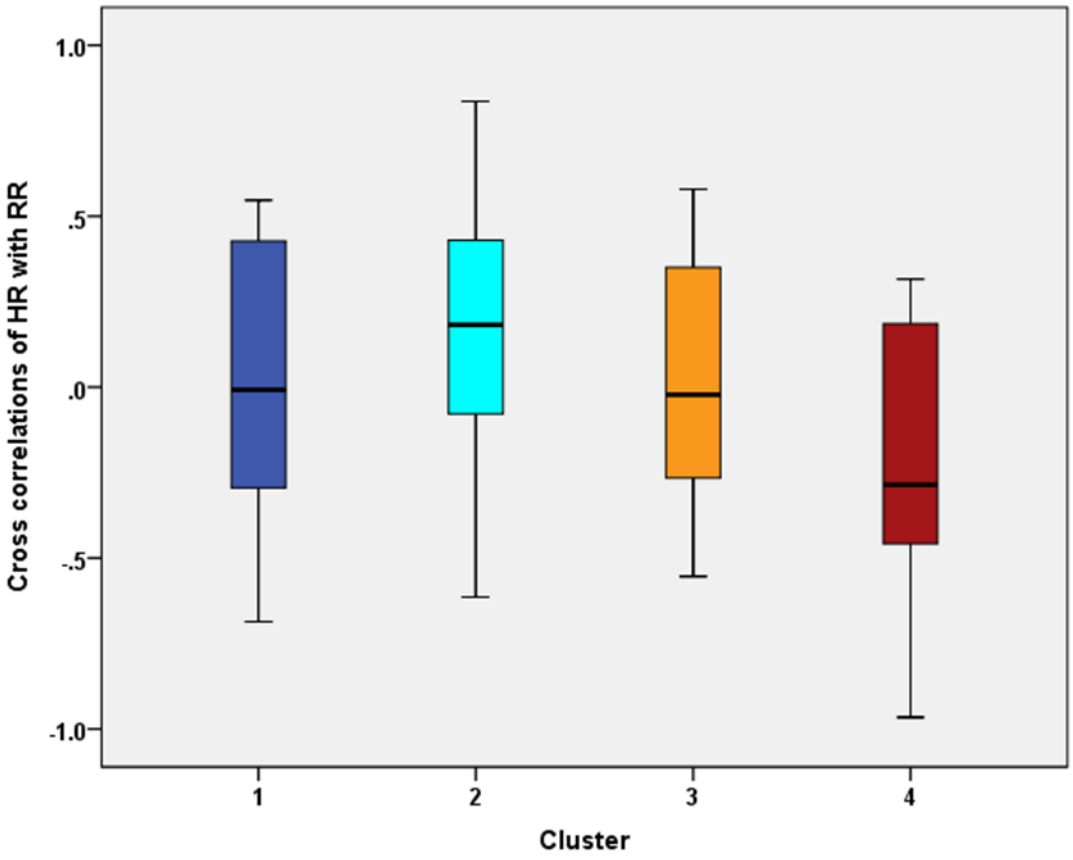

Figure 26. Box-plot of cross correlations for 4 cluster solution

This plot shows the cross-correlations between heart rate (HR) with respiratory rate (RR). In cluster 2 which was the majority group, HR and RR had a positive cross-correlation indicating synergistic effect. For cluster 4, HR and RR had a negative cross-correlation indicating that while HR increased RR decreased, and while RR increased, HR decreased. This (HR with RR) was the only significant cross-correlation as tested with ANOVA and a posthoc bonferroni test.

6.1.6 Admission characteristics and outcomes per cluster

There were significant differences between clusters in age, SDU admission source and Charlson Deyo comorbidity index (Table 4). The outcomes of hospital and SDU LOS did not differ between patients by cluster (Table 5).

6.1.7 Inter-cluster differences by medications

There were significant differences between patients in each cluster in terms of the medications that patients received 24 hours prior to and after CRI_1, as shown in Figure 27. Inter-cluster differences per cluster as well as per control group are shown in Table 6.

Table 4. Admission characteristics in patients with first instance of cardiorespiratory instability (CRI_1) event during the course of their stay on the step-down unit (SDU) by cluster.

Variable	**Total (N = 103) No. (%)**	**Cluster 1 (n=9) No. (%)**	**Cluster 2 (n=61) No. (%)**	**Cluster 3 (n=25) No. (%)**	**Cluster 4 (n=8) No. (%)**	p-value
Age (Mean ± SD)	60.1 ± 20	46.3 ± 23	66.5 ± 16	51.1 ± 20	54.7 ± 25	.001*
Gender						.549
Male	50 (51.5)	5 (55.6)	32 (52.5)	9 (36.0)	4 (50.0)	
Female	53 (48.5)	4 (44.4)	29 (47.5)	16 (64.0)	4 (50.0)	
Race						.288
White	81 (78.6)	5 (55.6)	51 (83.6)	19 (76.0)	6 (75.0)	
Black	9 (8.7)	2 (22.2)	4 (6.6)	3(12.0)	0 (0.0)	
Other	13 (12.6)	2 (22.2)	6 (9.8)	3 (12.0)	2 (25.0)	
Type of Service						.739
Surgical	57 (55.3)	5 (55.6)	33 (54.1)	13 (52.0)	6 (75.0)	
Medical	46 (44.7)	4 (44.4)	28 (45.9)	12 (48.0)	2 (25.0)	
Hospital Admission Diagnosis						.450
Trauma	54 (52.4)	6 (66.7)	32 (52.5)	10 (40.0)	6 (75.0)	
Diseases of Circulatory System	16 (15.5)	0 (0.0)	11 (18)	4 (16.0)	1 (12.5)	
Diseases of Digestive System	15 (14.6)	2 (22.2)	6 (9.8)	7 (28.0)	0 (0.0)	
All other diagnoses	18 (17.5)	1 (11.1)	12 (19.7)	4 (16.0)	1 (12.5)	
SDU Admission Source						.008**
Higher intensity monitoring unit	43 (41.7)	8 (88.9)	22 (36.1)	8 (32.0)	5 (62.5)	
Direct Admission, or lower intensity monitoring unit	60 (58.3)	1 (11.1)	39 (63.9)	17 (68.0)	3 (37.5)	
Charlson-Deyo Comorbidity Index						< .01**
0	49 (47.6)	7 (77.8)	20 (32.8)	15 (60.0)	7 (87.5)	
1	25 (24.3)	1 (11.1)	18 (29.5)	6 (24.0)	0 (0.0)	
≥ 2	29 (28.2)	1 (11.1)	23 (37.7)	4 (16.0)	1 (12.5)	

*Oneway ANOVA p-value; **Chi-square test p-value

Table 5. Outcomes between clusters of patients who developed cardiorespiratory instability event (CRI_1) during thecourse of their stay on the step-down unit (SDU) length of stay (LOS) by cluster.

Variable	**Total (N = 103)**	**Cluster 1 (n = 9)**	**Cluster 2 (n = 61)**	**Cluster 3 (n = 25)**	**Cluster 4 (n = 8)**	**p-value**
Hospital LOS, mean, SD	11.8 $\pm$ 11.1	14.2 $\pm$ 9.1	10.7 $\pm$ 10.9	11.8 $\pm$ 10.2	17.4 $\pm$ 16.7	.391
SDU LOS, mean, SD	6.3 $\pm$ 5.4	6.7 $\pm$ 6.2	5.8 $\pm$ 5.1	6.4 $\pm$ 6.1	8.6 + 4.9	.581
Transferred from SDU to a higher intensity monitoring unit n (%)	15 (14.6)	3 (33.3)	9 (14.8)	2 (8.0)	1 (12.5)	.315

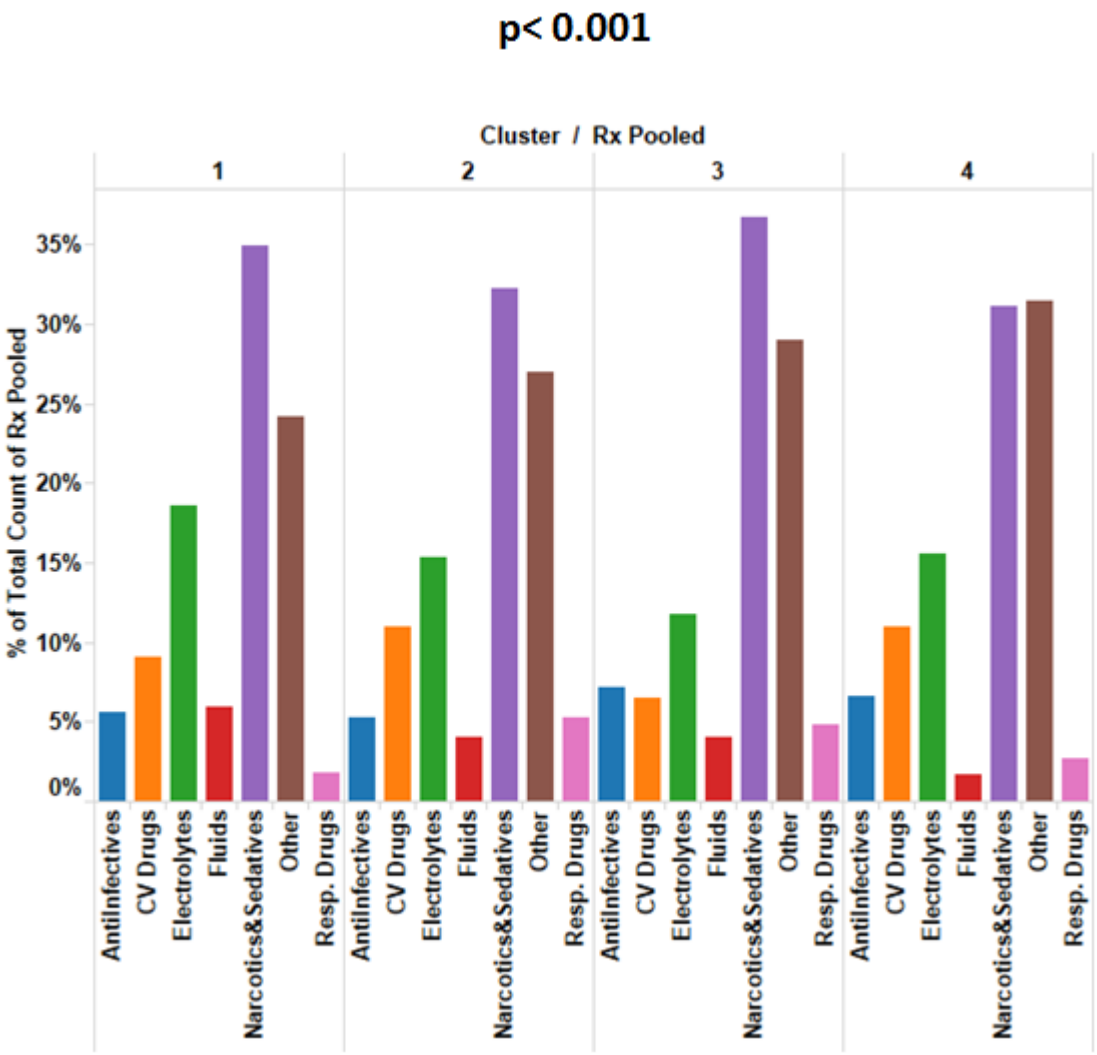

Figure 27. Inter-cluster differences by medication categories.

There were significant differences between patients in each cluster in terms of the medications that patients received 24 hours prior to and after CRI_1.

Table 6. Inter-cluster differences by medications as compared to the control group

Drug Category	**Cluster0** (n = 50) %	**Cluster1** (n = 9) %	**Cluster2** (n = 61) %	**Cluster3** (n = 25) %	**Cluster4** (n = 8) %	**p-value**
Cardiovascular Drugs	7.9	9.1	11.0	6.5	10.9	.003
Vit/Lytes/Hematinics	9.4	18.5	15.4	11.7	15.6	<.001
Fluids	7.2	5.9	4.0	4.1	1.6	<.001
Respiratory Drugs	3.0	1.7	5.2	4.8	2.7	.009
Narcotics & Sedatives	37.7	35.0	32.3	36.7	31.1	.036
Anti-Infectives	3.7	5.6	5.2	7.2	6.6	.059
Other	31.2	24.1	27	29	31	.075
CRI_1 Summary of VS	No CRI	Normal HR High RR Normal SpO2	Normal HR Low-Normal RR Low SpO2	Normal HR Low RR Normal SpO2	High HR Normal RR Normal SpO2	

Table 7. Cluster differences compared to control group

Control Group. Vs. Cluster	**p-value**
Cluster 0 – Cluster 1	.002
Cluster 0 – Cluster 2	.000
Cluster 0 – Cluster 3	.003
Cluster 0 – Cluster 4	.000
Cluster 0 – All Clusters	.000

6.2 DISCUSSION FOR SPECIFIC AIMS 2 & 3

This study is the first of its kind to use hierarchical and k-means clustering on the feature space of CRI_1 epoch to derive the VS pattern clusters of CRI_1. The key findings from this study are as follows. First, the most common driver of CRI_1 was SpO2, Second, four main clusters were derived: C1) normal HR and SpO2 but high RR; C2) normal HR, either low or normal RR and low SpO2; C3) normal HR, low RR, normal SpO2; and C4) high HR, normal RR and SpO2. Third, interactions among the VS suggest predictability of the driver; and finally, admission characteristics between patients placed within a cluster differed in regard to age, SDU admission source and Charlson Deyo comorbidity index.

Using features of mean, median, mode and maximum values for the VS of HR, RR and SpO2 for CRI1 epoch and applying clustering techniques, we found that a 4-cluster solution was best. An interesting finding was that within three of the clusters, the driver was identical for all patients in that cluster. For C2, the driver was SpO2, for C3 RR and for C4 HR. In C1 (normal HR and SpO2 and high RR), there were 2 patients whose driver was SpO2, while for the rest it was RR. On review of the actual data within the CRI1 epoch for these patients, we discovered that these patients' RR was 32-34 breaths/ min, (i.e. relatively high) similar to other patients in the cluster. However, due to our threshold definition (RR > 36), their CRI1 driver was not RR but instead was low SpO2 < 85%. Barring this exception, all patients within a cluster had the same CRI_1 driver.

We initially decided to use a total of 24 features derived from the CRI epoch per VS, which included the features shown in Table 1, similar to our previous work(M Hravnak et al., 2014). However, in testing clustering techniques, the only features which were consistently

found to contribute to clustering were the mean, median, mode, minimum and maximum value. A commonly employed procedure is to use the ANOVA table similar to our approach and only retain features which contributed significantly towards clustering (Cellucci, Tyrrell, Twilt, Sheikh, & Benseler, 2014; Haldar et al., 2008). Besides this, we also observed that Q-Q plots generated for the features of range, variance and standard error of the mean per VS showed fat tails and severe departures from normality for the distribution. Further, extremely high kurtosis values were observed especially for HR values. Removing outlier cases would have resulted in further loss of patients available for clustering. We chose to eliminate(Devaney & Ram, 1997; Talavera, 1999) these 9 features instead of the patients, leaving 15 features for cluster analysis.

We employed the most commonly used unsupervised machine learning techniques of hierarchical and k-means clustering to derive CRI patterns(Hastie, Tibshirani, & Friedman, 2009) and used them in a complementary way, with each approach giving slightly different information. We used hierarchical clustering and visualization of the dendrogram to potentially estimate where k-value could be set for k-means clustering. Our choice of a bottom-up approach such as agglomerative hierarchical clustering was to ensure that nearby and thus similar cases ended up within the same cluster, as opposed to top-down approaches.(Arai & Barakbah, 2007) While heuristic techniques exist for deciding on an optimal value for the number of clusters such as the use of an elbow plot (Mooi & Sarstedt, 2011) or other techniques,(Milligan & Cooper, 1985; Tibshirani et al., 2001) our use of hierarchical clustering was primarily to estimate potential k-values, similar to others (Cellucci et al., 2014; Hawkins et al., 2015). Our choice of Ward's linkage method was that besides being a commonly used approach (Stuetzle & Nugent, 2012), it used ANOVA to evaluate distances between clusters in an attempt to minimize sum of squares of any two clusters (Ward Jr, 1963), thus a more rigorous approach . Further, since our

goal was to use k-means clustering also, Ward's linkage method was ideal for comparing the two procedures. This is because it is also based on the same analysis of the clustering problem as k-means and usually gives clusters that appear well-defined (Clarke, Fokoue, & Zhang, 2009). After visualization of the dendrogram, we decided on limiting the k-value used in k-means clustering to between 3 and 5 clusters.

We implemented 10-fold stratified cross validation (CV) (Wagstaff, Cardie, Rogers, & Schrödl, 2001) to determine if a 4-cluster or 5-cluster solution was better. Given our small dataset, stratified cross-validation was used so that all the folds would likely contain at least a good proportion of patients even from the smallest cluster. We evaluated the performance of k-means algorithm by its accuracy, which is the degree of success in classifying correctly new instances as shown in Figure 4. While there is no universal algorithm giving the best performance in all possible learning situations,(Schaffer, 1994) CV was particularly suited in our study given the narrowed down option of two possible cluster solutions, as opposed to other boot-strapping procedures (Duda, Hart, & Stork, 2012) to decide the best cluster solution.

We used cross-correlations among the VS within the cluster to study the interactions within the 3 VS. For instance, a negative cross correlation between RR and SpO¬2 in a particular case would indicate that RR and SpO2 were moving in the opposite direction while a positive cross-correlation would suggest a synergistic effect. We expected that all patients within the cluster would exhibit certain pattern of changes for the three VS, but this was not noticed. This suggests that while there are broad cluster patterns within CRI epoch, there could be subsets of patterns within the cluster not captured by our analysis or subtle variations within VS even prior to entering into CRI epoch (Clermont, Sileanu, Pinsky, & Ogundele, 2012, 2013). Future studies are needed to explore this potential.

The only admission characteristics that differed significantly between the patients in each cluster were age, SDU admission status and comorbidity Index. In the largest cluster (C2), mean age was 66.5 and the driver for CRI1 was SpO2, indicating that older patients were more likely to develop CRI1 due to SpO2, with the pattern being normal HR, either low or normal RR and low SpO2. Even though we had an overall relatively healthy cohort of patients (greater number of patients with Charlson index at 0), we showed that increasing age and comorbidities placed patients at greater risk of developing CRI1 due to SpO2. From a clinical perspective, this indicates that older patients with increased comorbid conditions and those transferred from a higher intensity monitoring unit should be monitored more closely for changes in RR and SpO2.

Finally, we chose to study only the first instance of CRI (CRI_1) in this study. The clinical utility of our study is to aid CRI pattern recognition so as to eventually target surveillance and intervention based on probable cluster patterns, right from the first occurrence of CRI. While in the case of MET syndromes (Jones, Duke, et al., 2006) that eventually result in serious deterioration needing a MET call might be identifiable from the outset, CRI occurs with subtle changes in VS (Hravnak et al., 2008). Thus, studies of VS pattern recognition such as ours could eventually be used for designing intelligent monitoring systems. This study is also a stepping stone to identify if patients continue to remain within the same cluster, or if they eventually switch to a different pattern, should successive instances of CRI occur. Future studies to track cluster progression will explore whether or not patients change clusters during further instances of CRI.

6.3 LIMITATION FOR SPECIFIC AIMS 2 & 3

VS analyzed for this study were obtained from the SDU of one Level-1 Trauma Center and may not be reflective of other hospitals or patient populations. The thresholds used to define abnormality, although commonly used as thresholds for serious instability (Hravnak et al., 2011; Hravnak et al., 2008; Smith, Prytherch, Schmidt, Featherstone, & Higgins, 2008), differed from normal values remarkably. Use of lower thresholds of lesser instability magnitude might have altered our results. Also, we recorded our data at 1/20 Hz for each of the VS. With this recording frequency, there were a few instances when all values were not recorded. Nevertheless, we did not use missing value imputation or any other procedures commonly employed in time-series cross-section data to account for missing data (Honaker & King, 2010; Honaker, King, & Blackwell, 2011). We made this decision to insure the data were as accurate and as close to normal SDU monitoring practices as possible, yet seek features we could use for clustering. However, this may have resulted in loss of patients who could have otherwise been placed in one of the clusters. Finally, we employed a limited set of features and results could differ with increased features derived from CRI_1 epoch, although the parsimonious feature set we used enabled testing both clustering approaches with less than 10 iterations of the algorithms.

6.4 CONCLUSION FOR SPECIFIC AIMS 2 & 3

Our analysis, the first of its kind to use clustering techniques on the feature space of the VS of HR, RR and SpO2 on CRI_1 epochs in SDU patients, derived 4 different clusters of VS

presentations. The most common driver of CRI_1 was SpO2 with the cluster pattern of normal HR, low-normal RR and low SpO2. The cluster groups varied on age, number of comorbidities and SDU admission source. Inter-cluster differences exist between the medication categories administered. Patients within the clusters differed individually from the control group of patients. Patients with and without CRI differed by medications administered. There is evidence that there may be differences in the physiologic underpinnings of these clusters as demonstrated by differences in medication need. Future study will be needed to determine if there are common physiologic underpinnings of the VS clusters which might inform clinical decision-making even at the point where CRI first manifests.

7.0 CONCLUSIONS

CRI_1 most commonly occurred due to SpO_2 and was associated with prolonged hospital and SDU length of stay. Patients transferred from a higher level of care were more likely to develop CRI, suggesting that they are sicker when admitted to the SDU. Four different clusters of VS presentations for CRI_1 were identified, with C2 (normal HR, low-normal RR and low SpO_2) most prevalent. The cluster groups varied on age, number of comorbidities and SDU admission source. There is some evidence that there may be differences in the physiologic underpinnings of these clusters as demonstrated by differences in medication need and some admission characteristics. However, this requires future studies using more variables to hone in on disease process.

The clinical utility of our study was to aid pattern recognition so as to eventually target surveillance and intervention based on probable cluster patters, right from the first occurrence of CRI. While in the case of MET syndromes that eventually result in serious deterioration needing a MET call might be identifiable from the outset, CRI occurs with subtle changes in VS. Thus, studies of VS pattern recognition such as ours could eventually be used for designing intelligent monitoring systems. This study is also a stepping stone to identify if patients continue to remain within the same cluster, or if they eventually switch to a different pattern, should successive

instances of CRI occur. Future studies to track cluster progression will explore whether or not patients change clusters during further instances of CRI.

APPENDIX A

ASSESSMENT OF VOLUME STATUS AND CARDIAC OUTPUT

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A.1 INTRODUCTION

Why measure cardiac output (CO)? There is no "normal value" as its level rises and falls as metabolic demand and oxygen (O_2) carrying capacity dictate. Similarly absolute intravascular volume status varies widely across cohorts of presumably similar patient subsets. Clearly, the blind measure of either CO or intravascular volume status in isolation is often an unrewarding clinical exercise. However, when coupled with other measures of effectiveness of blood flow, pump function and metabolic demand, knowing both CO and volume status allow the bedside clinician to precise the cardiovascular state and to a large extent define cardiovascular reserve. Thus, the measure of cardiac output, though central to the definition of cardiovascular state is a dependent variable and needs to be used and monitored within this limited context.

Prior Art

> *"It is astonishing that no one has arrived at the following obvious method by which the amount of blood ejected by a ventricle of the heart with each systole may be determined directly…"*

with this introduction Adolf Fick [1] described, in the proceedings of the Wurzburg Physikalische Medizinische Gesellschaft on July 9, 1870, how to compute an animal's cardiac output (CO) from arterial and venous blood oxygen measurements. In order to employ the Fick Principle to determine blood flow through an organ it is necessary to have a substance which is either removed or added to the blood during its period of flow through the organ. The amount which is added or removed from the organ by the blood is equal to the difference between the amount brought into the organ and the amount carried away from the organ.[2] Therefore, one can

summarize the above statement by the following equation using oxygen consumption (VO_2) as the means to alter the arterio-venous O_2 content difference ($C_a - C_v$), as:

$$VO_2 = CO * C_a - CO * C_v$$

And solving for CO one gets:

$$CO = VO_2/(C_a - C_v)$$

Fick's original principle was later adopted in the development of Stewarts's indicator-dilution method in 1897.[3] Stewart injected a bolus of a sodium chloride solution into the central venous circulation of anesthetized dogs and rabbits, and then collected blood samples containing diluted sodium chloride from a femoral artery catheter. An electric transducer on the contralateral femoral artery sensed the arrival of diluted injectate. The cardiac output measurement by indicator dilution has three principle phases: a) an indicator is brought into the circulation (injection). b) the indicator mixes with the blood stream (mixing and dilution) and c) the concentration of the indicator is determined downstream (detection). The cardiac output would then be obtained using the Stewart-Hamilton formula. To derive the CO, Stewart used the following computation: let V_0 (mL) denote the initial injectate's volume and C_0 (mg/ml) its initial concentration. The circulation dilutes the injectate to a presumed uniform concentration C_1 occupying a volume V_1 where $V_1 = V_0 * (C_0 / C_1)$. The heart expels the diluted indicator over a period of *t* (seconds). Because the vascular resistance of the major arterial vessels are negligible, *t* is also the duration over which the downstream collection catheter encounters diluted indicator. The blood flow, i.e., the CO *F*(ml/s) is the blood volume transferred per unit time or

$$F = V_1/t = C_0 V_0/ C_1 t$$

However, contrary to his own observations, Stewart assumed in his formula that the indicator concentration at the collection site rises and declines in a stepwise manner over the collection interval. This technique, using indocyanine green as an indicator and a continuous withdrawal of blood into a sensing cuvette was the conventional indicator dilution method used to measure cardiac output in the critically ill patient. However, Stewart's computations excluded his own recognition that the indicator concentration at the collection catheter initially increased and subsequently decreased in a non-stepwise pattern over the collection interval. The Hamilton modification introduced in 1928, accounted for such non-stepwise pattern, substituting in the place of uniform concentration C_1, the time-averaged concentration of diluted indicator traversing the detector. The resulting CO *F*(ml/s) is calculated using the Stewart-Hamilton formula:

$$F = \frac{C0\ V0}{\int c(t)dt}$$

Fegler first described the use of thermodilution for measuring cardiac output.[4] In 1968, this method was then adapted for use in man by Branthwaite and Bradley[5] at St. Thomas' Hospital in London and then further developed by Ganz and others.[6, 7] Following the introduction of the pulmonary artery catheter (PAC) into clinical practice, the single-bolus thermodilution measurement of CO has been widely accepted as the "clinical standard" for advanced hemodynamic monitoring. The ability to monitor CO is a cornerstone of hemodynamic assessment for managing critically ill patients and in particular in patients with preexisting cardiovascular comorbidities. In critically ill patients, optimizing CO is considered an integral part of initial resuscitation approaches to increase O_2 delivery because oxygen delivery is primarily altered by varying CO.[8]

The introduction of the PAC in 1970 and its subsequent use in performing thermodilution CO measurements in humans translated the ability to measure CO from the experimental physiology laboratory to multiple clinical settings. Measuring CO by thermodilution using a PAC, ever since, has most frequently been used in the clinical setting and has been regarded as the *de facto* reference method. PACs provide CO and other hemodynamic measurements not obtainable by clinical examination.[9-11] Pulmonary blood flow, using a balloon floatation pulmonary artery catheter equipped with a distal thermistor, and transpulmonary blood flow using an arterial thermistor, both with a central venous cold volume injection, can be used. Cardiac output can be measured intermittently by bolus cold injection or continuously by cold infusion or heating coil upstream from the sensing thermistor. The advantage of the continuous CO technique and the transpulmonary technique is that neither is influenced greatly by the ventilation-induced swings in pulmonary blood flow. Since the PAC measures pulmonary blood flow, not aortic flow, variations in pulmonary blood flow will affect its measure. Thus, intermittent measures show profound ventilator cycle-specific patterns.[12] By making numerous measures at random with the ventilator cycle and then averaging all measures with proper thermal decay profiles, regardless of their values, an accurate measure of pulmonary blood flow can be derived.[13] If ventilatory cycle–specific changes in the proportion of tricuspid regurgitation are present, then averaging all thermodilution measures may result in inaccurate estimates of cardiac output. In the setting of cor pulmonale and pulmonary hypertension, inspiration- induced tricuspid regurgitation may occur. The clinician can easily identify this phenomenon by observing the respiratory cycle-specific ‘‘v’’ waves in the right atrial pressure (Pra) trace. If

phase-specific tricuspid regurgitation exists, estimates of cardiac output by the thermodilution technique will overestimate the actual cardiac output.

For more than 30 years, single-bolus thermodilution measurement through a pulmonary artery catheter for assessment of cardiac output has been widely accepted as the "clinical standard" for advanced hemodynamic monitoring.[8] The controversy over the use of the PAC in the management of critically ill patients continues to rage. Nevertheless, current users of PACs rely on an underlying assumption that these changes in management lead to improved patient outcomes.[14] Since there are no definitive studies, several professional groups have developed guidelines for PAC use.[15] Proponents of its use cite the physiologic rationale for diagnosis and titration of complex treatments that may otherwise be detrimental. Opponents of PAC use cite the almost total lack of data showing that its use in the management of critically ill patients improves outcome. Pulmonary arterial catheterization allows the measurement of intrapulmonary vascular pressures, cardiac output, RV ejection fraction, and SvO_2. It is logical that with the ability to measure these variables and calculate physiologic parameters such as total O_2 delivery, whole body O_2 consumption, pulmonary and systemic vascular resistance, pulmonary venous admixture, and RV and LV stroke work index, the pulmonary catheter would be invaluable in the assessment and management of the complex critically ill patient. That usefulness has not been documented, however.

A.2 MONITORING CARDIAC OUTPUT

Cardiac output can be estimated by invasive hemodynamic monitoring using the PAC. The intermittent thermodilution technique, in which boluses of ice-cold fluid are injected into the right atrium via a PAC and the change in temperature detected in the blood of the pulmonary artery used to calculate cardiac output, is still widely considered as the standard method of reference. Adaptation of the PAC to incorporate a thermal filament (Vigilance™, Edwards Life Sciences, Irvine, CA, USA) or thermal coil (OptiQ™, ICU Medical, San Clemente, CA, USA) that warms blood in the superior vena cava and measures changes in blood temperature at the PAC tip using a thermistor, provides a continuous measure of the trend in cardiac output, with the displayed values representing an average of the values over the previous 10 minutes. The averaged values have the advantage of eliminating variability in the presence of arrhythmias, but the disadvantage of not being real-time values, thus limiting the usefulness of this approach for assessing rapid hemodynamic changes in unstable patients. The PAC has a key advantage over many other systems in that it provides simultaneous measurements of other hemodynamic parameters in addition to cardiac output, including pulmonary artery pressures, right-sided and left-sided filling pressures, and SvO_2.[16]

A.2.1 Transpulmonary or ultrasound indicator dilution

The PiCCO® (Pulsion Medical Systems, Munich, Germany), LiDCO™ (LiDCO Ltd, London, UK), VolumeView™ (Edwards Life Sciences), and COstatus® (Transonic Systems Inc., Ithaca,

NY, USA) systems allow cardiac output to be investigated less invasively, using a central venous (to allow calibration) and an arterial catheter, rather than needing to introduce a catheter into the pulmonary artery. The PiCCO® and recently launched VolumeView™ systems require a femoral artery catheter. These devices use the same basic principles of dilution to estimate the cardiac output as with PAC thermodilution. PiCCO® and VolumeView™ use injections of ice cold intravenous fluid as the indicator, measuring change in temperature downstream to calculate cardiac output, whereas LiDCO™ uses minute amounts of lithium chloride as the indicator and measures levels using a lithium-selective electrode. COstatus® calculates cardiac output by using ultrasound technology to measure changes in blood ultrasound velocity and blood flow following an injection of warm saline solution. Cardiac output values measured using transpulmonary or ultrasound indicator dilution techniques correlate well with those measured using PAC thermodilution[17-20] and may show less respiratory phase-dependent variation.[18]

The PiCCO® and the VolumeView™ systems provide variables in addition to cardiac output, such as global end-diastolic volume and measurements of extravascular lung water. The COstatus® system also provides some derived variables, including total end diastolic volume index.

A.2.2 Arterial pressure trace-derived estimation of cardiac output

In addition to the intermittent indicator dilution cardiac output measurements discussed above, the PiCCO® and LiDCO™ systems can also estimate cardiac output on a continuous basis from the arterial pressure waveform with (PiCCO2® and LiDCOplus™) or without (LidCOrapid™)

the need for recalibration when changes in vascular compliance may have occurred. The PiCCO® system uses a pulse contour analysis and the LiDCO™ system a pulse power analysis. In addition to these, Vigileo™ (Edwards Life Sciences) and MostCare™ (Vytech, Padova, Italy) using the Pressure Recording Analytical Method (PRAM)) systems have been developed for arterial waveform analysis without external calibration. Each of these systems contains a proprietary algorithm for converting a pressure-based signal into a flow measurement. The specific algorithms have individual characteristics and make different assumptions - for example, related to arterial compliance (Vigileo™) or pressure (MostCare™) - which can make them more or less accurate depending on the clinical circumstances. The level of accuracy and precision of each device needs to be understood as the data cannot be superimposed from one system to another. The advantages of these arterial pressure-based cardiac output monitoring systems over PAC-derived measurements is primarily their less invasive nature. The major weakness of all these devices is the drift in values whenever there is a major change in vascular compliance, as, for example, in vascular leak syndrome with increased vessel wall edema leading to decreased arterial compliance. Aortic valve regurgitation may further decrease the accuracy of these techniques. Over or under-damped arterial pressure waveforms will also decrease the precision of these monitors.

A.2.3 Stroke Volume Variation

If absolute measures of cardiovascular values cannot be used effectively as parameters describing cardiovascular status or responsiveness, then more provocative maneuvers need to be

employed to improve the utility of these measures. Such provocative approaches comprise the broad field of monitoring techniques, referred to as functional hemodynamic monitoring.

Dynamic parameters can predict increases in cardiac output from volume expansion are better predictors of fluid resuscitation than static parameters.[21] Understanding how dynamic measures are predictors of fluid responsiveness requires an understanding of how respiratory variation can impact the preload, pulse pressure, and stroke volume. Spontaneous inspiration leads to a larger venous return to the right side of the heart but also leads to the displacement of the septum and pulmonary vein dilatation leading to reduced preload to the left side of the heart. This reduced preload results in less ventricular filling and a lower left ventricular (LV) stroke volume. Expiration leads to decreased intrathoracic pressure, higher preload, and larger stroke volumes on the left side of the heart. This increase in left cardiac preload occurs at expiration as a result of the transmission of the increase in right cardiac preload after the lung transit time. Such changes in pulse pressure during spontaneous respiration are otherwise known as pulsus paradoxus. Changes in intrathoracic pressure from mechanical ventilation can lead to cyclic changes, but reversed—otherwise termed reverse pulsus paradoxus. These small changes in right ventricular preload induced by mechanical ventilation can lead to significant changes in stroke volume in preload-dependent individuals. On the left side of the heart, if arterial compliance is constant through a respiratory cycle then variations in systolic blood pressure and pulse pressure (PP) will be reflected in LV stroke volume.

Positive pressure ventilation (PPV) when applied to a patient at rest and with no spontaneous respiratory effort is associated with a cyclic increase in Pra in phase with inspiration. Since Pra is the back-pressure to venous return, if upstream venous pressures do not

simultaneously increase[22] then RV filling will also decrease in a cyclic fashion. This cyclic variation in RV filling will induce a cyclic variation in LV filling if both RV and LV are preload responsive.[23] This cyclic variation in LV filling will induce a cyclic variation in LV stroke volume and arterial pulse pressure if the patient is preload responsive.

Stroke volume variation (SVV) is believed to be less affected by vasomotor tone than PPV and is, therefore, likely to be a better measure of fluid resuscitation in mechanically ventilated patients.[24,25] A study comparing SVV to pulmonary artery catheterization by thermodilution (PAC-TD) demonstrated SVV (ROC = 0.82) to be equivalent if not better than PPV (ROC = 0.80) in mechanically ventilated patients.[26] SVV, much like PPV, is limited to mechanically ventilated patients, as preload is highly susceptible to changes in intrathoracic pressure. Despite the promising results of studies of PPV and SVV in mechanically ventilated patients, limitations exist in these methodologies. In mechanically ventilated patients, a linear relationship exists between tidal volume and SVV or PPV; [27] tidal volumes of less than 8 mL/kg are no more accurate than traditional measures of preload.[28] Recent work has demonstrated that lower tidal volumes, impaired contractility, or elevated respiratory rates each independently result in lower SVV and PPV errantly leading to an increase in falsely negative tests for fluid responsiveness.[29,30] Meanwhile, right ventricular dysfunction may cause false positives of PPV[31] a result that could lead to volume overload and deleterious effects in certain populations.[32] Interestingly, increased contractility does not influence PPV or SVV.[29] Presently, PPV is easier to measure than SVV because it only requires inspection of the arterial pressure waveform over time[33] whereas SVV can be assessed by either esophageal Doppler echocardiography[34] or echocardiographic measures of aortic velocity.[35]Several commercially available technologies

have evolved based on arterial waveform analysis that can estimate stroke volume from the pulse pressure waveform.

There is a tight correlation between positive-pressure ventilation-induced changes in arterial pulse pressure (PP), also called PPV, and fluid responsiveness.[36] PPV is calculated as the ratio of difference between maximum and minimum PP to their mean as assessed over about 5 breaths or 20 seconds. The greater the PPV, the greater the CO increase. Not surprisingly, subsequent studies showed that similarly calculated SVV, when measured independently, also predicted volume responsiveness.[37] Theoretically, mean arterial pressure (MAP) and PP should co-vary with changes in CO if the heart rate remains constant. We previously predicted that PPV/SVV >0.8 would define pressure responsive subjects if CO increased.[38]

The FloTrac® device estimates SVV from the standard deviation of the individual arterial pressure values over single beats averaged over 20 seconds. Assuming the SV variance has a normal distribution, this assumption is valid for calculating SVV. Importantly, SVV as a time-series function may not be normally distributed during atrial fibrillation and with vigorous spontaneous inspiratory efforts. How much error such non-normal distribution would introduce into the SVV calculation is not known, but on theoretical modeling the degree of non-normal distribution would need to be great for it to affect SVV by the standard deviation method.

There also has been renewed interest in the estimation of LV stroke volume from the arterial pressure profile over ejection by a process referred to as arterial pulse contour analysis.[39] Because the only determinants of arterial pressure are LV stroke volume and the resistance, compliance, and inertance characteristics of the arterial tree and blood, if the arterial components are constant, then changes in pulse pressure most proportionally reflect changes in LV stroke

volume. Thus, it is not surprising that the aortic flow variation parallels arterial pulse pressure variation,[40] and pulse contour–derived estimates of stroke volume variation can be used to determine preload responsiveness.[41,42] However, caution must be exercised when using the pulse contour method because it is not validated in subjects with rapidly changing arterial tone, as often occurs in subjects with hemodynamic instability, and it requires, at least in the studies that used it, the application of abnormally large tidal volumes.[41-43] Thus, at present, the pulse contour–derived stroke volume variation technique represents a potentially great but still unproven clinical decision tool.[44]

A.2.4 End Diastolic Volume

Preload is defined as the degree of stretch of the isolated myocardial fiber at the onset of contraction. In the intact heart this corresponds to the ventricular volume at end-diastole and, although originally derived from experimental conditions, the concept of preload is commonly applied to the clinical situation. The determination of right ventricular (RV) end-diastolic volume (RVEDV) from a pulmonary artery catheter has been suggested as a more accurate method of reflecting right heart preload, [45] but the importance of right ventricular preload is unclear. Evaluation of preload status and subsequent volume loading are first-line therapy in the hemodynamic management of critically ill or injured patients. Although cardiac filling pressures, such as the central venous pressure (CVP) and pulmonary artery occlusion pressure (Ppao), have commonly been used to guide fluid therapy, several studies have shown that the Ppao may not provide a reliable guide to cardiac preload.[46-48] Some of the factors thought

to disturb the relationship between Ppao and ventricular end-diastolic volume include myocardial trauma or ischemia, pulmonary injury or dysfunction, and increases in juxtacardiac pressure caused by mechanical ventilation and PEEP.[46-48] Mechanical ventilation and PEEP may also cause movement of the interventricular septum to the left to reduce LV filling and alter the relationship between Ppao and LV end-diastolic volume and cardiac output.[49,50] The use of the pulmonary artery catheter has allowed thermodilution determination of RVEF and right ventricular volumes at the bedside. Published studies on RVEDV Index[51-55] suggest that right ventricular volumes provide a better index of cardiac filling than the Ppao.

Several studies have emphasized the good correlation between estimates of right ventricular end-diastolic volume (RVEDV) by thermodilution-derived right ventricular ejection fraction (RVEF) and surrogates of stroke volume.[56-59] However, the thermodilution technique for assessing RVEDV is still intermittent, and the value of RVEDV as a marker of fluid responsiveness in critically ill patients is controversial.[59-61] A recently available Swan–Ganz catheter with a rapid response thermistor permits nearly continuous assessment of cardiac output (CO), RVEF and RVEDV, which should be more applicable in the ICU. The measurement variability associated with the intermittent bolus technique is eliminated by this catheter, and continuously assessed RVEDV (CEDV) should be more accurate than RVEDV based on intermittent thermodilution; therefore, CEDV may be a valuable marker of cardiac preload and a predictor of fluid responsiveness.

A.2.5 Simpson's Rule

The simplest method for estimating left ventriclar (LV) volume is the cube formula, which assumes that the LV volume is that of a sphere with a diameter equal to the LV antero-posterior dimension. However, this method has proven to be inferior to other volume techniques.[62-64] LV volume may hence be measured using Simpson's rule, similar to its application for LV measurements, which states that the volume of a geometrical figure can be calculated from the sum of the volumes of smaller figures of similar shape. Most commonly, Simpson's algorithm divides the LV into a series of stacked oval disks whose height is "h" and whose orthogonal minor and major axes are D1 and D2 (method of disks). The volume of the entire left atrium can be derived from the sum of the volume of the individual disks. [65]

$$\text{Volume} = \frac{\pi}{4h}\sum D1D2$$

The formula is integrated with the aid of a computer and the calculated volume provided by the software package. The use of the Simpson's method in this way requires the input of biplane LV planimetry to derive the diameters. Optimal contours should be obtained orthogonally around the long-axis of the left atrium using transthoracic echocardiography (TTE) apical views. Three-dimensional echocardiography should provide the most accurate evaluation of LV volume and has shown promise, however no consensus exists to date on the specific method that should be used for data acquisition and there is no comparison with established normal values.[66-68]

Despite the difficulty in using ultrasound for the measurement of stroke volume and cardiac output, focused critical care echocardiography is increasingly being recognized as an

important adjunct in the care of critically ill patients because of the wealth of information one can obtain. Assessment of right ventricular function by echocardiography is important in certain types of shock and may contribute to limited responses to fluid resuscitation.[69-70] Currently, transesophageal echocardiography (TEE) may be one of the best measures of fluid responsiveness.[71, 72]

A.2.6 Echocardiography and Echo-Doppler

Echocardiography allows measurement of cardiac output using standard two-dimensional imaging or, more commonly, Doppler-based methods. The main interest in echocardiography in general is that it can be used not only for measurement of cardiac output but also for the additional assessment of cardiac function. Echocardiography is particularly useful as a diagnostic tool because it allows the visualization of cardiac chambers, valves and pericardium. Small ventricles (‘kissing ventricles’) may incite fluid administration whereas a poorly contractile myocardium may suggest that a dobutamine infusion is a better choice. Right ventricular dilatation may orient towards the diagnosis of massive pulmonary embolism or myocardial infarction whereas the presence of pericardial fluid may suggest a diagnosis of pericardial tamponade. Severe valvulopathy can also be recognized promptly. However, echocardiography instruments and expertise may not be readily available everywhere; in some institutions, this is still the domain of the cardiologists and they need to be called to do the procedure. If an ultrasound beam is directed along the aorta using a probe, part of the ultrasound signal will be reflected back by the moving red blood cells at a different frequency. The resultant Doppler shift

in the frequency can be used to calculate the flow velocity and volume and hence cardiac output. Echo-Doppler evaluation can provide reasonable estimates of cardiac output, but this procedure is operator dependent and continuous measurement of cardiac output using this technique is not possible. Echo-Doppler evaluation may be applied either trans thoracically or transesophageally. However, transthoracic techniques do not always yield good images and transesophageal techniques are more invasive such that some sedation, and often endotracheal intubation, is required in order to obtain reliable measurements. Moreover, the esophageal probe is uncomfortable in non-intubated patients, although may be better tolerated if inserted nasally, and should be used cautiously in patients with esophageal lesions. The signal produces different wave forms that can be used to distinguish to some extent changes in preload, afterload and LV contractility. Doppler flow studies focusing on the descending thoracic aorta may not provide a reliable measurement of the total cardiac output (for example, with epidural use), and are invalid in the presence of intra-aortic balloon pumping. Echo-Doppler cardiac output estimates vary considerably for several reasons, including difficulty in assessment of the velocity time integral, calculation error due to the angle of insonation, and problems with correct measurement of the cross-sectional area. Some training is required when using these techniques. Esophageal-Doppler techniques have been shown to be useful for optimizing fluid administration in high risk surgical patients.[73, 74] Simplified transesophageal Doppler techniques can be convenient as the probe is smaller than for standard esophageal echocardiography techniques. Simplified transthoracic Doppler systems allow estimation of aortic blood flow and may be even less invasive; however, although these techniques can be simple to perform in healthy volunteers, access to good images may be more difficult in critically ill patients. Moreover, there is a fairly prolonged learning

curve for correct use of this system.[75] These methods need further validation in critically ill patients.

A.2.7 CO_2 rebreathing

CO_2 rebreathing systems, based on the Fick principle, use a CO_2 sensor, a disposable airflow sensor and a disposable rebreathing loop. CO_2 production is calculated from minute ventilation and its CO_2 content, and the arterial CO_2 content is estimated from end-tidal CO_2. Partial rebreathing reduces CO_2 elimination and increases the end-tidal CO_2. By combining measurements taken during and without rebreathing, venous CO_2 content can be eliminated from the Fick equation. However, intrapulmonary shunting of blood and rapid hemodynamic changes affect the accuracy of the measurement, so that this technique is not considered to be reliable in acutely ill patients.

A.2.8 Bioimpedance and bioreactance

Bioimpedance is based on the fact that the conductivity of a high-frequency, low-magnitude alternating current passed across the thorax changes as blood flow varies with each cardiac cycle. These changes can be measured using electrodes placed on a patient's chest and used to generate a waveform from which cardiac output can be calculated. Bioreactance has developed out of bioimpedance and measures changes in the frequency of the electrical currents traversing the chest, rather than changes in impedance, potentially making it less sensitive to noise. These techniques are non-invasive and can be applied quickly. They have been used for physiological

studies in healthy individuals and may be useful in perioperative applications,[76] but are less reliable in critically ill patients.[77] Electrical interference may also occur if patients are placed in an ICU environment.

A.3 ETIOLOGIES OF SHOCK

Circulatory shock results primarily in inadequate tissue blood flow. Although most forms of shock may show some increase in cardiac output initially in response to fluid loading, fully one-half of all hemodynamically unstable intensive care unit patients are not preload responsive.[78] The etiologies of shock pathophysiology are usually categorized into four broad groups: hypovolemic, cardiogenic, obstructive, or distributive, all of which may have different causes and treatments. Since the primary goal of the cardiovascular system is to supply adequate amounts of oxygen to meet the metabolic demands of the body, calculation of systemic oxygen delivery (DO_2) and VO_2, identifying tissue ischemia (usually monitored by mixed venous oxygen saturation [SvO_2]) as well as measures of ventricular performance (stroke work) are often calculated from such primary variables. At this level, hemodynamic monitoring is used to define cardiovascular status, not response to treatments based on assumed pathophysiology, and predict outcome. Most of the rationale for hemodynamic monitoring resides at this pathophysiology level. The implied assumption here is that restoration of normal hemodynamic values will prevent further organ injury and reduce mortality. Unfortunately, this argument may not be valid, primarily because hemodynamic monitoring usually only assesses global circulatory

status, not organ function or microcirculation, and does not address the mechanisms by which disease occurs.[79-81]

Circulatory shock causes tissue hypoperfusion, cellular dysfunction, organ injury, and death may occur proportional to the degree and duration of tissue hypoperfusion as quantified by oxygen debt.[82] The four pathophysiologic categories of shock are usually characterized by different specific hemodynamic variables, induced by the associated primary hemodynamic event and the autonomic response to it. These variables can be measured by a variety of noninvasive and invasive means and derived hemodynamic parameters calculated that reflect global cardiovascular status. The relation between specific hemodynamic variables is complex in health, and even more complex is disease. However, a solid understanding of the cardiovascular underpinnings of blood flow homeostasis is required to interpret hemodynamic variables effectively. If disease causes cardiac output and DO_2 to decrease, mean arterial pressure (MAP) decreases as well. Baroreceptors in the aortic arch and carotid body alter vasomotor tone through modulation of sympathetic tone to maintain cerebral perfusion pressure (eg: MAP > 65 mm Hg).[83] The hemodynamic effects of this increased sympathetic tone are tachycardia and restoration of MAP toward normal values by reducing unstressed circulatory blood volume and increased arterial vasomotor tone. Thus, hypotension reflects failure of the sympathetic nervous system to compensate for circulatory shock, while normotension does not insure hemodynamic stability.[84] Since regulation of blood flow distribution occurs by regional vasodilation of arterial resistance vessels, hypotension impairs auto regulated blood flow distribution.[85,86] Except in conditions of severe hypoxemia and anemia, the primary means by which DO_2 is varied to match metabolic requirements is by varying cardiac output and tissue oxygen extraction. Since metabolic demands can vary widely, there is no normal cardiac output or DO_2 value, but rather

minimal thresholds for resting conditions and potentially adequate higher levels during stress. Operationally, it is better to access cardiac output as being either adequate or inadequate to meet the metabolic demands of the body. Inadequate DO_2 is presumed to occur if tissue oxygen extraction is markedly increased, as manifest by a decrease in SvO_2 <70%.[87]

Of the four categories of shock, only distributive shock states following intravascular volume resuscitation are associated with an increased cardiac output but decreased vasomotor tone.[88] Thus, cardiac output, stroke work, DO_2, and SvO_2 are decreased in cardiogenic, hypovolemic, and obstructive shock but may be normal or even increased in distributive shock. However, in all conditions, heart rate increases associated with an increased sympathetic tone. Cardiogenic shock represents primary cardiac failure. It can be due to impaired contractility (myocardial ischemia/infarction, electrolyte imbalance, hypoxemia, hypothermia, endocrinologic diseases, metabolic poisoning, beta-blockers), pump function (valvulopathy, ventriculoseptal defect, dyssrythmias), or diastolic compliance (fibrosis, infiltrative cardiomyopathies, hypertrophy). The specific cardinal findings of cardiogenic shock are increased back pressure to cardiac filling (right atrial pressure [Pra] and pulmonary artery occlusion pressure [Ppao]) and upstream edema (peripheral and pulmonary). Hypovolemic shock represents a decrease in effective circulating blood volume and venous return. It can be due to primary intravascular volume loss (hemorrhage, capillary leak), secondary intravascular volume loss (third-space loss, insensible loss through skin with burns, diarrhea, vomiting), and increased unstressed vascular volume (loss of sympathetic tone, spinal cord injury, vasodilating drugs). The specific findings of hypovolemic shock are decreased filling pressures. Obstructive shock represents a blockage of blood flow. It may be due to right ventricular (RV) outflow obstruction (pulmonary embolism,

hyperinflation), tamponade (pericardial effusion, hyperinflation), or LV outflow obstruction (aortic stenosis, dissecting aortic aneurysm). The specific findings of obstructive shock are often more subtle but include decreased LV diastolic compliance (small LV volume with increased Ppao) and signs of cor pulmonale (Pra greater than Ppao, tricuspid regurgitation). Distributive shock represents loss of normal sympathetic responsiveness resulting in decreased vasomotor tone. In the nonresuscitated subject, this presents as hypovolemic shock, [89] but with fluid resuscitation blood pressure (BP) does not increase despite an increase in cardiac output. It can be due to loss of vascular responsiveness (sepsis, spinal shock, vasodilating drugs, metabolic poisons). The specific findings of distributive shock are an increased cardiac output, DO_2, and SvO_2 despite persistent hypotension. Hemodynamic monitoring can aid in determining circulatory shock etiology. Since most forms of circulatory shock reflect inadequate tissue DO_2, a primary goal of resuscitation is to increase DO_2.

A.3.1 Minimally invasive techniques

Although the PAC measures CO easily at the bedside in critically ill patients,[6,90,91] the recent trend in intensive care unit (ICU) monitoring is toward minimally invasive methods.[92-96]Arterial pulse contour and pulse power analyses have emerged as less invasive alternatives to PAC-derived CO measures.[97,98] The accuracy of these devices for PAC-derived CO measures has not been systematically compared in response to therapies other than volume resuscitation.[99,100] These devices use different calibration schema and model the transfer of arterial pulse pressure to stroke volume differently. Thus, their cross-correlations may not be assumed to be similar. The LiDCO Plus™ (LiDCO Ltd, London, UK) uses a transthoracic lithium dilution estimate of

CO for calibration, whereas the PiCCO Plus™ (Pulsion Ltd, Munich, Germany) uses a transthoracic thermodilution approach to compensate for interindividual differences in arterial compliance.[101-103]

The number of novel noninvasive and minimally invasive hemodynamic monitoring gizmos currently available and being developed is amazing. Independent of their accuracy in measuring what they say they measure, how they are used in clinical decision making is potentially more important because monitoring devices will only improve outcome if coupled to a treatment that itself improves outcome. Non-invasiveness is not the only goal. Although it is always preferable to be less invasive, being non-invasive is not always possible and may even be counter effective. For example, continuous monitoring of arterial pressure is more invasive than intermittent monitoring but is helpful in hypotensive (or severe hypertensive) states. Likewise, a central venous catheter can be helpful to monitor the central venous pressure (CVP) and the $ScvO_2$ (and also facilitates the rapid administration of fluids). Whenever possible, we should of course try to be as non-invasive as possible, but arterial pressure monitoring by itself is still invasive. Echocardiography must be promoted more for its ability to offer a direct evaluation of cardiac function than for its non-invasiveness. Even though it is the most invasive method, the PAC is still of value in very sick patients with complex problems, for example, respiratory failure with shock and oliguria. At the other extreme, completely non-invasive bioimpedance has a place in healthy individuals, but little place in critically ill patients. Other monitoring systems are of use in patients with conditions somewhere between these two extremes. The optimal device depends on the type of patient, the question being asked, and the condition being managed or anticipated.

A.4 CONCLUSION

There is no normal CO. Cardiac output is either adequate or inadequate to meet the metabolic demands of the body. Monitoring of CO alone represents only a single aspect of hemodynamic assessment. Therefore, choices for a specific approach to monitoring cardiac performance should always reflect the necessity for information that might alter patient management. The diagnostic accuracy of preload responsiveness is markedly improved by the use of arterial pulse pressure or stroke volume variation, neither of which require pulmonary arterial catheterization. Interest in clinically relevant applications of PPV and SVV is growing as these parameters demonstrate their influence on patient outcomes. Great care should be taken, however, to ensure that limitations of these parameters are understood, because all measures need to be considered within the context of their physiological limitations.

No bedside method is available to directly assess cardiac output, so all values obtained are estimates. The intermittent thermodilution technique is generally considered as the 'reference' standard, but has its own limitations. A measurement obtained by a less invasive technique may be preferable if it can be obtained more rapidly and easily, even if it is slightly less accurate. Importantly, the accuracy of absolute values may be less important if one is following trends, for example, to track the short-term effects of therapies, such as fluid loading. It is important to be familiar with the technology being used, profiting from its advantages but recognizing its limitations. Most importantly, one must never forget that it is not the monitoring of cardiac output itself that can improve outcomes, but the changes in therapy guided by the data

obtained. Monitoring devices can improve outcome only if they are coupled to treatments that improve outcomes.

References

1. Fick A. Uber die Messung des Blutquantums in der Herzventrikeln. *Verh Phys Med Ges Wurzburg.* 1870;2:16-28.

2. Visscher MB, Johnson JA. The Fick Principle: Analysis of Potential Errors in its Conventional Application. *J Appl Physiol.* 1953;5:635-638.

3. Stewart GN. Researches on the circulation time and on the influences which affect it. IV. The output of the heart. *J Physiol (Lond).* 1897;22:159-183.

4. Fegler G. Measurement of cardiac output in anesthetized animals by a thermodilution method. *Q J Exp Physiol.* 1954;39:153-164.

5. Branthwaite MA, Bradley RD. Measurement of cardiac output by thermal dilution in man. *J Appl Physiol.* 1968;24:434-438.

6. Swan HJ, Ganz W, J.Forrester, Marcus H, Diamond G, Chonette D. Catheterization of the heart in man with use of a flow-directed balloon-tipped catheter. *N Engl J Med.* 1970; 283:447-451.

7. Ganz W, Donoso R, Marcus H, Forrester J, Swan H. A new technique for measuremen of cardiac output by thermodilution in man. *Am J Cardiol*. 1971;27:392-396.

8. Reuter D, Huang C, Edrich T, Shernan S, Eltzschig H. Cardiac Output Monitoring Using Indicator-Dilution Techniques: Basics, Limits, and Perspectives. *Anesth Analg.* 2010;110:799-811.

9. Linton RA, Linton NW, Kelly F. Is clinical assessment of the circulation reliable in postoperative cardiac surgical patients. *J Cardiothorac Vasc Anesth.* 2002;16:4-7.

10. Tibby SM, Hatherill M, Marsh MJ, Murdoch IA. Clinicians' abilities to estimate cardiac index in ventilated children and infants. *Arch Dis Child*. 1997;77:516-518.

11. Eisenberg PR, Jaffe AS, Schuster DP. Clinical evaluation compared to pulmonary artery catheterization in the hemodynamic assessement of critically ill patients. *Crit Care Med*. 1984;12:549-553.

12. Jensen JRC, Bogaard JM, Versprille A. Extrapolation of thermodilution curves obtained during a pause in artificial ventilation. *J Appl Physiol.* 1987;63(4):1551-1557.

13. Snyder JV, Powner DJ. Effects of mechanical ventilation on the measurement of cardiac output by thermodilution. *Crit Care Med*. 1982;10:677-682.

14. Cruz K, Franklin C. The pulmonary artery catheter: uses and controversies. *Crit Care Clin.* 2001;17:271-291.

15. American Society of Anesthesiologists Task Force on Pulmonary Artery Catheterization. Practice guidelines for pulmonary artery catheterization1993;78:380-94.

16. Vincent J-L, Rhodes A, Perel A, et al. Clinical review: Update on hemodynamic monitoring-a consensus of 16. *Critical Care.* 2011;15:229.

17. Goedje O, Hoeke K, Lichtwarck-Aschoff M, Faltchauser A, Lamm P, Reichart B: Continuous cardiac output by femoral arterial thermodilution calibrated pulse contour analysis: comparison with pulmonary arterial thermodilution. *Crit Care Med.* 1999;27:2407-2412.

18. Sakka SG, Reinhart K, Meier-Hellmann A. Comparison of pulmonary artery and arterial thermodilution cardiac output in critically ill patients. *Intensive Care Med.* 1999;25:843-846

19. Costa MG, Della Rocca G, Chiarandini P, Mattelig S, Pompei L, Barriga MS, Reynolds T, Cecconi M, Pietropaoli P: Continuous and intermittent cardiac output measurement in hyperdynamic conditions: pulmonary artery catheter vs. lithium dilution technique. *Intensive Care Med* 2008, 34:257-263.

20. Tsutsui M, Matsuoka N, Ikeda T, Sanjo Y, Kazama T: Comparison of a new cardiac output ultrasound dilution method with thermodilution technique in adult patients under general anesthesia. *J Cardiothorac Vasc Anesth* 2009, 23:835-840.

21. Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. *Chest.* 2002;121(6):2000-2008.

22. Van den Berg P, Jansen JRC, Pinsky MR. The effect of positive-pressure inspiration on venous return in volume loaded post-operative cardiac surgical patients. *J Appl Physiol* 2002; 92:1223–1231.

23. Vieillard-Baron A, Chergui K, Augarde R, et al. Cyclic changes in arterial pulse during respiratory support revisited by Doppler echocardiography. *Am J Respir Crit Care Med* 2003; 168:671–676.

24. Pinsky MR. Probing the limits of arterial pulse contour analysis to predict preload responsiveness. *Anesthesia and Analgesia*. 2003;96(5):1245-1247

25. Marx G, Cope T, McCrossan L. Assessing fluid responsiveness by stroke volume variation in mechanically ventilated patients with severe sepsis. European Journal of Anaesthesiology. 2004;21(2):132-138

26. Hofer CK, M¨uller SM, Furrer L, Klaghofer R, Genoni M, Zollinger A. Stroke volume and pulse pressure variation for prediction of fluid responsiveness in patients undergoing off-pump coronary artery bypass grafting. *Chest.* 2005;128(2):848-854.

27. Reuter DA, Bayerlein J, Goepfert MSG. Influence of tidal volume on left ventricular stroke volume variation measured by pulse contour analysis in mechanically ventilated patients. *Intensive Care Medicine*. 2003;29(3):476-480.

28. Backer DD, Heenen S, Piagnerelli M, Koch M, Vincent JL. Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. *Intensive Care Med.* 2005;31(4):517-523.

29. Kim HK, Pinsky MR. Effect of tidal volume, sampling duration, and cardiac contractility on pulse pressure and stroke volume variation during positive pressure ventilation. *Crit Care Med*. 2008; 36(10):2858-2862.

30. Backer DD, Taccone FS, Holsten R, Ibrahami F, Vincent JL. Influence of respiratory rate on stroke volume variation in mechanically ventilated patients. *Anesthesiology.* 2009; 110(5):1092-1097.

31. Mahjoub Y, Pila C, Friggeri A. Assessing fluid responsiveness in critically ill patients: false-positive pulse pressure variation is detected by Doppler echocardiographic evaluation of right ventricle. *Crit Care Med.* 2009; 37(9):2570-2575.

32. Wiedemann HP, Wheeler AP, Bernard GR. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med.* 2006; 354(24): 2564-2575.

33. Wesseling KH, Jansen JRC, Settels JJ, et al. Computation of aortic flow from pressure in humans using a nonlinear, three-element model. *J Appl Physiol* 1993; 74:2566–2573.

34. Slama M, Masson H, Teboul JL, et al. Monitoring of respiratory variations of aortic blood flow velocity using esophageal Doppler. *Intensive Care Med* 2004; 30:1182–1187.

35. Feissel M, Michard F, Mangin I, et al. Respiratory changes in aortic blood flow velocity as an indicator of fluid responsiveness in ventilated patients with septic shock. *Chest* 2001; 119:867–873.

36. Michard F, Chemla D, Richard C, Wysocki M, Pinsky MR et al. Clinical use of respiratory changes in arterial pulse pressure to monitor the hemodynamic effects of PEEP. *Am J Respir Crit Care Med* 1999;159:935-939.

37. Monnet X, Rienzo M, Osman D, Anguel N, Richard C, Pinsky MR et al. Esophageal Doppler monitoring predicts fl uid responsiveness in critically ill ventilated patients. *Intensive Care Med* 2005, 31:1195-1201.

38. Pinsky MR: Protocolized cardiovascular management based on ventricular–arterial coupling. In *Functional Hemodynamic Monitoring*. Edited by Pinsky MR, Payen D. Berlin: Springer-Verlag; 2006:381-395.

39. Tavernier B, Makhotine O, Lebuffe G, et al.: Systolic pressure variation as a guide to fluid therapy in patients with sepsis-induced hypotension. *Anesthesiology* 1998, 89:1313–1321.

40. Feissel M, Michard F, Mangin I, et al.: Respiratory changes in aortic blood velocity as an indicator of fluid responsiveness in ventilated patients with septic shock. *Chest* 2001, 119:867–873.

41. Reuter DA, Felbinger TW, Schmidt C, et al.: Stroke volume variations for assessment of cardiac responsiveness to volume loading in mechanically ventilated patients after cardiac surgery. *Intensive Care Med* 2002, 28:392–398.

42. Reuter DA, Felbinger TW, Kilger E, et al.: Optimising fluid therapy in mechanically ventilated patients after cardiac surgery by on-line monitoring of left ventricular stroke volume variations. Comparison with aortic systolic pressure variations. *Br J Anaesth* 2002, 88:124–126.

43. Berkenstadt H, Margalit N, Hadani M, et al.: Stroke volume variation as a predictor of fluid responsiveness in patients undergoing brain surgery. *Anesth Analg* 2001; 92:984–989.

44. Pinsky MR: Functional hemodynamic monitoring: asking the right question. *Intensive Care Med* 2002; 28:386–388.

45. Martyn JA, Snider MT, Farago LF, et al: Thermodilution right ventricular volume: A novel and better predictor of volume replacement in acute thermal injury. *J Trauma* 1981;21:619-626.

46. Calvin JE, Driedger AA, Sibbald WJ: Does the pulmonary capillary wedge pressure predict left ventricular preload in critically ill patients? *Crit Care Med* 1981;9:437.

47. Calvin JE, Driedger AA, Sibbald WJ: The hemodynamic effect of rapid fluid infusion in critically ill patients. *Surgery* 1981;90:61.

48. Raper R, Sibbald WJ: Misled by the wedge-The Swan-Ganz catheter and left ventricular preload. *Chest* 1986;89:427.

49. Glantz SA, Parmley WW: Factors which effect the diastolic pressure volume curve. *Circ Res.* 1978;42:171.

50. Glantz SA, Misbach GA, Mooses WY, et al: The pericardium substantially affects the left ventricular diastolic pressure volume relationship in the dog. *Circ Res* 1978;42:433.

51. Martyn JA, Snider MT, Farago LF, et al: Thermodilution right ventricular volume: A novel and better predictor of volume replacement in acute thermal injury. *J Trauma.* 1981; 21:619.

52. Brienza A, Dambrosio M, Bruno F, et al: Right ventricular ejection fraction measurement in moderate acute respiratory failure (ARF) effects of PEEP. *Intensive Care Med*. 1988;14:478.

53. Dhainaut JF, Lancre JJ, deGournoy JM, et al. Right ventricular dysfunction in patients with septic shock. *Intensive Care Med*. 1988;14:488.

54. Reuse C, Vincent JL, Pinsky MR: Measurement of right ventricular volume during fluid challenge. *Chest*. 1990; 98:1450.

55. Diebel LN, Wilson RF, Taggett MG, et al: End-diastolic volume: A better indicator of preload in the critically ill. *Arch Surg.* 1992; 127:817.

56. Cheatham ML, Nelson LD, Chang MC, Safcsak K: Right ventricular end-diastolic volume index as a predictor of preload status in patients on positive end-expiratory pressure. *Crit Care Med.* 1998, 26:1801-1806.

57. Diebel LN, Wilson RF, Tagett MG, Kline RA: End-diastolic volume. A better indicator of preload in the critically ill. *Arch Surg.*1992, 127:817-821.

58. Durham R, Neunaber K, Vogler G, Shapiro M, Mazuski J: Right ventricular end-diastolic volume as a measure of preload. *J Trauma.* 1995, 39:218-223.

59. Reuse C, Vincent JL, Pinsky MR: Measurements of right ventricular volumes during fluid challenge. *Chest* 1990,98:1450-1455.

60. Michard F, Teboul JL: Predicting fluid responsiveness in ICU patients. *Chest*. 2002; 121:2000-2008.

61. Wagner JG, Leatherman JW: Right ventricular end-diastolic volume as a predictor of the hemodynamic response to a fluid challenge. *Chest*. 1998;113:1048-1054.

62. Schabelman S, Schiller NB, Silverman NH, Ports TA. Left atrial volume estimation by two-dimensional echocardiography. *Catheterization Cardiovasc Diagn* 1981;7:165-78.

63. Lester SJ, Ryan EW, Schiller NB, Foster E. Best method in clinical practice and in research studies to determine left atrial size. *Am J Cardiol* 1999;84:829-32.

64. Khankirawatana B, Khankirawatana S, Porter T. How should left atrial size be reported? Comparative assessment with use of multiple echocardiographic methods. *Am Heart J* 2004;147:369-74.

65. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA et al. Recommendations for chamber quantification. *Eur J Echocardiogr.* 2006;7:79-108.

66. Keller AM, Gopal AS, King DL. Left and right atrial volume by freehand three-dimensional echocardiography: in vivo validation using magnetic resonance imaging. *Eur J Echocardiogr* 2000;1:55-65.

67. Khankirawatana B, Khankirawatana S, Lof J, Porter TR. Left atrial volume determination by three-dimensional echocardiography reconstruction: validation and application of a simplified technique. *J Am Soc Echocardiogr* 2002;15:1051-6.

68. Poutanen T, Ikonen A, Vainio P, Jokinen E, Tikanoja T. Left atrial volume assessed by transthoracic three dimensional echocardiography and magnetic resonance imaging: dynamic changes during the heart cycle in children. *Heart* 2000;83:537-42.

69. Vieillard-Baron A, Charron C. Preload responsiveness or right ventricular dysfunction? *Critical Care Med*, 2009; 37: 2662-2663.

70. Vieillard-Baron A. Assessment of right ventricular function. *Current Opinion in Critical Care.* 2009; 15:254-260.

71. Charron C, Caille V, Jardin F, Vieillard-Baron A. Echocardiographic measurement of fluid responsiveness. *Current Opinion in Critical Care*. 2006; 12:249-254.

72. Vieillard-Baron A, Chergui K, Rabiller A et al. Superior vena caval collapsibility as a gauge of volume status in ventilated septic patients. *Intensive Care Med*. 2004; 30:1734-1739.

73. Wakeling HG, McFall MR, Jenkins CS, Woods WG, Miles WF, Barclay GR et al.
Intraoperative oesophageal Doppler guided fluid management shortens postoperative hospital stay after major bowel surgery. *Br J Anaesth* 2005, 95:634-642.

74. Abbas SM, Hill AG: Systematic review of the literature for the use of oesophageal Doppler monitor for fl uid replacement in major abdominal surgery. *Anaesthesia*. 2008; 63:44-51.

75. Lelyveld-Haas LE, van Zanten AR, Borm GF, Tjan DH: Clinical validation of the non-invasive cardiac output monitor USCOM-1A in critically ill patients. *Eur J Anaesthesiol* 2008; 25:917-924.

76. Marque S, Cariou A, Chiche JD, Squara P: Comparison between Flotrac-Vigileo and Bioreactance, a totally noninvasive method for cardiac output monitoring. *Crit Care* 2009;13:R73.

77. Squara P, Denjean D, Estagnasie P, Brusset A, Dib JC, Dubois C: Noninvasive cardiac output monitoring (NICOM): a clinical validation. *Intensive Care Med* 2007; 33:1191-1194.

78. Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. *Chest*.2002; 121:2000-2008.

79. Schmidt-Nielsen K. Circulation. In: Animal physiology. 4th ed. Cambridge, UK: Cambridge University Press, 1983; 97–133.

80. Lush CW, Kvietys PR. Microvascular dysfunction in sepsis. *Microcirculation* 2000; 7:83–101.

81. Buwalda M, Ince C. Opening the microcirculation: can vasodilators be useful in sepsis? *Intensive Care Med* 2002; 28:1208–1217.

82. Shoemaker WC, Appel PL, Kram HR. Tissue oxygen debt as a determinant of lethal and non-lethal postoperative organ failure. *Crit Care Med* 1988; 16:1117–1120.

83. LeDoux D, Astix ME, Carpati C, et al. Effects of perfusion pressure on tissue perfusion in septic shock. *Crit Care Med* 2000; 28:2729–2732.

84. Partrick DA, Bensard DD, Janik JS, et al. Is hypotension a reliable indicator of blood loss from traumatic injury in children? *Am J Surg* 2002; 184:555–559.

85. Ruokonen E, Takala J, Uusaro A. Effect of vasoactive treatment on the relationship between mixed venous and regional oxygen saturation. *Crit Care Med* 1991; 19:1365-1369.

86. Bellomo R, Kellum JA, Wisniewski SR, et al. Effects of norepinephrine on the renal vasculature in normal and endotoxemic dogs. *Am J Respir Crit Care Med* 1999; 159:1186–1192.

87. Pinsky MR, Vincent JL. Let us use the pulmonary artery catheter correctly and only when we need it. *Crit Care Med* 2005; 33:1119–1122.

88. Weil MH, Shubin H. Shock following acute myocardium infarction: current understanding of hemodynamic mechanisms. *Prog Cardiovasc Dis* 1968; 11:1–17.

89. Carroll GC, Snyder JV. Hyperdynamic severe intravascular sepsis depends on fluid administration in cynomolgus monkey. *Am J Physiol* 1982; 243:R131–R141.

90. Gomez CM, Palazzo MG: Pulmonary artery catheterization in anaesthesia and intensive care. *Br J Anaesth* 1998;81:945-956.

91. Rapoport J, Teres D, Steingrub J, Higgins T, McGee W, Lemeshow S: Patient characteristics and ICU organizational factors that influence frequency of pulmonary artery catheterization. *JAMA* 2000;283:2559-2567.

92. Connors AF Jr, Speroff T, Dawson NV, Thomas C, Harrell FE Jr, Wagner D et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. *JAMA* 1996;276:889-897.

93. Sandham JD, Hull RD, Brant RF, Knox L, Pineo GF, Doig CJ et al. A randomized, controlled trial of the use of pulmonary artery catheters in high-risk surgical patients. *N Engl J Med* 2003;348:5-14.

94. Harvey S, Harrison DA, Singer M, Ashcroft J, Jones C, Elbourne D et al. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomized controlled trial. *Lancet* 2005;366:472-477.

95. National Heart and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wheeler AP, Bernard GR, Thompson BT, Schoenfeld D, Wiedemann HP, deBoisblanc B et al. Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. *N Engl J Med* 2006; 354:2213-2224.

96. Hadian M, Pinsky MR: Evidence based of the use of the pulmonary artery catheter: impact data and complications. *Crit Care* 2006;10(Suppl 3): S11-S18.

97. Wesseling KH, de Witt B, Weber JA: A simple device for continuous measurement of cardiac output. *Adv Cardiovasc Phys* 1983;5:16-52.

98. Tannenbaum GA, Mathews D, Weissman C: Pulse contour cardiac output in surgical intensive care unit patients. *J Clin Anesth* 1993; 5:471-478.

99. Godje O, Hoke K, Goetz AE, Felbinger TW, Reuter DA, Reichart B et al. Reliability of a new algorithm for continuous cardiac output determination by pulse-contour analysis during hemodynamic instability. *Crit Care Med.* 2002;30:52-58.

100. Headley JM. Arterial pressure-based technologies: a new trend in cardiac output monitoring. *Crit Care Nurs Clin North Am 2006;*18:179-187.

101. Hamilton TT, Huber LM, Jessen ME. PulseCO: a less-invasive method to monitor cardiac output from arterial pressure after cardiac surgery. *Ann Thorac Surg*. 2002;74:S1408-S1412.

102. Pittman J, Bar-Yosef S, SumPing J, Sherwood M, Mark J: Continuous cardiac output monitoring with pulse contour analysis: a comparison with lithium indicator dilution cardiac output measurement. *Crit Care Med* 2005; 33:2015-2021.

103. Felbinger TW, Reuter DA, Eltzschig HK, Bayerlein J, Goetz A: Cardiac index measurement during rapid preload changes: a comparison of pulmonary artery thermodilution with arterial pulse contour analysis. *J Clin Anesth* 2005;17:241-248.

APPENDIX B

THE INTERFACE BETWEEN MONITORING AND PHYSIOLOGY AT THE BEDSIDE

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B.1 ABSTRACT

Hemodynamic instability as a clinical state represents either a perfusion failure with clinical manifestations of circulatory shock and/or heart failure, or one or more out-of-threshold hemodynamic monitoring values, which may not necessarily be pathological. Different types of circulatory shock etiologies require different types of treatment modalities making these distinctions important. Diagnostic approaches or therapies based on data derived from hemodynamic monitoring assume that specific patterns of derangements reflect specific disease processes, which will respond to appropriate interventions. Hemodynamic monitoring at the bedside improves patient outcomes when used to make treatment decisions at the right time for patients experiencing hemodynamic instability.

B.1.1 Key points

1) Bedside measures of hemodynamic instability include mean arterial pressure (MAP), hypotension and mixed venous oxygen saturation. 1) Bedside measures of hemodynamic instability include mean arterial pressure (MAP), hypotension and mixed venous oxygen saturation.

2) Circulatory shock etiologies can be divided into hypovolemic, cardiogenic, obstructive and distributive shock, and the hemodynamic patterns are characteristic for each etiology.

3) The different etiologies of circulatory shock usually require different types of treatment modalities, making the correct etiologic diagnosis important.

4) Pharmacotherapies for hemodynamic instability include vasopressors, inotropes and vasodilators.

5) Technological advances to restore hemodynamic instability include the use of ventricular assist devices and continuous renal replacement therapies.

B.2 HEMODYNAMIC INSTABILITY

Hemodynamic instability Hemodynamic instability as a clinical state represents either a perfusion failure with clinical manifestations of circulatory shock and/or heart failure, or one or more out-of-threshold hemodynamic monitoring values, which may not necessarily be pathological. Circulatory shock can be produced by decreases in cardiac output relative to metabolic demands, such as decreased intravascular volume (hypovolemic), impaired ventricular pump function (cardiogenic), or mechanical obstruction to blood flow (obstructive) or by misdistribution of blood flow independent of cardiac output (distributive). The prompt identification and diagnosis of the probable cause of hemodynamic instability, coupled with appropriate resuscitation and (when possible) specific treatments, are the cornerstones of intensive care medicine.(M. R. Pinsky & Payen, 2005) Hemodynamic monitoring plays a pivotal role in the diagnosis and management of circulatory shock.

The management of the critically ill patient often requires continual monitoring of hemodynamic variables and the functional hemodynamic status owing to the level of cardiovascular instability the circulatory shock creates. Patterns of hemodynamic variables often

suggest hypovolemic, cardiogenic, obstructive, or distributive shock processes as the primary etiologies of hemodynamic instability. Since these different types of circulatory shock etiologies usually require different types of treatment modalities, making these differential distinctions important. Diagnostic approaches or therapies based on data derived from hemodynamic monitoring in the critically ill patient assume that specific patterns of derangement reflect specific disease processes, which will respond to appropriate interventions.(M. R. Pinsky, 2007)

B.2.1 Mean arterial pressure as a measure of hemodynamic instability

Organ perfusion is dependent on input organ perfusion pressure and local vasomotor tone. Local vasomotor tone varies inversely with local tissue metabolic demand. For most organs except the kidneys and heart, independent changes in arterial pressure above some minimal value are associated with increased vasomotor tone to keep organ perfusion constant, and are therefore not entirely dependent on cardiac function and cardiac output. In such situations, cardiac output is only important to allow parallel circuits to maintain flow without inducing hypotension, and cardiac function is only important in sustaining cardiac output and a given output pressure without causing too high a back pressure in the venous circuits. Hypotension, on the other hand, will decrease blood flow to all organs. Operationally, mean arterial pressure (MAP) is the input pressure to all organs other than the heart. Diastolic aortic pressure is the input pressure for coronary blood flow. MAP is estimated to be equal to the diastolic pressure plus one-third the pulse pressure between diastole and systole. Over a wide range of MAP values, regional blood flow to the brain and other organs remains remarkably stable owing to autoregulation of local vasomotor tone to keep that local blood flow constant despite changing MAP. However, in a

previously normotensive subject, once MAP decreases below ~60 mmHg, then tissue perfusion may decrease independent of metabolic demand and local autoregulatory processes. As tissue blood flow decreases independent of metabolic demand, then tissue O_2 extraction increases to keep local O_2 consumption and metabolic activity constant. This process occurs routinely in most individuals and if transient and is not pathological. However, if tissue blood flow decreases further than increased O_2 extraction can compensate for, then end-organ ischemic dysfunction follows. Despite the lack of sensitivity of a non-hypotensive MAP to reflect hemodynamic stability, measures of MAP to identify hypotension are essential in the assessment and management of hemodynamically unstable subjects, since hypotension must decrease autoregulatory control and increasing MAP in this setting will also increase organ perfusion pressure and organ blood flow.

B.2.2 Hypotension as a measure of hemodynamic instability

Hypotension directly reduces organ blood flow, is synonymous with hemodynamic instability and is a key manifestation in most types of circulatory shock. It also causes coronary hypoperfusion, impairing cardiac function and cardiac output. However, the assumption is often false that, because MAP is maintained in low cardiac output shock states by sympathetic tone mediated peripheral vasoconstriction, the patient is not unstable. Intra-organ vascular resistance and venous outflow pressure along with MAP are the two other determinants of organ blood flow, and therefore organ perfusion. The normal mechanism allowing autoregulation of blood flow distribution is local changes in organ inflow resistance, such that organs with increased metabolic demand enact arterial dilation to increase their blood flow. If there is hypotension,

then local arterial dilation will not result in increased blood flow because the lower inflow pressure will have minimal effect on the organ perfusion pressure. Thus, hypotension impairs autoregulation of blood flow distribution.(Kellum & Pinsky, 2002)

In shock states, normal homeostatic mechanisms functioning through carotid body baroreceptors vary arterial vascular tone so as to maintain MAP relatively constant despite varying cardiac output and metabolic demand. Presumably, this vasoconstriction occurs in low cardiac output states to maintain cerebral and myocardial blood flow at the expense of the remainder of the body. In subjects with normal renal function, oliguria is the immediate manifestation of this adaptive response, reflecting marked reduction in renal blood flow and solute clearance despite persisting “normal” MAP. As such, normotension does not insure hemodynamic sufficiency of all organ systems simultaneously. Hence, indirect measures of sympathetic tone, such as heart rate, respiratory rate, peripheral capillary filling and peripheral cyanosis are more sensitive estimates of increases circulatory stress and hemodynamic instability than is MAP.(M. R. Pinsky, 1998)

Although systemic hypotension can be identified non-invasively using a sphygmomanometer, in the treatment of hypotension not readily responsive to simple maneuvers like recumbency and an initial fluid bolus, invasive arterial catheterization and continuous monitoring of arterial pressure is indicated. There is no consensus as to the absolute indication for invasive arterial pressure monitoring, but caution should be aired in favor of monitoring as opposed to its avoidance in the patient who cannot be rapidly resuscitated. Although peripheral radial arterial catheterization is the most common site for arterial access, femoral arterial catheterization is also available and has the advantage of greater likelihood of successful arterial

cannulation in the setting of profound hypotension and shock. The femoral artery is also the preferred site if one specific minimally invasive arterial monitoring device (i.e. PiCCOplus) use is being considered. However, these issues are addressed in subsequent chapters in this volume on invasive monitoring and minimally invasive and non-invasive monitoring, respectively. Importantly, in conditions of marked vasoconstriction associated with profound hypovolemia and hypothermia, central arterial pressure may exceed peripheral arterial pressure because of increased arterial resistance between these two sites. Thus, assessing end-organ perfusion parameters like level of consciousness, urine output and vascular refill are important early measures of the effectiveness of blood flow. Finally, though early attention is appropriately focused on restoring MAP to some minimal threshold level, organ perfusion pressure is actually MAP minus output pressure. Thus, in the setting of increased intracranial or intra-abdominal pressures, cerebral and splanchnic/renal perfusion pressures will be less than MAP, respectively and these compartment pressures need to be directly measured so as to target an organ perfusion pressure of >60 mmHg.

B.2.3 Mixed venous oxygen saturation as a measure of hemodynamic instability

One cardinal sign of increased circulatory stress is an increased O_2 extraction ratio, which in the setting of an adequate arterial O_2 content manifests itself as a decreasing mixed venous O_2 saturation (SvO_2) in the face of adequate oxygen uptake in the lungs. SvO_2 can only be sampled using a pulmonary artery catheter (PAC), while central venous (unmixed superior vena cava) O_2 saturation can be assessed using a central venous catheter. The choice of the type of monitoring to be used and how it is interpreted is the subject for the invasive monitoring chapter later in the

volume. However, low SvO_2 values can also occur if arterial O_2 content is low, as is the case with anemia and hypoxemia or if O_2 consumption is increased as with muscular exercise.

Muscle activity effectively extracts O_2 from the blood because of the set-up of the microcirculatory flow patterns and the large concentration of mitochondria in these tissues. Thus, normal vigorous muscular activity can be associated with a marked decrease in SvO_2 despite adequate oxygen uptake and a normal circulatory system and metabolic demand.(M. R. Pinsky, 2007) Muscular activities, such as moving in bed or being turned, "fighting the ventilator," and labored breathing spontaneously increase O_2 consumption. In the patient with an intact and functioning cardiopulmonary apparatus, this will translate into an increase in both oxygen delivery (DO_2) and O_2 consumption and a decrease in SvO_2 only to the extent that the increased DO_2 cannot supply the needed O_2 for this increased demand. Under normal conditions of submaximal exercise, DO_2 is the parameter increasing most markedly, although some decrease in SvO_2 also occurs. However, in the sedated and mechanically ventilated patient, decreased SvO_2 is a very sensitive marker of diminished circulation. Although muscle activity is minimal, the diminished flow permits more time for oxygen extraction across the transversed tissue and organ capillary beds. Although there is no level of cardiac output which is 'normal,' there are DO_2 thresholds below which normal metabolism can no longer occur.(M. Pinsky, 2009) Nevertheless, SvO_2 can be utilized as a sensitive but nonspecific marker of circulatory stress, with values less than 70% connoting circulatory stress, less than 60% identifying significant metabolic limitation, and values less than 50% indicating frank tissue ischemia.(Rivers, Ander, & Powell, 2001)

B.3 PRINCIPLES OF HEMODYNAMIC MONITORING BASED ON SHOCK ETIOLOGY

Weil and Shubin defined circulatory shock in 1968 as a decreased effectiveness of circulatory blood flow to meet the metabolic demands of the body.(Weil & Shubin, 1968) The heart, vascular integrity, vasomotor tone, and autonomic control all interact to sustain circulatory sufficiency. Circulatory shock reflects a failure of this system and results in an inadequate perfusion of the tissues to meet their metabolic demand, which can lead to cellular dysfunction and death.(Shoemaker, 1996)

Four basic functional etiologies of circulatory shock can be defined: (1) hypovolemic, due to inadequate venous return (hemorrhage, dehydration [absolute hypovolemia]), (2) cardiogenic, due to inadequate ventricular pump function (myocardial infarction, valvulopathy), (3) obstructive, due to impingement on the central great vessels, (pulmonary embolism, tamponade), and (4) distributive, due to loss of vasoregulatory control (sepsis, anaphylaxis, neurogenic shock, adrenal insufficiency [relative hypovolemia])(Table 1).

Tissue hypoperfusion is common in all forms of shock, with the possible exception of hyperdynamic septic shock, and results in tissue hypoxia and a switch from aerobic to anaerobic metabolism, inducing both hyperlactacidemia and metabolic acidosis. However, hyperlactacidemia is not a reliable marker of ongoing tissue hypoperfusion because lactate clearance is often delayed or impaired in shock states, and processes such as exercise (seizure activity) and inflammation can induce hyperlactacidemia without cardiovascular insufficiency.(James, Luchette, McCarter, & Fischer, 1999) Sustained circulatory shock results in cellular damage, not from anaerobic metabolism alone, but also from an inability to sustain

intermediary metabolism and enzyme production necessary to drive normal mitochondrial performance.(Crouser, 2004) Metabolic failure due to sustained tissue hypoxia may explain why surgical preoptimization(Kern & Shoemaker, 2002) and early goal-directed therapy(Rivers, Nguyen, Huang, & Donnino, 2004) improve outcome, whereas aggressive resuscitation after cellular injury has already occurred is not effective at reducing mortality from a variety of insults.(Gruen, Jurkovich, McIntyre, Foy, & Maier, 2006)

Since most forms of hemodynamic monitoring measure global systemic blood flow parameters like arterial pressure, heart rate, other central vascular pressures and cardiac output, the assessment of the severity of shock and its initial response to therapy is often limited if monitoring is limited to these global variables alone. Since cellular respiration does not cease when tissue blood flow decreases until some very low level of blood flow occurs, tissue CO_2 production usually continues at a normal rate, resulting in an increased venous PCO_2. Potentially, measuring SvO_2, or alternatively the difference between tissue PCO_2 ($PvCO_2$) and arterial PCO_2 ($PaCO_2$), referred to as the Pv-aCO_2 gap, would allow one to assess effective tissue blood flow, since decreases in capillary blood flow initially causes CO_2 from aerobic metabolism to accumulate.(Silva, De Backer, Creteur, & Vincent, 2004) Currently, global measures of circulatory function are being used to determine which of the four shock categories is the most likely cause of organ dysfunction by noting their characteristic patterns or groupings of abnormalities, referred to as hemodynamic profile analysis.(FIDDIAN-GREEN, Haglund, GUTIERREZ, & SHOEMAKER, 1993).

B.3.1 Hypovolemic shock

Hypovolemia is the cardiovascular state in which the effective circulating blood volume is inadequate to sustain adequate venous return and thus cardiac output to support normal function without invoking supplemental sympathetic tone or postural changes to provide venous return assistance. It is a process of absolute hypovolemia, which can occur through loss of blood, such as with hemorrhage and trauma, or with fluid and electrolyte loss, as with diuresis, diarrhea, vomiting, or evaporation from large burn surfaces, or with severe fluid intake restriction resulting in dehydration.(Piper & Kaplan, 2012) The normal reflex response to absolute hypovolemia is increased sympathetic tone causing selective vasoconstriction. Cardiac output is often sustained by this vasoconstrictive maneuver, and venous return is maintained by diverting blood away from the skin, resting muscles, and gut and into the central circulation. The cardinal sign of this circulatory stress is increased heart rate owing to increased sympathetic tone. If the hypovolemic state progresses, this vasoconstriction becomes inadequate to sustain venous return and cardiac output decreases. Under these conditions, heart rate increases but stroke volume decreases more such that cardiac output declines. With tissue hypoperfusion, increased O_2 extraction occurs across the capillary beds, but eventually even increased extraction fails to sustain aerobic metabolism, and lactic acidosis develops as a marker of tissue anaerobic metabolism.(M. Fink, 1996) Thus, hypovolemia initiates tachycardia, reduced arterial pulse pressure, and (often) hypertension with a near normal resting cardiac output, followed by signs of end-organ hypoperfusion (oliguria, confusion) as cardiac output decreases.

Hypovolemic shock represents a decrease in effective circulating blood volume and venous return. It can be due to primary intravascular volume loss (hemorrhage, capillary leak) or secondary intravascular volume loss (third-space loss, insensible loss through skin with burns, diarrhea, vomiting). The specific findings of hypovolemic shock are decreased cardiac filling pressures (low venous return manifested by low right atrial pressure [Pra] and low left atrial pressure [pulmonary artery occlusion pressure or Ppao]) accompanied by low cardiac output and high systemic vascular resistance (reflexive or sympathetically induced vasoconstriction manifested by high systemic vascular resistance index).(M. R. Pinsky, 2007) Systemic hypotension is the final presentation of hypovolemic shock(Parks, Elliott, Gentilello, & Shafi, 2006) and if the clinician waits for hypotension to identify circulatory shock before intervening, ischemic tissue injury is almost always already present.

B.3.2 Cardiogenic shock

Cardiac pump dysfunction can be due to left ventricle (LV), right ventricle (RV) failure, or both. LV failure is usually manifested by an increased LV end-diastolic pressure and left atrial pressure, which must exist to sustain an adequate LV stroke volume. Tachycardia is universal in the patient who is not β-blocked. The most common cause of isolated LV failure in the critically ill patient is acute myocardial infarction.(Menon et al., 2000) However, in post-operative cardiac surgery patients, myocardial stunning can also cause transient LV failure. In acute isolated LV failure, LV stroke work is reduced and heart rate increased. In chronic heart failure, cardiac output may be adequate, or the periphery may have adapted enough to increase O_2 extraction

such that tissue hypoperfusion is not present, with the only sign of heart failure being peripheral edema and increased sympathetic tone. However, in acute LV failure cardiac output may be normal or even increased, owing to increased sympathetic tone. However, LV filling pressure becomes markedly elevated as the increased sympathetic tone decreases unstressed volume increasing mean systemic pressure and augmenting the pressure gradient for venous return. This causes a marked increase in intrathoracic blood volume which may induce flash hydrostatic pulmonary edema, also known as cardiogenic pulmonary edema. However, neither cardiac output nor systemic vascular resistance are sensitive markers of LV failure until after cardiogenic shock develops.(M. R. Pinsky, 1998a)

The normal adaptive response of the patient to impaired LV contractile function and resulting low organ and tissue perfusion is to increase sympathetic tone, induce tachycardia, activate the renin-angiotensin system, retain sodium by the kidneys, and thus increase the circulating blood volume. In essence, the body does not differentiate its adaptive response to low tissue perfusion caused by either hypovolemic or cardiogenic shock. Fluid retention as a compensatory mechanism, if present, takes time to evolve, whereas acute impairments of LV contractility can occur over seconds in response to myocardial ischemia. Thus, the hemodynamic profile of acute and chronic LV failure can be different. Acute LV failure is manifest by increased sympathetic tone (tachycardia, hypertension), impaired LV function (increased left atrial filling pressure and reduced stroke volume), with minimal RV effects (normal central venous pressure, unless RV infarction also occurs), and increased oxygen extraction manifested by a low SvO_2. Cardiac output may not be reduced and may actually be slightly elevated early on, owing to the release of catecholamines as part of the acute stress response.(Sapolsky,

Romero, & Munck, 2000) Vascular resistance, therefore, is increased. By contrast, in chronic heart failure, although sympathetic tone is elevated, the heart rate is rarely >105 beats/min, while filling pressures are elevated in both atria consistent with combined LV failure and fluid retention. Importantly, cardiac output is not reduced except in severe chronic heart failure states. Importantly, a cardinal finding of heart failure is the inability of the heart to increase cardiac output in response to a volume load or metabolic stress state (exercise). Furthermore, owing to the increased sympathetic tone, splanchnic and renal blood flows are reduced and can lead to splanchnic or renal ischemia.(Gelman & Mushlin, 2004) Although acute heart failure may present with shock, more commonly patients with preexisting chronic heart failure develop a new illness, or acute exacerbation of their heart failure. Thus, their new pathology is superimposed upon the preexisting heart failure. Such mixed process shock states are often difficult to treat because of the limitations of the patient's cardiac response created by the prior heart failure, and it is quite easy to induce pulmonary and peripheral edema using routine fluid resuscitation.

Cardiogenic shock represents primary cardiac failure. It can be due to impaired myocardial contractility (myocardial ischemia/infarction, electrolyte imbalance, hypoxemia, hypothermia, endocrinologic diseases, metabolic poisoning, beta-blockers), pump function (valvulopathy, ventriculoseptal defect, dysrhythmias), or diastolic compliance (left ventricular hypertrophy, fibrosis, infiltrative cardiomyopathies, asymmetric septal hypertrophy, cor pulmonale). The specific cardinal findings of cardiogenic shock are increased back pressure to cardiac filling (increased right atrial pressure [Pra] and pulmonary artery occlusion pressure [Ppao]) and upstream edema owing to compensatory fluid retention (peripheral and pulmonary).(M. R. Pinsky, 2007)The hemodynamic profile pattern therefore seen in cardiogenic

shock is as it progresses is low cardiac output, high right atrial pressure [Pra] and pulmonary artery occlusion pressures [Ppao], and high systemic vascular resistance (reflexive or sympathetically induced vasoconstriction manifested by high systemic vascular resistance index).

B.3.3 Obstructive shock

Obstructive shock represents a blockage of blood flow in one of the heart's outflow tracts. It may be due to right ventricular (RV) outflow obstruction (pulmonary embolism, lung hyperinflation and pulmonary artery compression), LV outflow obstruction (aortic stenosis, dissecting aortic aneurysm) or cardiac tamponade (pericardial effusion, lung hyperinflation and atrial compression).The specific findings of obstructive shock are often difficult to separate from cardiogenic shock, and may be different relative to the ventricle with the obstructive pathophysiology.

The most common cause of obstructive shock is pulmonary embolism and RV outflow obstruction leading to acute RV failure (Torbicki et al., 2008). However, isolated RV dysfunction can occur in the setting of an acute inferior wall myocardial infarction, and also as a consequence of pulmonary vascular disease (chronic obstructive pulmonary disease, primary pulmonary hypertension) and hyperinflation. Neither pulmonary vascular resistance nor mean pulmonary artery pressure need be grossly elevated for RV failure to be present. Indeed, and importantly, if pulmonary arterial pressures are greater than 30 to 35 mmHg, then pulmonary hypertension is probably chronic in nature because acute elevations of pulmonary arterial pressures above this level are physiologically tolerable. Elevations in central venous pressure of

more than 12 mmHg also reflect fluid retention, suggesting further that RV decompensation or massive volume overload from LV failure has occurred. The most common hemodynamic monitoring pattern in acute pulmonary embolism is that of elevated central venous pressure, decreased pulmonary artery occlusion pressures [Ppao] relative to the CVP (since preload to the left ventricle is diminished but LV contractility remains normal), and low cardiac output accompanied by high systemic vascular resistance (reflexive or sympathetically induced vasoconstriction manifested by high systemic vascular resistance index). However, in severe cor pulmonale, RV and LV diastolic pressure equalization occurs and it is indistinguishable from pericardial tamponade, as indeed acute RV dilation will induce tamponade physiology. Echocardiography is extremely useful in making the diagnosis of acute cor pulmonale because it can be performed immediately at the bedside and is non-invasive. Echocardiographic studies will reveal RV diameters greater than LV diameters and a paradoxical intraventricular septal shift. These points are discussed in detail in the chapter on ultrasonography.

When RV dysfunction predominates and is induced by pulmonary parenchymal disease, it is referred to as cor pulmonale, which is associated with signs of backward failure, elevated RV volume and pressures, systemic venous hypertension, low cardiac output, as well as reduced renal and hepatic blood flow.(M. R. Pinsky, 2007) LV diastolic compliance decreases as the right ventricle dilates due to ventricular interdependence, either from intraventricular septal shift or absolute limitation of biventricular volume due to pericardial restraint. Thus, Ppao is often elevated for a specific LV stroke work, giving the erroneous appearance of impaired LV contractility. (M. R. Pinsky, 2006)

Cardiac tamponade, another cause of obstructive shock, can occur from either (1) biventricular dilation limiting biventricular filling due to pericardial volume limitation, (2) acute

pericardial fluid accumulation due to either effusion fluid (inflammation, severe uremia) or blood (hemorrhage), which needs not be great in quantity, and (3) lung hyperinflation resulting in mechanical compression of the heart from without, which acts like pericardial tamponade to limit biventricular filling.(Spodick, 1998) The first two etiologies are rarely seen, whereas hyperinflation commonly occurs. The cardinal sign of tamponade is diastolic equalization of all intrathoracic vascular pressures (CVP, pulmonary arterial diastolic pressure, and Ppao).(Aksoy & Rodriguez, 2013) Since RV compliance is greater than LV compliance early on in tamponade, there may be selective reduction in RV filling.(M. Pinsky, 2002)

B.3.4 Distributive shock

Loss of blood flow regulation occurs as the end-stage of all forms of circulatory shock owing to hypotension, but is one of the initial presenting processes seen in sepsis, neurogenic shock, and adrenal insufficiency. The hemodynamic profile of sepsis is one of increased cardiac index, low right and left filling pressures, elevated SvO_2, low mean arterial pressure, and low systemic vascular resistance consistent with loss of peripheral vasomotor tone and pooling of blood in the vascular system manifesting as a relative hypovolemia.

Sepsis is a systemic process characterized by activation of the intravascular inflammatory mediators resulting in generalized vascular endothelial injury, but it is not clear that tissue ischemia is an early aspect of this process.(Hack & Zeerleder, 2001) Acute septicemia is associated with increased sympathetic activity (tachycardia, diaphoresis) and increased capillary leak with secondary loss of intravascular volume, and inappropriate clotting in the microcirculation. Before fluid resuscitation, this combination of processes resembles simple

hypovolemia, with decreased cardiac output, normal to increased peripheral vasomotor tone, and very low SvO_2, reflecting systemic hypoperfusion. LV function is often impaired, but usually in parallel with depression of other organs, and this effect of sepsis is usually masked by the associated hypotension that maintains low LV afterload.(M. R. Pinsky & Rico, 2000) Initially, decreased adrenergic responsiveness and impaired diastolic relaxation characterize septic cardiomyopathy. If sepsis remains ongoing, impaired LV contractile function also occurs. However, most patients with such a clinical presentation receive initial volume expansion therapy such that the clinical picture of sepsis reflects a hyperdynamic state rather than hypovolemia, which has been referred to as 'warm shock' in contrast to all other forms of shock.(Rabuel & Mebazaa, 2006)

Neurogenic shock results from an acute spinal injury above the upper thoracic level, spinal anesthesia, general anesthesia, neurotoxic poisoning and central nervous system catastrophe. All of these states induce a profound loss of sympathetic tone and pooling of blood in the vascular compartment causing a relative hypovolemic state. In neurogenic shock, the resulting hypotension is often not associated with compensatory tachycardia, hence systemic hypotension can be severe and precipitate cerebral vascular insufficiency and myocardial ischemia.(Kiss & Tator, 1993) Since neurogenic shock reduces sympathetic tone, the biventricular filling pressures, arterial pressure and cardiac output are all decreased. Treatment consists of reversing the primary process and supporting the circulation with volume loading and an infusion of an α-adrenergic agonist, such as norepinephrine, dopamine or phenylephrine to induce vasoconstriction and reverse vascular pooling of blood.(Müllner et al., 2004)

Acute adrenal insufficiency can present with hyperpyrexia and circulatory collapse. This is more common than might be realized based on the epidemiology of adrenal cortical disease,

because many patients in the community are receiving chronic corticosteroid therapy for the management of chronic systemic and localized inflammatory states, such as asthma or rheumatoid arthritis. In such cases the added stress of trauma, surgery, or infection can precipitate secondary adrenal insufficiency, as can the discontinuation of long-term steroid treatment.(Sabharwal, Fishel, & Breslow, 1998) Patients typically present with nausea and vomiting, diarrhea, confusion, hypotension, and tachycardia. Cardiovascular collapse is similar to that seen in neurogenic shock, except that the vasculature is not as responsive to sympathomimetic support.(Bouachour et al., 1994) Since systemic hypotension is a profound stimulus of the adreno-cortical axis, measures of random cortisol levels in a patient with systemic hypotension will show low values in patients with adrenal insufficiency, and an ACTH-stimulation test is not needed to make the diagnosis. Accordingly, failure to respond to vasoactive pharmacological support in a patient who is hypotensive should suggest the diagnosis of adrenal insufficiency, while giving stress doses of corticosteroids usually reverses the unresponsive nature of the shock process.(CLAUSSEN, LANDERCASPER, & COGBILL, 1992) Since there is little detrimental effect of providing adrenal replacement levels of hydrocortisone in the short term, it is reasonable to start low dose hydrocortisone (60-80 mg intravenously every eight hours) while awaiting the response to resuscitation, and results of the plasma cortisol test.

B.4 CIRCULATORY SUPPORT OF THE PATIENT WITH HEMODYNAMIC INSTABILITY

A brief summary of the four main shock states has been provided in Table 1. Of the four categories of shock, only distributive shock states following intravascular volume resuscitation are associated with an increased cardiac output but decreased vasomotor tone. Thus, cardiac output, stroke work, DO_2, and SvO_2 are decreased in cardiogenic, hypovolemic, and obstructive shock, but may be normal or even increased in distributive shock. However, in all conditions, heart rate increases associated with an increased sympathetic tone (except in neurogenic shock and sympathetic impairment). Hemodynamic monitoring can aid in determining circulatory shock etiology and in assessing response to therapy. Since most forms of circulatory shock reflect inadequate tissue DO_2, a primary goal of resuscitation is to increase DO_2.(Moore, McKinley, & Moore, 2004)

If the cause of hypotension is diminished intravascular volume, either absolute or relative, then cerebral and coronary perfusion pressures must be maintained while fluid resuscitation is begun, otherwise cerebral ischemia and cardiac pump failure may develop and limit the effectiveness of fluid resuscitation.(Mehta & Pinsky, 1998) Infusions of vasoactive agents with both α and β-1 adrenergic agonist properties will increase both MAP and cardiac output at the expense of the remaining vascular beds, hence fluid resuscitation to achieve an adequate intravascular blood volume is an essential co-therapy for sustaining organ perfusion pressure. Isolated vasopressor therapy in the setting of systemic hypotension causes worsening hypoperfusion of the periphery and organs excluding the heart and brain. Thus, though giving

vasopressor therapy in the setting of acute hypotension is often indicated, it is essential to assess volume status as well, because the pathologic ischemic effects of hypovolemia will be heightened by isolated vasopressor therapy. Many pathological states and acute stress conditions are associated with either adrenergic exhaustion or blunted responsiveness to otherwise adequate circulating levels of catecholamines (e.g. diabetes, adrenal insufficiency, hypothermia, hypoglycemia, and hypothyroidism). Furthermore, acute sepsis and systemic inflammation are associated with reduced adrenergic responsiveness or relative adrenal insufficiency.(Hennein et al., 1994; Oddis & Finkel, 1997) Thus, even if the patient produces an otherwise adequate sympathetic response, the vasomotor and inotropic response may be inadequate, requiring transient use of potent sympathomimetic agents to sustain hemodynamic stability, and adrenocortical hormone replacement to support relative adrenal insufficiency is also often needed.

B.4.1 Pharmacotherapies for hemodynamic instability

Pharmacotherapies for hemodynamic instability are directed at the pathophysiological processes that either induce or compound it. Hemodynamic monitoring plays a central role in assessing the effectiveness of these therapies in an iterative fashion. These therapies can be loosely grouped into one of three processes: (1) those that increase vascular smooth muscle tone (vasopressor therapy), (2) those that increase cardiac contractility (inotropic support), and (3) those that decrease smooth muscle tone (vasodilator therapy).

Infusion of vasopressor agents are indicated to sustain a MAP greater than 60 mmHg to prevent coronary or cerebral ischemia while other resuscitative measures like volume

resuscitation and specific treatments of the underlying condition are initiated. This level of MAP is clearly arbitrary since some patients maintain adequate coronary and cerebral blood flow at lower MAP levels, whereas others, notably those with either pre-existent systemic hypertension or atherosclerotic cerebrovascular disease, may not tolerate MAP decreasing more than 30 mmHg below their baseline value.(M. Pinsky, 2005) Once an “adequate” MAP has been achieved and intravascular volume losses corrected, care shifts toward maintaining adequate blood flow to perfuse metabolically active tissues in order to sustain organ performance while minimizing the detrimental effects of these vasoactive therapies.

B.4.2 Vasopressor agents for hemodynamic instability

Vasopressor therapy can reverse systemic hypotension, but at a price: the only means whereby it can increase systemic MAP is by reducing blood flow through vasoconstriction. Importantly, cerebral vascular circuits have no α-adrenergic receptors, and coronary vascular circuits have minimal α-adrenergic receptors, and therefore their facular beds will not constrict in the presence of exogenous -adrenergic stimulation. Unfortunately, in hypovolemic states vasopressor support may transiently improve both global blood flow and MAP, but at the expense of worsening local non-vital blood flow and hastening tissue ischemia. Initial resuscitative efforts should therefore always include an initial volume expansion component and fluid challenge while diagnostic approaches that identify shock states ensue, before relying on vasopressors alone to support the hemodynamically unstable patient.(M. R. Pinsky, 2005)

B.4.3 Phenylephrine

The only non-catecholamine sympathomimetic used, phenylephrine differs chemically from other sympathomimetics by the absence of a hydroxyl group on position 4 of the benzene ring. This deletion reduces its potency relative to other sympathomimetics. It acts as a moderately potent α1-agonist and is used in those patients in whom hypotension is due to decreased arterial elastance (it only activates β-adrenoreceptors at high doses). A modest direct coronary vasoconstrictor effect appears to be offset by autoregulatory mechanisms in the absence of flow-limiting coronary disease. It is not metabolized by catecholamine O-methyltransferase (COMT), which metabolizes catecholamines, and therefore its absolute half-life is considerably longer than catecholamine sympathomimetics.(Westfall & Westfall, 2006) Thus, if phenylephrine is used to treat hypotension, it universally causes cardiac output to decrease. This is because α1-agonist activity results in an MAP increase purely on the basis of the associated increase in vascular resistance and therefore increased left ventricular afterload, but without by β1 stimulation to assist with improved contractility. Accordingly, its prolonged use is potentially detrimental to tissue blood flow, though it's acute use may reverse hypotension and transiently sustain cerebral and coronary blood flow.

B.4.4 Norepinephrine

Norepinephrine has significant activity at α and β1-adrenoreceptors, resulting in a positive vasoconstrictor and inotropic effect. Its accompanying β1 activity makes it the α1-agonist of choice in the patient with hypotension and known LV dysfunction.(Skomedal, Borthne, Aass,

Geiran, & Osnes, 1997) Its positive vasopressor effect may enhance renal perfusion and indices of renal function in hemodynamically stable patients and this effect may also be seen at higher doses when norepinephrine is used as a vasopressor in those patients with sepsis. Both effects are likely related to elevation of MAP, the input pressure for organ perfusion. If norepinephrine is used to treat hypotension and decreased vasomotor tone, then one usually sees MAP increase with minimal changes in cardiac output because the increase in afterload is balanced by the associated increased contractility. However, this balance is also dependent on the LV being responsive to adrenergic stimulation. Maas et al. demonstrated that when post-operative cardiac surgery patients had their MAP increased by 20 mmHg by norepinephrine infusion, cardiac output increased in those with normal cardiac reserve and decreased in those with impaired cardiac reserve.(Maas, Pinsky, de Wilde, de Jonge, & Jansen, 2013) Thus, the cardiac output response to increasing MAP with norepinephrine is variable and dependent on baseline cardiac contractile reserve.

B.4.5 Epinephrine

Epinephrine is a very potent catecholamine sympathomimetic that has markedly increased β2-adrenoreceptor activity compared with its molecular substrate, noradrenaline. Adrenaline has potent chronotropic, inotropic, β2-vasodilatory, and α1-vasoconstrictor properties. Its net vasopressor effect is the end result of the balance between adrenaline-mediated β2 and α1 adrenoreceptors stimulation. At low doses this balance may result in no net pressor effect, with a fall in the diastolic blood pressure. Thus, the effects of epinephrine on hemodynamics will be variable and dependent on dosage, perhaps more so than other sympathomimetic agents.

Epinephrine, like norepinephrine, is known to have potent renovascular and splanchnic vasoconstrictor properties.(Mehta & Pinsky, 1998) Clearance rates are variable and mediated by both the COMT and monoamine oxidase systems.

B.4.6 Dopamine

Dopamine is the most controversial of the clinically utilized catecholamine sympathomimetics. This stems largely from claims for selective, dose-dependent, splanchnic and renovascular vasodilatory properties. Its dopaminergic properties do not reduce the incidence of renal failure in patients with shock when compared to noradrenaline.(Perdue, Balser, Lipsett, & Breslow, 1998) Dopamine stimulates the release of norepinephrine from sympathetic nerve terminals in a dose-dependent manner, with this indirect norepinephrine effect accounting for up to half of dopamine's clinically observed physiological activity.(A. Smith, 1973) Cardiomyocyte norepinephrine stores are finite, accounting for tachyphylaxis to the positive inotropic effects of dopamine observed after approximately 24 h in patients with acute myocardial infarction.(Parissis, Farmakis, & Nieminen, 2007)

Recent clinical trials showing norepinephrine beneficial effects over dopamine

Consensus guidelines and expert recommendations suggest that either norepinephrine or dopamine may be used as a first-choice vasopressor in patients with shock.(Antman et al., 2004; Dellinger et al., 2008; Hollenberg et al., 2004) However, observational studies have shown that the administration of dopamine may be associated with mortality rates that are higher than those associated with the administration of norepinephrine in patients with septic shock.(Boulain et al.,

2009; Martin, Viviand, Leone, & Thirion, 2000; Sakr et al., 2006) The Sepsis Occurrence in Acutely Ill Patients (SOAP) study, which involved 1058 patients with shock, demonstrated that administration of dopamine was an independent risk factor for death in the intensive care unit. In a recent multicenter, randomized, blinded trial comparing dopamine and norepinephrine as the initial vasopressor therapy in the treatment of shock,(De Backer et al., 2010) there was no significant difference in mortality at 28 days between patients who received dopamine and those who received norepinephrine, although dopamine was associated with more severe arrhythmic events than was norepinephrine. Other studies in patients with cardiogenic shock have shown that the mortality rate was significantly higher in the dopamine group than in the norepinephrine group,(LOEB, WINSLOW, RAHIMTOOLA, ROSEN, & GUNNAR, 1971; Ungar et al., 2004; Winslow, Loeb, Rahimtoola, Kamath, & Gunnar, 1973) with higher heart rates in patients who received dopamine as a potential contributor to the occurrence of ischemic events. Clinical trials in critically ill patients at risk for renal failure have also shown no renal vascular saving-effect of low dose dopamine. (R. Bellomo, Chapman, Finfer, Hickling, & Myburgh, 2000; D. Jones & Bellomo, 2005)In summary, recent clinical trials have raised serious concerns about the safety and efficacy of dopamine therapy in the treatment of hypotensive circulatory shock.

B.4.7 Inotropic agents

B.4.8 Dobutamine

Dobutamine is a synthetic analogue of dopamine. It is utilized by continuous infusion as a positive inotrope, with the improvement in cardiac output noted to potentially increase renal blood flow, creatinine clearance, and urine output. Dobutamine also induces vasodilation that can cause profound hypotension in the hypovolemic patient. As a β1-agonist it increases myocardial oxygen consumption, although autoregulatory increases in coronary blood flow usually fully compensate in the absence of flow-limiting coronary artery disease. A noted problem with dobutamine is the development of tachyphylaxis with prolonged (as little as 72 hours) infusions, suggested to be due to the down-regulation of β1-adrenoreceptors. (Klein, Siskind, Frishman, Sonnenblick, & Lejemtel, 1981; O'Connor et al., 1999; Unverferth, Blanford, Kates, & Leier, 1980) A recent randomized, double blind, placebo-controlled clinical trial in septic shock patients with low cardiac output and persistent hypoperfusion showed that dobutamine failed to improve sublingual microcirculatory, metabolic, hepatosplanchnic or peripheral perfusion parameters despite inducing a significant increase in systemic hemodynamic variables.(Hernandez et al., 2013) Thus, changes in measures of macrocirculatory flow may not be translated into changes in microcirculatory tissue blood flow. This unfortunate potential dissociation between macrocirculatory and microcirculatory is not unique to dobutamine, but may be seen in response to volume resuscitation and both vasopressor and vasodilator therapies.

B.4.9 Dopexamine

Dopexamine is a synthetic dopamine analogue with significant β2-adrenoreceptor agonist activity. Its splanchnic blood flow effects and positive inotropic activity have led to enthusiasm for potential utility outside its primary indication—decrease of afterload in acute heart failure syndromes with hypertension and oliguria. Randomized controlled clinical investigations have demonstrated improvement in morbidity and mortality outcomes when dopexamine was utilized as the pharmaceutical of choice in achieving goal-oriented oxygen delivery values in perioperative critically ill patients. (Boyd, Grounds, & Bennett, 1993; Hayes et al., 1994) Though widely utilized outside of North America, it is not licensed for use in North America.

B.4.10 Phosphodiesterase inhibitors

Although these agents are not widely used in the management of circulatory shock, but the two most commonly employed agents in this class are amrinone and milrinone. Both are bipyridines, and the class of drugs is otherwise known as ‘inodilators’ with reference to the two predominant dose-dependent modes of action—inotropy and vasodilation .(Dei Cas, Metra, & Visioli, 1989) Milrinone has a shorter half-life and is a more potent (10–15-fold) inotropic agent than amrinone, but from all other aspects they are similar agents.(Alousi & Johnson, 1986; Earl, Linden, & Weglicki, 1985) Both are eliminated by conjugation, with amrinone’s biological half-life known to be extended in the presence of congestive heart failure. Their mechanism of action is not precisely known, but at least part of their activity is related to inhibition of phosphodiesterase type 3, found in high concentrations in cardiomyocytes and smooth muscle

cells, and they may activate a sodium-dependent calcium channel. The end result is an increase in intracellular cAMP and calcium, with the physiological effect being an improvement in diastolic myocardial function, and for this reason these agents are felt to be positive lusiotropes.(Lipskaia, Chemaly, Hadri, Lompre, & Hajjar, 2010) Clinically, they are used as positive inotropes, given by continuous intravenous infusion following a loading dose, with their catecholamine-independent mechanism of action making them theoretically attractive as an inotropic support of choice in patients with potential β1-adrenoreceptor down-regulation.

B.4.11 Levosimendan

Levosimendan, as a pharmacological agent, exerts positive inotropic effects by binding to cardiac troponin C, thus sensitizing the myofilaments to calcium(Haikala, Kaivola, et al., 1995; Haikala, Nissinen, Etemadzadeh, Levijoki, & Lindén, 1995) and increasing the effects of calcium during systole, thereby improving contraction. During diastole, it causes calcium concentration to decline, allowing normal or improved diastolic relaxation.(Follath et al., 2002) Levosimendan also has vasodilatory properties due to its facilitation of an adenosine triphosphate-dependent potassium channel opening(Yokoshiki, Katsube, Sunagawa, & Sperelakis, 1997) as well as anti-ischemic effects.(Kersten, Montgomery, Pagel, & Warltier, 2000) In clinical studies, levosimendan increased cardiac output and lowered cardiac filling pressures and was associated with reduced cardiac symptoms, risk of death, and hospitalization in patients . (Moiseyev et al., 2002; Nieminen et al., 2000; Slawsky et al., 2000) Unlike other positive inotropic agents, the primary actions of levosimendan are independent of interactions with β-adrenergic receptors. (Haikala, Kaheinen, Levijoki, & Lindén, 1997) In the

Levosimendan Infusion versus Dobutamine (LIDO) study(Follath et al., 2002), levosimendan was shown to exert superior hemodynamic effects compared with the β-adrenergic agonist dobutamine, and in secondary and post hoc analyses was associated with a lower risk of death after 31 and 180 days.

B.4.12 Vasodilators

Afterload reducing vasodilators act via vascular smooth muscle relaxation. Vascular dilatation is mediated by both nitric oxide (NO) and non-NO-based mechanisms, NO being a powerful, locally acting vascular smooth muscle relaxant. Among commonly used vasodilators in hemodynamically unstable patients, both sodium nitroprusside and glyceryl trinitrate (nitroglycerine) function as NO donors. Numerous other non-NO donor vasodilating agents are available, with hydralazine, clonidine, and inhibitors of the renin-angiotensin system being the most commonly employed non-NO-based vasodilators in patients with hemodynamic instability. Although uncommonly needed in the management of circulatory shock, their use in combination with vasopressor therapy has recently been advocated to increase microcirculatory flow since nitrate releasing agents cause microcirculatory flow to increase even in the setting of vasopressor-induced arteriolar vasoconstriction.(Trzeciak et al., 2008) However, this is an approach still under investigation and not ready yet for general clinical use. (De Backer et al., 2007)

B.5 VENTRICULAR ASSIST DEVICES

Ventricular assist devices (VADs) are artificial pumps that take over the function of the damaged ventricle so as to restore hemodynamic stability and end-organ blood flow. These devices are useful in two groups of patients. The first group consists of patients who require ventricular assistance to allow the heart to rest and recover its function. In such situations, it is critical to obtain complete drainage of the ventricle so as to unload the ventricle, diminish myocardial work, and maximize subendocardial perfusion.(EMERY & JOYCE, 1991) The second group consists of patients with myocardial infarction, acute myocarditis, or end-stage heart disease who are not expected to recover to adequate cardiac function and who require mechanical support as a bridge to transplantation.(Frazier et al., 1992; Pae & Pierce, 1981) Patients on VAD support often require hemodynamic monitoring to assess their cardiovascular state both in the perioperative state and afterward.

B.5.1 Left Ventricular Assist Device (LVAD)

Left ventricular assist devices (LVADs), which are rapidly evolving, are used to treat patients with advanced stages of heart failure. While the main goals of LVAD therapy are to improve symptoms of heart failure and quality of life, they also reverse pulmonary vascular hypertension in the setting of venous back-pressure induced increased pulmonary vasomotor tone, thus reversing right ventricular dysfunction.(Lund, Matthews, & Aaronson, 2010)

Patient selection is a crucial consideration that determines the ultimate outcome of patients who receive a LVAD. In general, patients who receive LVADs have end-stage heart

disease without irreversible end-organ failure. For patients who are too ill to undergo heart transplantation, such as those who cannot be weaned from cardiopulmonary bypass, use of a short-term extracorporeal LVAD is a first-line therapy. For patients who are suitable candidates to receive a heart transplant but are unlikely to survive the wait required before transplantation, LVADs are an effective bridge to transplantation.(Goldstein, Oz, & Rose, 1998)

Complications that could occur in the post-implant period include infection, thromboembolism and failure of the device. The most common causes of early morbidity and mortality after placement of a LVAD include air embolism, bleeding, right-sided heart failure, and progressive multisystem organ failure.(Potapov, Stepanenko, Krabatsch, & Hetzer, 2011) In general, complications are less with the smaller pumps and drivelines, and in those that use axial rather than pulsatile flow. Pump thrombosis, a complication with high mortality or one requiring a pump change, can occur causing an obstruction of the pump,(Frazier et al., 1992; Lund et al., 2010) but can be treated with tirofiban/tissue plasminogen activator.

Since 60-70% of RV systolic power comes from LV contraction,(Damiano, La Follette, Cox, Lowe, & Santamore, 1991) acute cor pulmonale can occur post LVAD insertion. This can be corrected by applying therapies aimed at sustaining coronary blood flow (i.e. increased MAP) and minimizing any increased pulmonary vasomotor tone (i.e. intravenous prostacyclin or inhaled nitric oxide). Hemodynamic monitoring often requires echocardiographic support, as described later in this volume. Importantly, the unsupported right ventricle will be minimally responsive to positive inotropic drug infusion since most of the beneficial effects of increased inotropy on the right ventricle are derived from increased LV contraction. Thus, volume

overload and acute RV dilation are serious concerns and need to be closely monitored using echocardiographic techniques.

B.5.2 Right ventricular assist device (RVAD)

Right ventricular (RV) dysfunction occurs in clinical scenarios such as RV pressure overload due to increased pulmonary vascular resistance, cardiomyopathies, arrhythmias, RV ischemia, congenital or valvular heart diseases, and sepsis.(Simon & Pinsky, 2011) The most common cause of increased pulmonary vascular resistance is pulmonary arterial hypertension (PAH), which is defined as the mean pulmonary artery pressure > 25 mmHg with a Ppao, left atrial pressure or LV end-diastolic pressure $\leq$ 15 mmHg.(McLaughlin et al., 2009) The critical determinant of patient outcomes in PAH is the functioning of the right ventricle, and has been recognized as an important avenue for further research.(Voelkel et al., 2006) Historically, long-term outcomes for patients with PAH are poor. Progressively increasing PAH results in severe RV failure, since the RV, in an attempt to adapt to the pressure overload, becomes hypertrophied and eventually dilated, with diminished systolic and diastolic function. RV failure is the end result of PAH and the cause of at least 70% of all PAH deaths.(D'Alonzo et al., 1991) Mechanical support for the RV may be appropriate in etiologies where it is likely to be reversed (i.e. acute vasospastic disease) or as a bridge to definitive treatment (i.e. lung transplantation). RVADs may be used in primary RV dysfunction(Giesler, Gomez, Letsou, Vooletich, & Smalling, 2006) and have been used with coexisting PAH.(Fonger et al., 1985; Nagarsheth et al., 2008) In patients with PAH, however, there is concern that pulsatile devices may cause pulmonary microcirculatory damage.(Berman, Tsui, Vuylsteke, Klein, & Jenkins, 2008)

Although theoretically an RVAD may be beneficial for decreasing right-side atrial and ventricular filling pressures, decongesting the liver, and increasing LVAD flow, the RVAD itself has complications, with the current RVAD technologies requiring external pumps with a cumbersome drive system, making hospital discharge difficult to achieve.(Chen et al., 1996; Farrar et al., 1997) Furthermore, it is difficult to assess volume status in RVAD patients because the RV is the primary balance in between volume and volume response. Thus, no clear guidelines as to minimal CVP values can be made even when individualized to a given patient's cardiac output, since unstressed intravascular volume can vary widely.

B.5.3 BiVentricular Assist Device (BiVAD)

The rationale for the use of a BiVAD in patients with heart failure is still controversial. These patients are typically more severely ill preoperatively, have a higher serum creatinine, and a greater proportion of them are ventilator dependent before VAD insertion.(Farrar et al., 1997; Tsukui et al., 2005) While the selection of patients for BiVAD support is crucial to obtaining successful outcomes, criteria for predicting the need for a BiVAD have not been well established and remain a major focus for future research. While rates of survival to discharge have been shown to be similar to LVAD when used post transplantation,(Tsukui et al., 2005) patient survival to transplantation is much lower with BiVAD than LVAD.(Farrar et al., 1997) Patients on BiVAD therapy are at a greater risk of complications with higher incidences of infection, thromboembolism and failure of the device due to twice as many cannulae and pumps. (Pennington et al., 1990) As may be expected, BiVAD patients are monitored more by their

VAD-displayed cardiac output estimates and measures of MAP than central venous O_2 saturation. Volume status and need for vasopressor therapy are usually accomplished through therapeutic trials to observe if changes in cardiac output and MAP occur, rather than on predefined physiological conditions.

B.6 ACUTE KIDNEY INJURY

Fluid resuscitation together with attention to DO_2 are the cornerstones of resuscitation in all critically ill patients.(M. R. Pinsky & Payen, 2005) However, acute kidney injury (AKI) is a common complication of circulatory shock, and is associated with high mortality.(Rinaldo Bellomo, Kellum, & Ronco, 2001; Chertow et al., 1998) Circulating fluid deficits can occur as a result of absolute or relative hypovolemia, resulting in inadequate blood flow to meet the metabolic requirements of the kidneys. Low cardiac output, either as a primary mechanism in cardiogenic shock or a secondary mechanism in the other forms of shock also decreases kidney perfusion. Both of these volume and flow problems must be treated urgently if AKI is to be avoided.(Blow, Magliore, Claridge, Butler, & Young, 1999; Claridge et al., 2000) Although the importance of fluid management is generally recognized, the choice and amount of fluid, and fluid status end-points are controversial,(Michard et al., 2000; M. R. Pinsky, 2012; M. Pinsky, 2002) requiring special attention to monitoring hemodynamic patterns of fluid resuscitation in patients at risk for AKI.

B.6.1 Risk of starches to cause AKI

Hydroxylethyl starches (HES) are identified by three numbers corresponding to concentration, molecular weight, and molar substitution (e.g.: 6% HES, 130/0.4). According to the number of hydroxyethylations at carbon positions C2, C3, or C6 (degree of substitution), the HES are more or less resistant to degradation by plasma α-amylase. Molar substitution is the most clinically significant number since it relates to the rate of enzymatic degradation of the starch polymer. (Westphal et al., 2009) Pharmacokinetic characteristics of HES solutions are based upon the molecular weight, and degree of substitution and C2/C6 hyrdoxyethylation ratio.(Ragaller, Theilen, & Koch, 2001) Renal toxicity of HES depends on the level of molar substitution, although a meta-analysis of randomized clinical trials in surgical patients failed to show any difference in the incidence of renal impairment between patients who received low substituted HES and other forms of fluid therapy.(Van Der Linden, James, Mythen, & Weiskopf, 2013) However, in the intensive care units, renal toxicity has been reported even with low substituted HES, due to concurrent sepsis and distributive shock,(Sear, 2005) with the initiation of renal replacement therapies significantly greater in patients who received HES than those who received saline for fluid management.(Rahbari et al., 2009)

B.6.2 Continuous Renal Replacement Therapies

In general, critically ill patients receive high daily amounts of volume infusions: continuous infusions, vasopressors, blood or fresh frozen plasma. Patients with renal failure and in septic

shock continue to receive large amounts of fluid resuscitation thus leading to fluid overload. The consequent positive fluid balance necessitates water removal, with a major consequence of rapid fluid removal being hemodynamic instability.(Ronco, Bellomo, & Ricci, 2001)

Daily or every other day conventional hemodialysis (HD) is the standard dialysis regimen for hemodynamically stable patients with renal failure. However, hypotension during HD due to rapid fluid and solute removal is the most common complication of this therapy, and can prolong renal insufficiency in critically ill AKI patients. The rapid rate of solute removal during HD results in an abrupt fall in plasma osmolality which induces further extracellular volume depletion by promoting osmotic water movement into the cells. This reduction in plasma osmolality may contribute to the development of hypotension. Severe hypotension still accompanies 20-30% of HD sessions in patients with AKI.(Hakim, Wingard, & Parker, 1994) It was for that reason that continuous renal replacement therapy (CRRT) was developed. With CRRT, volume control is more gently continuous and immediately adaptable to changing circumstances (e.g. the immediate need for blood or blood products in a patient at risk for ARDS). Because of this adaptability, volume overload can be immediately treated or prevented, and volume depletion avoided.

The ideal renal replacement therapy would be one that achieves slow yet adjustable fluid removal, in order to easily meet the highly variable required daily fluid balance. At the present time, by mimicking urine output, CRRT slowly and continuously removes a patient's plasma water. It must be emphasized, however, that the protection afforded by CRRT is relative and not absolute, since hypotension can still occur if too much fluid is removed or if fluid is removed too quickly, irrespective of the therapy name. Studies comparing CRRT to HD in patients with AKI have not shown a survival benefit for one approach versus the other.(Jun et al., 2010) It remains

a controversial matter as to which clinical parameter (dry weight, MAP, Ppao, SvO_2, etc.) or currently available invasive monitoring (central venous catheter, pulmonary artery catheter, etc.) should be utilized in order to define the concept of 'fluid overload' and subsequent therapies thereof to be employed for fluid removal.(Vincent, Abraham, Kochanek, Moore, & Fink, 2011)

B.7 CONCLUSION

Hemodynamic monitoring at the bedside improves patient outcomes when used to make treatment decisions at the right time for patients experiencing hemodynamic instability. For monitoring to provide any benefit, the clinician must be able to use the information to guide management within the context of known physiological principles and an understanding of the pathological processes that may be in play. Three basic guiding principles could be used to effectively manage patients with hemodynamic instability associated with signs and symptoms of tissue hypoperfusion. If blood flow to the body increases with fluid resuscitation, then treatment must include volume expansion. If the patient is also hypotensive and has reduced vasomotor tone, then vasopressor therapy might be initiated simultaneously. If the patient is neither preload responsive nor exhibiting reduced vasomotor tone and is hypotensive, then the problem is the heart, and both diagnostic and therapeutic actions must be initiated to address these specific problems. Protocolized management, based on existing hemodynamic monitoring technologies at the bedside, is both pluripotential (different monitoring devices can drive the same protocol) and scalable (can alter the resuscitation intensity) and thus lends itself to automation.

References

1. Pinsky MR, Payen D. Functional hemodynamic monitoring. Crit Care 2005;9:566-572.
2. Pinsky MR. Hemodynamic evaluation and monitoring in the ICU. CHEST 2007;132:2020-2029.
3. Kellum JA, Pinsky MR. Use of vasopressor agents in critically ill patients. Curr Opin Cri Care. 2002;8):236-241.
4. Pinsky MR. Applied cardiovascular physiology. Critical Care Nephrology: Springer; 1998:1-8.
5. Pinsky MR. Hemodynamic evaluation and monitoring in the ICU. CHEST 2007;132:2020-2029.
6. Pinsky M. Functional Hemodynamic Monitoring: A Personal Perspective. in: Vincent JL (ed.) Yearbook of Intensive Care and Emergency Medicine: Springer; 2009:306-310.
7. Rivers EP, Ander DS, Powell D. Central venous oxygen saturation monitoring in the critically ill patient. Curr Opin Crit Care 2001;7:204-211.
8. Weil MH, Shubin H. Shock following acute myocardial infarction current understanding of hemodynamic mechanisms. Progr Cardiovasc Dis 1968;11:1-17.
9. Shoemaker WC. Oxygen transport and oxygen metabolism in shock and critical illness: invasive and noninvasive monitoring of circulatory dysfunction and shock. Crit Care Clin 1996;12:939-969.
10. James JH, Luchette FA, McCarter FD, Fischer JE. Lactate is an unreliable indicator of tissue hypoxia in injury or sepsis. Lancet 1999;354:505-508.
11. Crouser ED. Mitochondrial dysfunction in septic shock and multiple organ dysfunction syndrome. Mitochondrion 2004;4:729-741.
12. Kern JW, Shoemaker WC. Meta-analysis of hemodynamic optimization in high-risk patients. Crit Care Med 2002;30:1686-1692.
13. Rivers EP, Nguyen HB, Huang DT, Donnino M. Early goal-directed therapy. Crit Care Med 2004;32:314-315.
14. Gruen RL, Jurkovich GJ, McIntyre LK, Foy HM, Maier RV. Patterns of errors contributing to trauma mortality: lessons learned from 2594 deaths. Ann Surg 2006;244:371-379.
15. Silva E, De Backer D, Creteur J, Vincent J-L. Effects of fluid challenge on gastric mucosal PCO2 in septic patients. Intensive Care Med 2004;30:423-429.
16. Fiddian-Green RG, Haglund U, Gutierrez G, Shoemaker WC. Goals for the resuscitation of shock. Crit Care Med 1993;21:S25-31.
17. Piper GL, Kaplan LJ. Fluid and electrolyte management for the surgical patient. Surg Clin N A 2012;92:189-205.
18. Fink M. Does tissue acidosis in sepsis indicate tissue hypoperfusion? Intensive Care Med 1996;22:1144-1146.
19. Parks JK, Elliott AC, Gentilello LM, Shafi S. Systemic hypotension is a late marker of shock after trauma: a validation study of Advanced Trauma Life Support principles in a large national sample. AmJ Surg 2006;192:727-731.

20. Menon V, White H, LeJemtel T, Webb JG, Sleeper LA, Hochman JS. The clinical profile of patients with suspected cardiogenic shock due to predominant left ventricular failure: a report from the SHOCK Trial Registry. J Am Coll Cardiol 2000;36:1071-1076.
21. Pinsky MR. Rationale and application of physiologic monitoring. Critical Care Nephrology: Springer; 1998:33-42.
22. Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions 1. Endocrine rev 2000;21:55-89.
23. Gelman S, Mushlin PS. Catecholamine-induced changes in the splanchnic circulation affecting systemic hemodynamics. Anesthesiology 2004;100:434-439.
24. Torbicki A, Perrier A, Konstantinides S, et al. Guidelines on the diagnosis and management of acute pulmonary embolism The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Euro HeartJ 2008;29:2276-2315.
25. Pinsky MR. Heart–lung interactions. Curr Opin Crit Care 2007;13:528-531.
26. Pinsky MR. Clinical significance of pulmonary artery occlusion pressure. Applied Physiology in Intensive Care Medicine: Springer; 2006:53-56.
27. Spodick DH. Pathophysiology of cardiac tamponade. CHEST. 1998;113:1372-1378.
28. Aksoy O, Rodriguez L. Tamponade. Cardiovascular Hemodynamics: Springer; 2013:181-196.
29. Pinsky M. Functional hemodynamic monitoring: applied physiology at the bedside. Intensive Care Medicine: Springer; 2002:537-552.
30. Hack CE, Zeerleder S. The endothelium in sepsis: source of and a target for inflammation. Crit Care Med 2001;29:S21-S27.
31. Pinsky MR, Rico P. Cardiac contractility is not depressed in early canine endotoxic shock. Am J Respir Crit Care Med 2000;161:1087-1093.
32. Rabuel C, Mebazaa A. Septic shock: a heart story since the 1960s. Intensive Care Med 2006;32:799-807.
33. Kiss ZH, Tator CH. Neurogenic shock. Shock and Resuscitation. New York, NY: McGraw-Hill. 1993:421-440.
34. Müllner M, Urbanek B, Havel C, Losert H, Waechter F, Gamper G. Vasopressors for shock. Cochrane Database Syst Rev. 2004;3.
35. Sabharwal M, Paramjeet, Fishel M, Rhonda S, Breslow M, Michael J. Adrenal Insufficiency-An unusual cause of shock in postoperative patients. Endocrine Practice. 1998;4:387-390.
36. Bouachour G, Tirot P, Varache N, Gouello J, Harry P, Alquier P. Hemodynamic changes in acute adrenal insufficiency. Intensive Care Med 1994;20:138-141.
37. Claussen MS, Landercasper J, Cogbill TH. Acute adrenal insufficiency presenting as shock after trauma and surgery: three cases and review of the literature. J Trauma 1992;32:94-100.
38. Moore FA, McKinley BA, Moore EE. The next generation in shock resuscitation. Lancet 2004;363:1988-1996.
39. Mehta NK, Pinsky MR. Pharmacologic support of the hemodynamically unstable patient. Critical Care Nephrology: Springer; 1998:43-50.

40. Hennein HA, Ebba H, Rodriguez JL, et al. Relationship of the proinflammatory cytokines to myocardial ischemia and dysfunction after uncomplicated coronary revascularization. J Thorac Cardiovas Surg 1994;108:626-635.
41. Oddis CV, Finkel MS. Cytokines and nitric oxide synthase inhibitor as mediators of adrenergic refractoriness in cardiac myocytes. Euro J Pharmacol 1997;320:167-174.
42. Pinsky M. Protocolized cardiovascular management based on ventricular-arterial coupling. Functional hemodynamic monitoring: Springer; 2005:381-395.
43. Pinsky MR. Assessment of indices of preload and volume responsiveness. Curr Opin Crit Care 2005;11:235-239.
44. Westfall TC, Westfall DP. Adrenergic agonists and antagonists. Goodman and Gilman's The Pharmacological Basis of Therapeutics, 11th ed. Edited by Brunton LL, Lazo JS, Parker KL. New York, McGraw-Hill. 2006:237-315.
45. Skomedal T, Borthne K, Aass H, Geiran O, Osnes J-B. Comparison between alpha-1 adrenoceptor-mediated and beta adrenoceptor-mediated inotropic components elicited by norepinephrine in failing human ventricular muscle. J Pharmacol Exper Therap 1997;280:721-729.
46. Maas JJ, Pinsky MR, de Wilde RB, de Jonge E, Jansen JR. Cardiac Output Response to Norepinephrine in Postoperative Cardiac Surgery Patients: Interpretation With Venous Return and Cardiac Function Curves. Crit Care Med 2013;41:143-150.
47. Perdue PW, Balser JR, Lipsett PA, Breslow MJ. " Renal dose" dopamine in surgical patients: dogma or science? Ann Surg 1998;227:470.
48. Smith A. Mechanisms involved in the release of noradrenaline from sympathetic nerves. Br Medl Bull 1973;29:123-129.
49. Parissis JT, Farmakis D, Nieminen M. Classical inotropes and new cardiac enhancers. Heart failure reviews 2007;12:149-156.
50. Hollenberg SM, Ahrens TS, Annane D, et al. Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update. Crit CareMed 2004;32:1928-1948.
51. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summaryA report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2004;44:671-719.
52. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Med 2008;34:17-60.
53. Sakr Y, Reinhart K, Vincent J-L, et al. Does dopamine administration in shock influence outcome? Results of the Sepsis Occurrence in Acutely Ill Patients (SOAP) Study. Crit Care Med. 2006;34:589-597.
54. Martin C, Viviand X, Leone M, Thirion X. Effect of norepinephrine on the outcome of septic shock. Critical Care Med 2000;28:2758-2765.
55. Boulain T, Runge I, Bercault N, Benzekri-Lefevre D, Wolf M, Fleury C. Dopamine therapy in septic shock: Detrimental effect on survival? J Crit Care 2009;24:575-582.
56. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med 2010;362:779-789.
57. Loeb HS, Winslow EB, Rahimtoola SH, Rosen KM, Gunnar RM. Acute hemodynamic effects of dopamine in patients with shock. Circulation 1971;44:163-173.

58. Winslow EJ, Loeb HS, Rahimtoola SH, Kamath S, Gunnar RM. Hemodynamic studies and results of therapy in 50 patients with bacteremic shock. Am J Med 1973;54:421-432.
59. Ungar A, Fumagalli S, Marini M, et al. Renal, but not systemic, hemodynamic effects of dopamine are influenced by the severity of congestive heart failure. Crit Care Med 2004;32:1125-1129.
60. Bellomo R, Chapman M, Finfer S, Hickling K, Myburgh J. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. Lancet 2000;356:2139-2143.
61. Jones D, Bellomo R. Renal-dose dopamine: from hypothesis to paradigm to dogma to myth and, finally, superstition? J Intensive Care Med 2005;20:199-211.
62. Klein NA, Siskind SJ, Frishman WH, Sonnenblick EH, Lejemtel TH. Hemodynamic comparison of intravenous amrinone and dobutamine in patients with chronic congestive heart failure. AmJ Cardiol 1981;48:170-175.
63. Unverferth DV, Blanford M, Kates RE, Leier CV. Tolerance to dobutamine after a 72 hour continuous infusion. Am J Med 1980;69:262-266.
64. O'Connor CM, Gattis WA, Uretsky BF, et al. Continuous intravenous dobutamine is associated with an increased risk of death in patients with advanced heart failure: insights from the Flolan International Randomized Survival Trial (FIRST). Am Heart J 1999;138:78-86.
65. Hernandez G, Bruhn A, Luengo C, et al. Effects of dobutamine on systemic, regional and microcirculatory perfusion parameters in septic shock: a randomized, placebo-controlled, double-blind, crossover study. Intensive Care Med 2013;39:1435-1443.
66. Hayes MA, Timmins AC, Yau E, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 1994;330:1717-1722.
67. Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. JAMA 1993;270:2699-2707.
68. Dei Cas L, Metra M, Visioli O. Clinical pharmacology of inodilators. J Cardiovas Pharmacol 1989;14:S60-S71.
69. Alousi A, Johnson D. Pharmacology of the bipyridines: amrinone and milrinone. Circulation 1986;73:III10-24.
70. Earl C, Linden J, Weglicki W. Biochemical mechanisms for the inotropic effect of the cardiotonic drug milrinone. J Cardiovas Pharmacol 1985;8:864-872.
71. Lipskaia L, Chemaly ER, Hadri L, Lompre A-M, Hajjar RJ. Sarcoplasmic reticulum Ca2+ ATPase as a therapeutic target for heart failure. Expert opin biol ther 2010;10:29-41.
72. Haikala H, Kaivola J, Nissinen E, Wall Pi, Levijoki J, Lindén I-B. Cardiac troponin C as a target protein for a novel calcium sensitizing drug, levosimendan. J Mol Cell Cardiol 1995;27:1859-1866.
73. Haikala H, Nissinen E, Etemadzadeh E, Levijoki J, Lindén I-B. Troponin C-mediated calcium sensitization induced by levosimendan does not impair relaxation. J Cardiovas Pharmacol 1995;25:794-801.

74. Follath F, Cleland J, Just H, et al. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. Lancet 2002;360:196-202.
75. Yokoshiki H, Katsube Y, Sunagawa M, Sperelakis N. Levosimendan, a novel Ca+2 sensitizer, activates the glibenclamide-sensitive K+ channel in rat arterial myocytes. Euro J Pharmacol 1997;333:249-259.
76. Kersten JR, Montgomery MW, Pagel PS, Warltier DC. Levosimendan, a new positive inotropic drug, decreases myocardial infarct size via activation of KATP channels. Anesth Analg 2000;90:5.
77. Nieminen MS, Akkila J, Hasenfuss G, et al. Hemodynamic and neurohumoral effects of continuous infusion of levosimendan in patients with congestive heart failure. J Am Coll Cardiol 2000;36:1903-1912.
78. Slawsky MT, Colucci WS, Gottlieb SS, et al. Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. Circulation 2000;102:2222-2227.
79. Moiseyev V, Poder P, Andrejevs N, et al. Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction. A randomized, placebo-controlled, double-blind study (RUSSLAN). Euro HeartJ 2002;23:1422-1432.
80. Haikala H, Kaheinen P, Levijoki J, Lindén I-B. The role of cAMP-and cGMP-dependent protein kinases in the cardiac actions of the new calcium sensitizer, levosimendan. Cardiovasc res 1997;34:536-546.
81. Trzeciak S, McCoy JV, Dellinger RP, et al. Early increases in microcirculatory perfusion during protocol-directed resuscitation are associated with reduced multi-organ failure at 24 h in patients with sepsis. Intensive Care Med 2008;34:2210-2217.
82. De Backer D, Hollenberg S, Boerma C, et al. How to evaluate the microcirculation: report of a round table conference. Crit Care 2007;11(5):R101.
83. Emery RW, Joyce LD. Directions in cardiac assistance. J Cardiac Surg 1991;6:400-414.
84. Pae W, Pierce W. Temporary left ventricular assistance in acute myocardial infarction and cardiogenic shock: rationale and criteria for utilization. CHEST 1981;79:692-695.
85. Frazier O, Rose EA, Macmanus Q, et al. Multicenter clinical evaluation of the HeartMate 1000 IP left ventricular assist device. Ann Thorac Surg 1992;53:1080-1090.
86. Lund LH, Matthews J, Aaronson K. Patient selection for left ventricular assist devices. Euro J Heart Failure 2010;12:434-443.
87. Goldstein DJ, Oz MC, Rose EA. Implantable left ventricular assist devices. N EnglJ Med 1998;339:1522-1533.
88. Potapov EV, Stepanenko A, Krabatsch T, Hetzer R. Managing long-term complications of left ventricular assist device therapy. Curr Opin Cardiol 2011;26:237-244.
89. Damiano R, La Follette P, Cox J, Lowe J, Santamore W. Significant left ventricular contribution to right ventricular systolic function. Am J Physiol 1991;261:H1514-H1524.
90. Simon MA, Pinsky MR. Right ventricular dysfunction and failure in chronic pressure overload. Cardiol Res Pract 2011;23:5680-5695.
91. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension. J Am Coll Cardiol 2009;53:1573-1619.

92. Voelkel NF, Quaife RA, Leinwand LA, et al. Right Ventricular Function and Failure Report of a National Heart, Lung, and Blood Institute Working Group on Cellular and Molecular Mechanisms of Right Heart Failure. Circulation 2006;114:1883-1891.
93. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertensionResults from a national prospective registry. Ann Intern Med 1991;115:343-349.
94. Giesler GM, Gomez JS, Letsou G, Vooletich M, Smalling RW. Initial report of percutaneous right ventricular assist for right ventricular shock secondary to right ventricular infarction. Catheterizat Cardiovas Intervent 2006;68:263-266.
95. Fonger J, Borkon A, Baumgartner W, Achuff S, Augustine S, Reitz B. Acute right ventricular failure following heart transplantation: improvement with prostaglandin E1 and right ventricular assist. J Heart ranspl 1985;5:317-321.
96. Nagarsheth NP, Pinney S, Bassily-Marcus A, Anyanwu A, Friedman L, Beilin Y. Successful placement of a right ventricular assist device for treatment of a presumed amniotic fluid embolism. Anesth Analg 2008;107:962-964.
97. Berman M, Tsui S, Vuylsteke A, Klein A, Jenkins DP. Life-threatening right ventricular failure in pulmonary hypertension: RVAD or ECMO? J Heart Lung Transpl 2008;27:1188-1189.
98. Chen JM, Levin HR, Rose EA, et al. Experience with right ventricular assist devices for perioperative right-sided circulatory failure. Ann Thorac Surg 1996;61:305-310.
99. Farrar DJ, Hill JD, Pennington DG, et al. Preoperative and postoperative comparison of patients with univentricular and biventricular support with the Thoratec ventricular assist device as a bridge to cardiac transplantation. J Thor Cardiovas Surg 1997;113:202-209.
100. Tsukui H, Teuteberg JJ, Murali S, et al. Biventricular assist device utilization for patients with morbid congestive heart failure A justifiable strategy. Circulation 2005;112:I-65-I-72.
101. Pennington D, Reedy J, Swartz M, et al. Univentricular versus biventricular assist device support. J HeartLung Transplant 1990;10:258-263.
102. Chertow M, Glenn M, Levy M, et al. Independent association between acute renal failure and mortality following cardiac surgery. Am J Med 1998;104:343-348.
103. Bellomo R, Kellum J, Ronco C. Acute renal failure: time for consensus. Intensive Care Med 2001;27:1685-1688.
104. Blow O, Magliore L, Claridge JA, Butler K, Young JS. The golden hour and the silver day: detection and correction of occult hypoperfusion within 24 hours improves outcome from major trauma. J Trauma Acute Care Surg 1999;47:964.
105. Claridge JA, Crabtree TD, Pelletier SJ, Butler K, Sawyer RG, Young JS. Persistent occult hypoperfusion is associated with a significant increase in infection rate and mortality in major trauma patients. J Trauma2000;48:8.
106. Michard F, Boyssats S, Chemla D, et al. Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. Am J Respir Crit Care Med 2000;162:134-138.
107. Pinsky MR. Pulmonary artery occlusion pressure. Applied Physiology in Intensive Care Medicine 1: Springer; 2012:83-86.

108. Westphal M, James MF, Kozek-Langenecker S, Stocker R, Guidet B, Van Aken H. Hydroxyethyl starches: different products--different effects. Anesthesiology 2009;111:187-202.
109. Ragaller MJ, Theilen H, Koch T. Volume replacement in critically ill patients with acute renal failure. J Am Soc Nephrol 2001;12:S33-S39.
110. Van Der Linden P, James M, Mythen M, Weiskopf RB. Safety of modern starches used during surgery. Anesth Analg 2013;116:35-48.
111. Sear JW. Kidney dysfunction in the postoperative period. Br J Anaesthes 2005;95:20-32.
112. Rahbari NN, Zimmermann JB, Schmidt T, Koch M, Weigand MA, Weitz J. Meta-analysis of standard, restrictive and supplemental fluid administration in colorectal surgery. B J Surg 2009;96:331-341.
113. Ronco C, Bellomo R, Ricci Z. Continuous renal replacement therapy in critically ill patients. Nephrol Dial Transpl 2001;16(suppl 5):67-72.
114. Hakim RM, Wingard RL, Parker RA. Effect of the dialysis membrane in the treatment of patients with acute renal failure. N Engl J Med 1994;331:1338-1342.
115. Jun M, Heerspink HJL, Ninomiya T, et al. Intensities of renal replacement therapy in acute kidney injury: a systematic review and meta-analysis. Clin J Am Soc Nephrol 2010;5:956-963.
116. Vincent J-L, Abraham E, Kochanek P, Moore FA, Fink MP. Textbook of Critical Care: Expert Consult Premium. Elsevier Health Sciences; 2011.

Table 1. Categorization of Shock States based on the Weil and Shubin[8] Nosology

Shock state	Pathophysiology	Disease States	Hemodynamic Monitoring Pattern
Hypovolemic	Decrease in effective circulating blood volume and venous return	Primary intravascular volume loss (hemorrhage, capillary leak) Secondary intravascular volume loss (third-space loss, burns, diarrhea, vomiting)	↓ filling pressures (↓Pra and Ppao) ↓ CO ↑ SVR
Cardiogenic	Primary cardiac failure	Impaired contractility (myocardial ischemia/infarction, electrolyte imbalance, hypoxemia, hypothermia, endocrinologic diseases, metabolic poisoning, beta-blockers) Pump function (valvulopathy, ventriculoseptal defect, dysrhythmias) Diastolic compliance (left ventricular hypertrophy, fibrosis, infiltrative cardiomyopathies, asymmetric septal hypertrophy, cor pulmonale)	↑ back pressure to cardiac filling (↑Pra and Ppao) ↓ CO ↑ SVR
Obstructive	Blockage of blood flow in heart's outflow tracts	RV outflow obstruction (pulmonary embolism, lung hyperinflation and pulmonary artery compression) LV outflow obstruction (aortic stenosis, dissecting aortic aneurysm) Cardiac Tamponade (pericardial effusion, lung hyperinflation and atrial compression)	↑CVP ↓ Ppao relative to CVP ↓ CO ↑ SVR
Distributive	Loss of blood flow regulation	Sepsis (increased capillary leak with secondary loss of intravascular volume, and inappropriate clotting in the microcirculation) Neurogenic shock (acute spinal injury above the upper thoracic level, spinal anesthesia, general anesthesia, neurotoxic poisoning and central nervous system catastrophe) Acute adrenal insufficiency (hyperpyrexia and circulatory collapse)	↓CVP ↓ filling pressures (↓Pra and Ppao) ↑ SvO_2 ↓ MAP

Abbreviations: right atrial pressure, Pra; pulmonary artery occlusion pressure, Ppao; cardiac output, CO; systemic vascular resistance, SVR; mean arterial pressure, MAP, central venous pressure, CVP, venous oxygen saturation, SvO_2.

APPENDIX C

PSYCHOMETRIC ANALYSIS OF THE CHARLSON COMORBIDITY INDEX DEYO METHOD

Poster presented at the Society of Critical Care Medicine (SCCM) conference, Spring 2013

Psychometric Analysis of the Charlson Comorbidity Index Deyo Method

Eliezer Bose, Marilyn Hravnak, Lauren Terhorst

Introduction: The Charlson Comorbidity Index (CCI) Deyo method is widely employed in acute care. This scoring system uses abstraction from administrative databases, with 17 comorbidities assigned a score (1-6 based on risk of dying associated with the condition) and summed for a mortality risk score. Since CCI items were empirically derived, this study sought to provide psychometric information about the CCI Deyo through exploratory factor analysis (EFA).

Hypothesis: EFA of CCI items will expose factor structure of items and construct validity. **Methods:** CCI items and scores were electronically abstracted from 634 neurotrauma step-down unit patient records. Univariate analyses of individual items were explored. Inter-item correlations, multivariate outliers with Mahalanobis distance, and KMO and Bartlett's tests were verified for EFA application. Principal component analysis (PCA) using promax rotation, assuming associations among the factors, produced form factors and subscales. Cronbach's alpha for factors reliability was computed. Pearson correlation of each subscale score was compared to overall CCI scores testing construct validity.

Results: The sample mean age was 57 yrs, and 49% had a CCI score of 0 (24%=CCI 1, 15%=CCI 2, 6%=CCI 3, 6% CCI ≥4). Diabetes (DM) was the most prevalent comorbidity (21%) followed by COPD (18%), then MI, PVD and CHF (10% each) and cerebral vascular disease (6%), and the other 11 comorbidities prevalence ≤4%. A KMO value of 0.546 and Bartlett's $p<0.001$ denoted adequate sample size for EFA, and no multicollinearity (no inter-item

correlation >0.68). PCA with eigenvalues>1 extracted 7 factors which explained 59% of the variance. Pearson correlation of Factor 2 loaded items (CHF, MI, COPD, DM and PVD) had the highest value of 0.707 with overall CCI score, indicating strong predictive relationship of this factor. However, all 7 subscales scores obtained $p<0.01$ compared to overall CCI score. **Conclusion:** EFA revealed co-occurrence of certain disease items, indicating common underlying pathologic mechanisms, as well as propensity of multiple comorbidity groupings. However, as a scoring mechanism the composite CCI Deyo may be only moderately helpful as construct validity was poor.

APPENDIX D

EXAMINATION OF THE INTERNAL STRUCTURE OF THE CHARLSON COMORBIDITY INDEX DEYO METHOD

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D.1 ABSTRACT

Background and Purpose: Since the Charlson Comorbidity Index Deyo–method (CCI-D) is widely used in nursing research, this study examines the internal structure of the CCI-D method. **Methods**: CCI-D scores were obtained from 634 in-patients. Principal component analysis (PCA) was utilized to investigate the internal structure and identify subscales. **Results**: Four factors had eigenvalues >1 and accounted for 49.4% of the extracted variance. The four subscales were not strongly correlated, providing evidence of dimensionality within CCI-D. **Conclusions**: Even though CCI-D is commonly used as a variable in nursing research and can be easily obtained from administrative data, its internal structure is multidimensional. The subscales may provide more information than the overall index. Further complex psychometric testing of CCI-D is warranted to interpret utility.

Keywords: comorbidity; principal component analysis; ICD-9-CM; hospital mortality

D.2 INTRODUCTION

Patient co-morbidity is a variable that must be taken into account when assessing the impact of nurse characteristics or nursing interventions upon patient care and outcomes. The Charlson Comorbidity Index has been frequently employed in nursing research to account for a patient's

pre-existing comorbid conditions when studying nurse staffing (Rafferty et al., 2007; Rochefort, Ward, Ritchie, Girard, & Tamblyn, 2012; Xue, Aiken, Freund, & Noyes, 2012), and the impact of nurses upon hospital mortality (Aiken et al., 2014; Schubert, Clarke, Aiken, & De Geest, 2012; Sermeus et al., 2011), and post-surgical outcomes (Carthon et al., 2012). Nurse researchers as well as clinicians operate under the assumption that 'true comorbidity' is correlated with worse health outcomes. Methods that evaluate comorbidity generally assign scores to all relevant comorbid conditions, with the "comorbidity index" obtained by the summation of these scores. Charlson et.al developed a weighted index of comorbidity, known as the Charlson Comorbidity Index or CCI (Charlson, Pompei, Ales, & MacKenzie, 1987). A few years later, with the wide-spread use of electronic health records, Deyo et al. (Deyo, Cherkin, & Ciol, 1992) developed an electronic version of the CCI which we refer to as CCI-Deyo or CCI-D, which has been used more commonly in nursing literature (Aiken et al., 2014; Collins et al., 2013; Hravnak, Chen, Dubrawski, Bose, & Pinsky, 2015; Ott et al., 2012; Yousef, Pinsky, DeVita, Sereika, & Hravnak, 2012). Nurse researchers should become more aware of this method of measuring comorbidity, particularly as the use of large electronic databases and "big" data become more prevalent. The overall purpose of this study was to examine the internal structure of the CCI-D. With the recent shift towards ICD-10 coding system and few studies (Sundararajan et al., 2004; Sundararajan et al., 2007; Thygesen, Christiansen, Christensen, Lash, & Sørensen, 2011) already having validated the CCI as a valuable predictive tool for hospital mortality, nurse researchers and nurses using that research to develop evidence-based practice will only find its use much more widespread for assessing in-hospital comorbidities and mortality.

D.3 BACKGROUND

The comorbidity index developed empirically by Charlson and colleagues was based on 1-yr mortality from a cohort of 604 patients admitted to a particular service at one hospital during one month in 1984 (Charlson, Pompei, Ales, & MacKenzie, 1987). This empirically derived CCI had a list of 19 comorbid conditions. Charlson et al. assigned each condition an associated weight from 1 to 6 according to their associated risk for 1-year mortality. The overall CCI was obtained by the summation of the weights for the existing comorbid conditions that a patient had. The CCI was then validated for its ability to predict mortality in a cohort of 685 patients who were treated for primary breast cancer. Its performance was compared to the method of classifying comorbid disease previously developed by Kaplan and Feinstein (Kaplan & Feinstein, 1974). The relative risk of 1-year mortality for each increasing point of the CCI was 2.3 (95% CI 1.9-2.8) and CCI was a highly significant predictor of mortality ($p<.0001$) (Charlson et al., 1987). In a much later study, similar results were obtained when the CCI was used as a predictor for measuring post-operative survival in patients with hypertension or diabetes (Charlson, Szatrowski, Peterson, & Gold, 1994), thus establishing the validity of the instrument. However, in order for CCI to be computed, each patient's hospital record had to be reviewed manually for the comorbid conditions. Deyo et al. used a method whereby the comorbid conditions were determined, not by manual review of hospital records, but by electronically assigning ICD-9-CM codes for 17 comorbid conditions used in the CCI. They used the method for medical record abstraction of administrative databases in 27,111 Medicare beneficiaries who underwent lumbar spine surgery in order to identify the comorbidities, assign the weighted scores and thus compute CCI-D (Deyo et al., 1992).

Across the nursing and other healthcare literature, the accuracy of an index such as CCI or CCI-D depends on how well the index separates the two groups of patients compared (e.g. those with mortality/died vs. those without mortality/lived). In order to do so, a commonly employed procedure includes the use of Area under receiving operator characteristics (AUROC) curves. AUROCs are designed to plot the false positive rate of a score (1-specificity) on the x-axis and the true positive rate (sensitivity) on the y-axis. In terms of discrimination between the groups, an AUROC value between 0.7 and 0.8 indicates fair while a value between 0.8 and 0.9 indicates good and a value > 0.9 is excellent. CCI-D demonstrated good discrimination of in-hospital mortality with AUROC values of .86 - .87. Few subsequent studies validated the CCI-D (Kieszak, Flanders, Kosinski, Shipp, & Karp, 1999; Melfi, Holleman, Arthur, & Katz, 1995; Poses, Smith, McClish, & Anthony, 1995).

D.4 PURPOSE

While the CCI-D has been extensively utilized and its performance validated in samples of patients with breast cancer, hypertension and diabetes, lumbar spine surgery etc. as described in a systematic review by Sharabiani et al. (Sharabiani, Aylin, & Bottle, 2012), it has never been examined using a sample of patients in a step down unit (SDU). According to the American Education Research Association's standards, when an instrument is utilized in a new or different population, its performance with the new population should be examined. The purpose of the current study was to examine the internal structure of the CCI-D using a sample of 634 patients admitted to the SDU of a Level I trauma center. Principal components analysis (PCA) was used

to analyze and discover simple pattern of relationships among the list of comorbid conditions of the CCI-D. This study, about the internal structure of a commonly used comorbidity index in nursing literature, will offer nurse researchers, and nurses utilizing that research, an overview of the relationship among the different comorbid conditions within the CCI-D. Such information can be invaluable for nurse researchers working on large databases and "big" data, thereby reducing the risk of the "curse of dimensionality" when gathering data related to comorbid conditions.

D.5 METHODS

D.5.1 Sample

This study was approved by the local institutional review board (IRB PRO12070002). The unit providing the data was a 24 bed trauma/surgery step-down unit (SDU). Demographic information was obtained from the medical record for all patient admissions (N = 634; 73% white, 60% male). Entry criteria for the parent study required that the patients were >21 years of age during the study periods (11/06-8/07; 16 weeks). There were no special efforts to direct patient admissions to the study unit.

D.5.2 Instrument

The CCI-D was calculated electronically using the ICD-9 CM codes for each of the 17 CCI items—myocardial infarction (MI), congestive heart failure (CHF), peripheral vascular disease

(PVD), cerebral vascular disease (CVD), dementia (DEM) , chronic pulmonary disease (CPD), rheumatoid disorder (RMD), peptic ulcer disease (PUD), mild liver disease (MLD), diabetes (DIAB), diabetes with complications (DIABCC), hemiparesis (HEMIPARA), renal (RENAL), metastatic tumor (METATUMR), malignant tumor (MALIG), severe liver disease (SLD) and acquired immune deficiency syndrome (AIDS). Individual items were coded as either 0 or 1. If a patient had a particular disease in the list of CCI items, it was scored as 1 for that item while if the patient did not have the disease, it was scored as a 0 for that item.

D.6 ANALYSIS

All statistical analyses were conducted on the data from 634 participants using Statistical Packages for the Social Sciences (SPSS) version 21. The assumptions for PCA should first be verified ensuring that the data can be analyzed using PCA. These assumptions included testing for sampling adequacy using the Kaiser-Myer-Olkin (KMO) and Bartlett's test of sphericity as well as a check to assess for individual item distributions, which in this sample was the list of 17 comorbid conditions of the CCI-D.

Item Distributions and Preliminary Analyses. The responses for each of the 17 CCI-D items for each patient, and their overall prevalence of occurrence in the total sample were examined. If items were not endorsed by at least 2% of the patients in the sample, they were considered non-representative and were dropped from further analysis.

Next, we proceeded to assess for sampling accuracy. Tabachnick's rule-of-thumb suggests having at least 300 cases for performing PCA (Tabachnick & Fidell, 2007). The classic Kaiser-

Myer-Olkin (KMO) statistic (Kaiser, 1974) and Bartlett's test of sphericity (Bartlett, 1950) were computed to establish the appropriateness of performing the factor analysis. The KMO index ranges from 0 to 1, with .50 considered suitable for PCA. A KMO value < .5 would render the data unsuitable for PCA, according to Kaiser Criterion. Bartlett's test of sphericity was also tested and must be significant for PCA to be suitable. Next, a correlation matrix was computed to investigate the interrelationships among the individual items, and to identify possible clusters of items. Generally, the correlation matrix is inspected to check for correlation coefficients over .30 (Tabachnick & Fidell, 2007) to identify item patterns. Items with correlations higher than .8 may be redundant and should be inspected further.

Principal Component Analysis. PCA is a statistical technique in which the interrelationship among many correlated variables may be reproduced, and the data represented by a smaller number of variables or principal components (Nunnally & Bernstein, 1994). The components are arranged in a decreasing order of the percentage of the total variance accounted for by each of the components. PCA searches for the fewest number of components that could explain the variance in the items and outputs the variance in terms of a combination of both unique and shared variance (Costello & Osborne, 2005).

The rationale for the use of principal components analysis (PCA) was to examine the internal structure of the CCI-D. Reduction into components established underlying dimensions between the items used for measuring the construct of comorbidity. In order to make the pattern of factor loadings clearer, researchers commonly employ the use of two types of rotation procedures—either orthogonal or oblique. Orthogonal rotation assumes that the factors in the analysis are uncorrelated while oblique rotation assumes that the factors are correlated. The internal structure was examined using both orthogonal (Varimax) rotation as well as oblique (Promax) rotation;

however only Promax results were reported. This is because, from a physiological standpoint, there seemed to be a correlation between the various comorbid conditions and oblique rotation accounts for such correlations.

PCA was then performed by extracting components with eigenvalues > 1, which meant that a component was dropped unless it extracted at least as much as the equivalent of one original item, as per Kaiser criterion (Kaiser, 1974). A Cattell scree plot, a 2 dimensional plot with the components on the X axis and their corresponding eigenvalues as the Y-axis (Catell, 1978) was also examined. Upon examination of component loadings, items with component loadings > .32 were retained to form subscales (Tabachnick & Fidell, 2007). Items with loadings higher than .32 on more than one component were considered cross-loaders. The magnitude and direction of the relationships among the emergent subscales, and between the subscales and the total CCI score were then inspected to further examine the internal structure of the CCI.

Once subscales were confirmed, labels were created based on the prominent pathophysiological mechanisms of the comorbid conditions, in consultation with members of the research team. Labels were assigned primarily with the intent of reflecting the theoretical and conceptual intent of the constructs. Conventionally, variables that have a loading of .32 or greater within a particular component are considered to be its major contributors, and subscales are usually given names relating to their main emphasis (Tabachnick & Fidell, 2007).

D.7 RESULTS

D.7.1 Sample Demographics

The demographic characteristics of the sample are provided in Table 1. There were 634 subjects with CCI scores obtained using the Deyo Method. About 48.6% of the patients had age ranges over 59, placing them at potentially greater risk of comorbidities. The median length of hospital stay for the sample was five days. The resulting sample had a median CCI total score = 0 and inter quartile range = 1, indicating a population with a low risk of 1-yr mortality. Table 2 provides the frequencies of each of the CCI items as well as the means and the standard deviations. Although there were 17 initial items, it was discovered that dementia (DEM) was a constant (all 0's); so it was removed from the analysis, as none of the sample of patients either had or were recorded as having dementia. Additionally, several items were not endorsed by at least 2% of the patients: these were hemiparesis, metastatic tumor, renal, mild liver disease, severe liver disease, and AIDS. These items were also dropped from further analyses, resulting in 10 items for the PCA.

D.7.2 Analysis

Preliminary Analyses. The correlation matrix displaying the relationships between the 10 items has been provided in Table 3, and indicated that the items may be clustering to form factors. No inter-item correlations exceeded r =.24, thus indicating no problems with multicollinearity. The

item-to-total scale correlations ranged from .077 (MALIG) to .350 (CHF). This range of item-total correlations was considered to be acceptable (Bernstein & Nunnally, 1994) . The sample of 634 subjects and 10 items, revealed a KMO statistic (.636) and a Bartlett's test of sphericity (χ 2 (45) = 188.6 with p< .001) both indicating that PCA was acceptable.

Principal Component analysis. Table 4 reports pattern matrix item loadings, communalities, and total variance explained from the PCA solution. Four components explained 49.38% of the total variance. Communalities, which provide information on how much item variance is explained by the extracted components, ranged from .334 (CVD) to .702 (DIABCC). Two items were considered cross-loaders with component loadings greater than .32 on more than one component. CHF had a higher loading on component 1 (.557) and a lower loading on component 2 (.369), while MALIG had a higher loading on component 4 (.528) and a lower loading on component 2 (.350). Cross-loading items were retained on the component on which they had the highest loading for interpretation and further analysis. Correlations from the extracted components ranged from r =.003 to r =.206, providing evidence that the subscales were somewhat related. The strongest relationship was between component 1 and component 2 (r=.206, p<.001), while the weakest relationship occurred between components 3 and 4 (r =.003, p=.931). The relationship between components 2 and 3 was also weak (r =.065, p =.105). Components 1 and 3 were not strongly correlated (r =.079, p=.048), but it was noted that the relationship was significant. The relationship between components 1 and 4 was also significant (r =.102, p =.011), providing evidence that component 1 was related to all other emergent components. Additionally, each of the four components was significantly related to the overall comorbidity score. Component 1 had the strongest correlation with the overall score (r =.742, p <.001), and component 2 also had a strong correlation with the CCI score (r =.563, p <.001). Components 3

and 4 had moderate correlations with the overall CCI score, r =.284, p<.001 and r =.369, p<.001, respectively. Subscale labels were formed with consideration of the particular items that formed the four components. Component 1 was labeled as “cardiovascular;” component 2 was labeled “hypertensive;” component3 was labeled “rheumatic/peptic;” and component 4 was labeled “malignancies.”

D.8 DISCUSSION

The purpose of the study was to explore the internal structure and relationships among the items of the CCI-D using a sample of 634 patients admitted to the SDU of a Level I trauma center. The majority of patients (71%) had a CCI-D score of 0. PCA with oblique rotation revealed four subscales which explained 49.38% of the variance. The four emergent subscales were not strongly correlated, providing evidence of dimensionality within the CCI-D.

The finding that most patients had a CCI-D score of 0 probably reflects the nature of the patient population on this trauma-SDU. The population was relatively young and victims of an acute accident or injury, and thus was relatively healthy prior to hospitalization. Therefore, the range of comorbidity scores was relatively small, with very few patients having a score of three or more. In order to accurately reflect the type of patient that would receive services in the SDU, all patients were retained in the analysis.

Seven of the 17 CCI items were endorsed by less than 2% of the 634 patients, indicating that a smaller set of items may address the comorbidities experienced by the patients in the step down units. Using an instrument with fewer items reduces participant burden in research and

therefore this finding should be further investigated to determine the best set of items to be used in studies of comorbidities in patients placed in SDUs. However, this may also be a reflection of the young age and acute-onset illness in this unit. A population of older patients on a medical specialty unit might have yielded different results.

An inspection of the item loadings on the four components led to a few considerations. Firstly, in prior research, patient responses to CCI items have been generally summed to provide an overall score (Deyo et al., 1992), which implies unidimensionality. In this study, all four components were significantly related to the total score, providing evidence that they do measure an overall similar construct. However, the findings of this investigation imply that the internal structure of the CCI is multidimensional, and that the subscale scores may be utilized to provide additional information by which to assess patient comorbidities.

The subscale labeled Rheumatic/peptic which contained both Rheumatic disease and Peptic ulcer disease was an interesting finding of this project. Upon discovering that both of these items loaded on a subscale, which at first seemed to be a disparate finding, a literature search was conducted to examine the physiological relationship, if any, that existed between the two items. Surprisingly, the correlation of these two diseases with a common underpinning of physiologic stress has been a well-known fact established in medical literature with the findings provided as early as 1988 in the Annals of Rheumatic Disease (Farah, Sturrock, & Russell, 1988).

D.9 LIMITATIONS

There were several limitations associated with the current investigation. Most of the patients in the SDU did not have comorbidities and thus did not contribute to the variability in responses. Also, only 10 of the 17 CCI items were assigned to the patient sample, thus the full range of conditions available within the CCI were not represented. The 10 items that were used in the analysis did not provide a clean solution, with two cross-loading items. Further investigation into the cross-loading items to determine appropriate component placement is warranted. The current study was exploratory in nature, and the results should be confirmed using a different sample of patients placed in a SDU. More detailed investigation into item level performance should be undertaken using psychometric methods such as a Rasch analysis or confirmatory factor analysis.

D.10 CONCLUSIONS

This study explored the internal structure of the CCI Deyo method in a sample of patients in a SDU of a Level-1trauma center. Findings revealed that most patients were healthy; indicating that a smaller set of items could capture the common comorbidities experienced by this population. PCA revealed co-occurrence of certain disease items, indicating common underlying pathologic mechanisms, as well as propensity of multiple comorbidity groupings. The finding of a multidimensional internal structure implies that subscale scores could provide more detailed information on patient comorbidities than an overall index. Future, more confirmatory studies are

needed to support the results of the current investigation. Nevertheless, this study about the internal structure of a widely used comorbidity index in nursing literature can offer nurse researchers an overview of the relationship among the different comorbid conditions within the CCI-D. Since CCI-D is multidimensional, the use of subscales can prove to be invaluable for nurse researchers, thereby reducing the risk of the "curse of dimensionality" when gathering data related to comorbid conditions, especially when tapping into large databases and "big" data to answer nursing questions.

REFERENCES

Aiken, Sloane, D. M., Bruyneel, L., Van den Heede, K., Griffiths, P., Busse, R., . . . Lesaffre, E. (2014). Nurse staffing and education and hospital mortality in nine European countries: a retrospective observational study. *The Lancet, 383*(9931), 1824-1830.

Bartlett, M. S. (1950). Tests of significance in factor analysis. *British Journal of statistical psychology, 3*(2), 77-85.

Bernstein, I. H., & Nunnally, J. (1994). Psychometric theory. *New York: McGraw—Hill*.

Carthon, B., Margo, J., Kutney-Lee, A., Jarrín, O., Sloane, D., & Aiken, L. H. (2012). Nurse staffing and postsurgical outcomes in black adults. *Journal of the American Geriatrics Society, 60*(6), 1078-1084.

Catell, R. (1978). The scientific use of factor analysis. *Behavioural and Life Sciences. Plenum Press. New York and London*, 205-238.

Charlson, Pompei, P., Ales, K. L., & MacKenzie, C. R. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of chronic diseases, 40*(5), 373-383.

Charlson, Szatrowski, T. P., Peterson, J., & Gold, J. (1994). Validation of a combined comorbidity index. *Journal of clinical epidemiology, 47*(11), 1245-1251.

Collins, S. A., Cato, K., Albers, D., Scott, K., Stetson, P. D., Bakken, S., & Vawdrey, D. K. (2013). Relationship between nursing documentation and patients' mortality. *American Journal of Critical Care, 22*(4), 306-313.

Deyo, R. A., Cherkin, D. C., & Ciol, M. A. (1992). Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *Journal of clinical epidemiology, 45*(6), 613-619.

Farah, D., Sturrock, R., & Russell, R. (1988). Peptic ulcer in rheumatoid arthritis. *Annals of the rheumatic diseases, 47*(6), 478-480.

Hravnak, M., Chen, L., Dubrawski, A., Bose, E., & Pinsky, M. R. (2015). Temporal distribution of instability events in continuously monitored step-down unit patients: Implications for Rapid Response Systems. *Resuscitation, 89*, 99-105.

Kaiser, H. F. (1974). An index of factorial simplicity. *Psychometrika, 39*(1), 31-36.

Kaplan, M. H., & Feinstein, A. R. (1974). The importance of classifying initial co-morbidity in evaluating the outcome of diabetes mellitus. *Journal of chronic diseases, 27*(7), 387-404.

Kieszak, S. M., Flanders, W. D., Kosinski, A. S., Shipp, C. C., & Karp, H. (1999). A comparison of the Charlson comorbidity index derived from medical record data and administrative billing data. *Journal of clinical epidemiology, 52*(2), 137-142.

Melfi, C., Holleman, E., Arthur, D., & Katz, B. (1995). Selecting a patient characteristics index for the prediction of medical outcomes using administrative claims data. *Journal of clinical epidemiology, 48*(7), 917-926.

Ott, L. K., Pinsky, M. R., Hoffman, L. A., Clarke, S. P., Clark, S., Ren, D., & Hravnak, M. (2012). Medical emergency team calls in the radiology department: patient characteristics and outcomes. *BMJ quality & safety, 21*(6), 509-518.

Poses, R. M., Smith, W. R., McClish, D. K., & Anthony, M. (1995). Controlling for confounding by indication for treatment: Are administrative data equivalent to clinical data? *Medical care,* AS36-AS46.

Rafferty, A. M., Clarke, S. P., Coles, J., Ball, J., James, P., McKee, M., & Aiken, L. H. (2007). Outcomes of variation in hospital nurse staffing in English hospitals: cross-sectional analysis of survey data and discharge records. *International journal of nursing studies, 44*(2), 175-182.

Rochefort, C. M., Ward, L., Ritchie, J. A., Girard, N., & Tamblyn, R. M. (2012). Patient and nurse staffing characteristics associated with high sitter use costs. *Journal of advanced nursing, 68*(8), 1758-1767.

Schubert, M., Clarke, S. P., Aiken, L. H., & De Geest, S. (2012). Associations between rationing of nursing care and inpatient mortality in Swiss hospitals. *International Journal for Quality in Health Care, 24*(3), 230-238.

Sermeus, W., Aiken, L. H., Van den Heede, K., Rafferty, A. M., Griffiths, P., Moreno-Casbas, M. T., . . . Bruyneel, L. (2011). Nurse forecasting in Europe (RN4CAST): Rationale, design and methodology. *BMC nursing, 10*(1), 6.

Sharabiani, M. T., Aylin, P., & Bottle, A. (2012). Systematic review of comorbidity indices for administrative data. *Medical care, 50*(12), 1109-1118.

Sundararajan, V., Henderson, T., Perry, C., Muggivan, A., Quan, H., & Ghali, W. A. (2004). New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. *Journal of clinical epidemiology, 57*(12), 1288-1294.

Sundararajan, V., Quan, H., Halfon, P., Fushimi, K., Luthi, J.-C., Burnand, B., & Ghali, W. A. (2007). Cross-national comparative performance of three versions of the ICD-10 Charlson index. *Medical care*, 1210-1215.

Tabachnick, B., & Fidell, L. (2007). Multivariate analysis of variance and covariance. *Using multivariate statistics, 3*, 402-407.

Thygesen, S. K., Christiansen, C. F., Christensen, S., Lash, T. L., & Sørensen, H. T. (2011). The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC medical research methodology, 11*(1), 83.

Xue, Y., Aiken, L. H., Freund, D. A., & Noyes, K. (2012). Quality outcomes of hospital supplemental nurse staffing. *Journal of Nursing Administration, 42*(12), 580-585.

Yousef, K., Pinsky, M. R., DeVita, M. A., Sereika, S., & Hravnak, M. (2012). Characteristics of patients with cardiorespiratory instability in a step-down unit. *American Journal of Critical Care, 21*(5), 344-350.

Table 1: Demographic Characteristics of the Sample (N = 634)

VARIABLE	N	%
AGE (YEARS)	57.68 ± 19.94	
< 21	17	2.7
21-30	67	10.6
31-39	36	5.7
40-49	82	12.9
50-59	124	19.6
59 AND OVER	308	48.6
ETHNICITY		
WHITE/CAUCASIAN	461	72.7
BLACK/AFRICAN	85	13.4
AMERICAN		
HISPANIC	81	12.8
NATIVE AMERICAN	3	.5
ASIAN	2	.3
OTHER	2	.4
HOSPITAL LENGTH OF STAY		
MEAN	9.05 days	
MEDIAN	5 days	
MODE	2 days	

Table 2: Table of means and standard deviations of all items in 634 patients

CHARLSON/DEYO COMORBIDITY INDEX INDIVIDUAL ITEM	N	MEAN	SD
MYOCARDIAL INFARCTION (MI)	66	.10	.306
CONGESTIVE HEART FAILURE (CHF)	67	.11	.308
PERIPHERAL VASCULAR DISEASE (PVD)	68	.11	.310
CEREBRAL VASCULAR DISEASE (CVD)	36	.06	.232
DEMENTIA	0	.0	.00
CHRONIC PULMONARY DISEASE (CPD)	115	.18	.386
RHEUMATOID DISORDER (RMD)	27	.04	.202
PEPTIC ULCER DISEASE (PUD)	13	.02	.142
MILD LIVER DISEASE (MLD)	12	.02	.136
DIABETES	128	.20	.402
DIABETES WITH COMPLICATIONS (DIABCC)	19	.03	.171
HEMIPARESIS (HEMIPARA)	3	.00	.069
RENAL (RENAL)	7	.01	.105
METASTATIC TUMOR (METATUMR)	5	.01	.089
MALIGNANT TUMOR (MALIG)	16	.03	.157
SEVERE LIVER DISEASE (SLD)	8	.01	.112
AIDS (AIDS)	2	.00	.056

Table 3: Correlation Matrix, Means, and Standard Deviations for the 10-Item Charlson Comorbidity Index-Deyo Method

Item	MI	CHF	PVD	CPD	CVD	RMD	PUD	DIAB	DIABC	MALIG
MI	1.000									
CHF	.236	1.000								
PVD	.166	.163	1.000							
CPD	.161	.184	.088	1.000						
CVD	.028	.093	.047	.026	1.000					
RMD	.005	.055	.028	.043	.050	1.000				
PUD	.024	.023	.058	.076	.013	.135	1.000			
DIAB	.112	.211	.080	.069	.097	.011	.038	1.000		
DIABCC	.061	.120	.118	.013	-.003	.009	-.025	.004	1.000	
MALIG	.011	.043	-.023	.029	.004	.066	.048	.094	.031	1.000

MI= Myocardial infarction, CHF = congestive heart failure, PVD = peripheral vascular disease, CPD = chronic pulmonary disease, CVD = cerebral vascular disease, RMD = rheumatoid disease, PUD = peptic ulcer disease, DIAB = diabetes, DIABCC = diabetes with complications, MALIG = malignant tumor

Table 4: Principal Component Analysis Solution of the Charlson Comorbidity Index-Deyo method (CCI-D).

	COMPONENTS				
ITEM	I	II	III	IV	COMM
MI	.631				.418
CHF	.557	*.369*			.491
PVD	.589				.387
CPD	.516				.356
CVD		.580			.334
DIAB		.720			.530
RMD			.707		.504
PUD			.754		.567
DIABCC				.794	.702
MALIG		*.350*		.528	.648
Total Variance Explained (49.38%)	16.99	11.64	10.55	10.20	
Eigenvalues	1.70	1.17	1.05	1.02	

MI= Myocardial infarction, CHF = congestive heart failure, PVD = peripheral vascular disease, CPD = chronic pulmonary disease, CVD = cerebral vascular disease, RMD = rheumatoid disease, PUD = peptic ulcer disease, DIAB = diabetes, DIABCC = diabetes with complications, MALIG = malignant tumor, COMM = communalities

APPENDIX E

EARLY PHYSIOLOGIC PREDICTORS OF CARDIORESPIRATORY INSTABILITY IN STEP-DOWN UNIT PATIENTS

Poster Presented at the Eastern Nursing Research Society, Boston, MA, Summer 2012

Early Physiological Predictors of Cardiorespiratory Instability in Step-Down Unit Patients

Eliezer Bose, Marilyn Hravnak

Background: Patients hospitalized on step-down units (SDUs) undergo continuous physiological monitoring due to presumed risk for cardiorespiratory instability (CRI), which occurs in only a subset of patients but is associated with significant morbidity and mortality. Early detection and recognition of CRI is crucial. **Purpose:** To: 1) identify and compare the characteristics of SDU patients who develop CRI (unstable) with patients who never develop CRI (stable), 2) identify interactive differences in dynamic physiologic patterns of stable and unstable patients, and 3) develop models to predict CRI before its overt manifestation. **Methods:** Prospective, longitudinal evaluation of a retrospective convenience sample of SDU patients over 8 weeks (n=646; 32,000 monitoring hours). An amalgamated database containing patients' continuous physiologic data streams, clinical characteristics (age, gender, race, diagnoses, comorbidities), and CRI class will be created. A MATLAB filter will be applied to the continuous physiological signals to identify and tag CRI, defined as 1) HR <40 or >140 bpm, 2) RR <8 or >36 bpm, 3) systolic BP <80 or >200 mmHg, 4) diastolic BP >110 mmHg or 5) SpO2 <85%. Patients who at any point cross a CRI threshold are classified as unstable, and patients who never did as stable. Stable and unstable patients will be compared to identify which characteristics are either singly or in combination associated with instability. Rolling 5-minute time windows of the physiologic data will be assessed for emerging interactive pattern differences leading to overt CRI using a weighted threshold test based on standard deviation of the changes. Regression models incorporating various iterations of physiologic and clinical data to dynamically predict instability will be developed, and prediction accuracy evaluated in 30% of

the sample not used for calibration. **Implications**: Study findings will provide direction for improved CRI detection and prediction, to shift CRI care from a reactive to preemptive approach.

APPENDIX F

DIURNAL VARIATION IN VITAL SIGN ALERTS ACCORDING TO MEDICAL EMERGENCY TEAM (MET) TRIGGER CRITERIA IN CONTINUOUSLY MONITORED STEP-DOWN UNIT (SDU) PATIENTS

Eliezer Bose, Lujie Chen, Michael Pinsky, Marilyn Hravnak

Poster presented at the Rapid Response Systems (RRS) Conference, Summer 2014—Best posters final list

Diurnal variation in vital sign alerts according to Medical Emergency Team (MET) trigger criteria in continuously monitored step-down unit (SDU) patients.

Background: MET calls are made more frequently during mid-day hours. It is unknown if this is due to true diurnal variation in instability incidence, or a product of having more staff in the presence of the patient during those hours to recognize instability. We hypothesize the latter, and that real vital sign (VS) variations indicating instability according to MET trigger criteria occur consistently around the clock, representing missed opportunity to deploy the MET. **Methods**: This is a retrospective analysis of prospectively collected data in 634 patients (41,635 monitoring hours total; 80 mean monitoring hours/patient; 55 median monitoring hours/patient) who underwent continuous noninvasive VS monitoring (heart rate [HR], respiratory rate [RR; bioimpedance], and noninvasive oscillometric (systolic [SysBP] and diastolic [DiaBP]) blood pressure, and peripheral oximetry (SpO2) recorded at a 1/20Hz frequency. VS deviations beyond our local MET trigger values (HR< 40 or >140, RR< 8 or >36, SysBP < 80 or >200, DiaBP>110, SpO2< 85%) for 80% of a 5-min moving window were visually annotated by two expert clinician reviewers as real alerts or artifacts. Artifacts were discarded, leaving 1,399 MET threshold alerts (50% RR, 30% SpO2, 10% HR and 10% BP). Alerts were tallied according to hour of the day, and then calculated as the probability of incurring an alert for each hour of the day. R open source statistical software (Version 2.15.2) was used to test if differences existed in alert probability for each of the 24 hours of the clock (test for equality in proportions).

Results: The sample was primarily male (59%) and white (73%), with a mean age of 58 years, and a mean length of days on SDU 3.1$\pm$ 3.1 days. Admissions were highest from 1400 to 2400. The probability for a MET threshold alert per hour of the clock ranged from a low of 0.019 $\pm$ 0.003 at 0400, to a high of 0.034 $\pm$ 0.004 at 2200 (Table 1), and there were no significant

differences in alert probability by hours of the clock (p=0.4072). When examining MET threshold alerts by categorized time blocks (Probability 0000-0800= 0.026 ± 0.003, probability 0801-1600= 0.027 ± 0.003, probability 1601-2359 = 0.029 ± 0.003) there were no statistical differences in probability (p=0.361). **Conclusions**: Patients become unstable and meet MET trigger criteria throughout the clock without specific clustering relative to time of the day. Methods to improve clinicians' detection of patient instability are needed.

Table 1. Probability of instability fulfilling MET trigger alert threshold by hour of the clock.

Hour	**0000**	**0100**	**0200**	**0300**	**0400**	**0500**	**0600**	**0700**
Probability ± SD	.0030 ±. 0038	.0271 ± .0036	.0285 ±. 0037	.0275 ±. 0036	.0189 ± .0030	.0279 ±. 0036	.0025 ±. 0035	.0219 ±. 0033
Hour	**0800**	**0900**	**1000**	**1100**	**1200**	**1300**	**1400**	**1500**
Probability ± SD	.0233 ± .0034	.0288 ± .0037	.0232 ± .0033	.0301 ± .0038	.0286± .0037	.0286± .0037	.0271± .0036	.0277 ± .0036
Hour	**1600**	**1700**	**1800**	**1900**	**2000**	**2100**	**2200**	**2300**
Probability ± SD	.0259 ± .0035	.0247 ± .0035	.0278 ± .0037	.0227 ± .0033	.0264 ± .0036	.0327 ± .0040	.0345 ± .0041	.0343 ± .0040

The authors have no conflicts of interest to disclose. Funding NIH R01NR013912, National Institute of Nursing Research.

APPENDIX G

VECTOR AUTOREGRESSIVE (VAR) MODEL FOR EXPLORING CAUSAL DYNAMICS OF CARDIORESPIRATORY INSTABILITY

Eliezer Bose, Marilyn Hravnak, Gilles Clermont

Poster presented at the Society of Critical Care Medicine (SCCM), Spring 2015

Vector Auto-regressive (VAR) model for exploring causal dynamics of cardiorespiratory instability

Introduction: Patients undergo continuous physiologic monitoring of vital signs (heart rate [HR], respiratory rate [RR], pulse oximetry [SpO2]). Vital signs undergo inter-related changes in situations of stress, and upon recovery from stress. Patterns of this cross-talk could portend impending cardiorespiratory instability (CRI). We proposed using VAR modeling and Granger causality to explore causal dynamics across the vital signs time-series (VSTS) in patients prior to overt CRI. We hypothesize that patient-specific VAR modeling of VSTS will expose Granger causal dynamics in evolving CRI. Such information could help target surveillance monitoring. **Methods**: CRI was defined as vital signs beyond normality thresholds (HR=40-140/min, RR=8-36/min, SpO2>85%) and persisting for 4-mins of a 5-min moving window. A 6-hr window prior to first CRI onset was chosen in 25 CRI patients. The uniform time series (freq=1/20 Hz) for each vital was assessed for stationarity, followed by: VAR model construction and diagnostics such as significant lags, LM test for residual autocorrelation, AR roots and Wald test. With the final stable model, Granger causality/block exogeneity Wald chi-square test assessed for significance of the lagged variable on the dependent variable. **Results**: The primary cause of CRI was SpO2 (48% cases), followed by RR (28%) and HR (24%). Within CRI cases, Granger causality revealed that HR Granger-caused (GC) RR (28%) (i.e. HR changed before RR changed) more often than RR GC HR (13%). Similarly, HR GC SpO2 (20%) was more common than SpO2 GC HR (15%). For RR and SPO2, RR GC SPO2 (17%) was more common than SpO2 GC RR (6%). **Conclusions**: VAR modeling indicates that, within this sample, HR changes seem to occur before those in RR. It is unclear if this means that HR is causative, or if HR is a more nimble vital sign and able to attempt compensation in response to subtle abnormalities in

RR or SpO2 before overt CRI. Nevertheless, our data suggests that contextual assessment of HR changes as the earliest sign of CRI is warranted. More rigorous testing of causal dynamics in a larger sample is needed.

APPENDIX H

VECTOR AUTOREGRESSIVE (VAR) MODEL AND GRANGER CAUSALITY IN TIME SERIES ANALYSIS OF VITAL SIGNS FOR NURSING RESEARCH

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Conflicts of Interest: None declared

H.1 ABSTRACT

Background-- Patients undergoing continuous physiologic monitoring of vital signs (heart rate [HR], respiratory rate [RR], pulse oximetry [SpO2]) display inter-related vital sign changes in situations of physiologic stress. Patterns in this cross-talk could portend impending cardiorespiratory instability (CRI).

Objective-- We proposed using vector autoregressive (VAR) modeling and Granger causality to explore causal dynamics across the vital sign time series (VSTS) in patients prior to overt CRI.

Method-- CRI was defined as vital signs beyond normality thresholds (HR=40-140/min, RR=8-36/min, SpO2<85%) and persisting for 3 minutes (60%) of a 5 minute moving window. A 6-hour window prior to first CRI onset was chosen for time-series modeling in 20 patients. The uniform time series for each vital sign was assessed for stationarity, followed by VAR model construction and stability check of the VAR system. With the final stable model, Granger causality was assessed for the lagged predictor variable on the dependent variable.

Results-- The primary cause of CRI was SpO2 (60% of cases), followed by RR (30%) and HR (10%). Granger causality testing revealed that RR caused HR (21%) (i.e., RR changed before HR changed) more often than HR causing RR (15%). Similarly, that RR caused SpO2 (15%) was more common than SpO2 causing RR (9%).

Discussion-- Within this sample of acutely ill patients with CRI, VAR modeling indicates that RR changes tend to occur before changes in HR and SpO2. Our findings suggest that contextual assessment of RR changes as the earliest sign of CRI is warranted, with more modeling and testing in a larger sample being advisable.

Keywords: Time series analysis, vector autoregressive modeling, vital sign time series, physiological nursing research

H.2 MANUSCRIPT

H.2.1 BACKGROUND

Physiologic nursing research often depends on the collection of time series data to be used in various statistical models (Knobel, Levy, Katz, Guenther, & Holditch-Davis, 2013; Tsai, Barnard, Lentz, & Thomas, 2010). Vital sign time series (VSTS) usually involve the collection of monitored physiologic vital signs (VS), such as heart rate (HR), respiratory rate (RR) or pulse oximetry (SpO2). Physiologically, there are constant interactions among the VS indicative of the patient's effort to compensate and attain homeostasis when threshold values exceed normal limits (Chester & Rudolph, 2011), the failure of which leads to cardiorespiratory instability (CRI). Patient-specific multivariate time series modeling approaches (Schulz et al., 2013) can be used to study the causal characteristics of the changes in physiological variables as they progress in time towards the development of CRI. The vector autoregressive (VAR) model, a type of time-series modeling approach, is one of the most flexible models for the analysis of causality in multivariate time series (Lütkepohl, 2011). The general structure of the VAR model used in multivariate time series is that each variable is a linear function of past lags of both itself and the other variables. The vector autoregressive model of order 1 with 3 variables (HR, RR, SpO2) is denoted as VAR (1) and is as follows

$$\begin{bmatrix} y_{HR,t} \\ y_{RR,t} \\ y_{SpO2,t} \end{bmatrix} = \begin{bmatrix} c_{HR} \\ c_{RR} \\ c_{SpO2} \end{bmatrix} + \begin{bmatrix} A_{1,1} & A_{1,2} & A_{1,3} \\ A_{2,1} & A_{2,2} & A_{2,3} \\ A_{3,1} & A_{3,2} & A_{3,3} \end{bmatrix} \begin{bmatrix} y_{HR,t-1} \\ y_{RR,t-1} \\ y_{SpO2,t-1} \end{bmatrix} + \begin{bmatrix} e_{HR,t} \\ e_{RR,t} \\ e_{SpO2,t} \end{bmatrix}$$

This model has been widely employed in econometric analyses (Granger & Newbold, 2014) and in neurobiology (Tang, Bressler, Sylvester, Shulman, & Corbetta, 2012) for elucidating underlying causal mechanisms using Granger causality, but, to the best of our knowledge, has never been implemented in studying causality in physiologic time-series variables of HR, RR and SpO_2 as inputs to the development of CRI. The purpose of this study was to develop a patient-specific multivariate time series VAR model using HR, RR and SpO_2 in a sample of acutely ill monitored step-down unit (SDU) patients in order to study the Granger casual dynamics among the VS leading up to CRI. Since CRI can occur at different times during the hospitalization of unstable patients, we decided to consider only their first instance of CRI, which we called CRI_1 for the purposes of this study.

H.2.2 METHODS

Research Design

This is an analysis of prospectively collected physiologic data in patients who underwent continuous noninvasive VS monitoring (heart rate [HR], respiratory rate [RR; bioimpedance], peripheral oximetry [SpO2; plethysmography]) recorded once every 20 seconds (δ t = 20 seconds) for the entire monitoring period of their hospitalization on the SDU. VS deviations beyond local instability threshold limits 40-140 beats per minute for HR, 8-36 breaths per minute for RR and SpO2< 85%, any of which persists for 3-minutes (60% duty cycle) of a 5-minute

moving window denote instability epochs. These instability epochs were then visually annotated by two expert critical care clinician reviewers as real CRI or monitoring artifacts. We created a .csv subset from the first instances of the real CRI, CRI1, using VSTS prior to the onset of CRI1, to up to a maximum of 6-hours prior to the start of CRI1.

Sample and Setting

The study was approved by the University of Pittsburgh Institutional Review Board (IRB). The sample for the study (N=20) was recruited from a 24-bed trauma SDU, located in a tertiary academic medical center. For the study, data were extracted from input obtained from beside monitors (model M1204, Philips Medical, Bothell, WA) and included noninvasive monitoring of continuous HR (3-lead ECG), RR (bioimpedance signal), and plethysmographic peripheral blood oxygen saturation (SpO2) signal (model M1191B, Philips Medical Systems). Patient entry criteria for the study were: 1) admitted to a monitored bed on the SDU and 2) age >21 years during the study periods (11/06-8/07; 8 weeks). All patients were admitted to the study unit according to the usual standard of care for monitored bed admission and utilization. This methodology yielded a convenience sample of 20 patients, whose ages ranged from 35 to 92 years, and was equally male and female (50% each) and mostly of white race (80%).

Data Analysis

Data analysis consisted of the following steps: data pre-processing, testing the stationarity of the VSTS individually for each of the variables, lag-length selection criteria, building a VAR model with appropriate lags, assessing the residual autocorrelation with the Lagrange Multiplier (LM) test, assessing the stability of the VAR system with the autoregressive (AR) roots graph and Granger Causality test. All data analysis was performed using EViews® 8 Student version.

Data Pre-processing

The first point in the patient's streaming data where the patient develops CRI (CRI1) –i.e. any VS first crosses the instability threshold- denotes the start of the epoch, and the point at which all VS return within the normal threshold denotes the end of the epoch. Using the beginning of the CRI1 epoch, a 6-hour window period prior to that time was chosen for VAR analysis. This was because Hravnak et al., in the same group of patients, revealed that vital sign changes occur at least 6 hours prior to the onset of CRI (Hravnak et al., 2008). The first step was to pre-process the data to verify that a data value existed at every 20 seconds. There were certain portions within the data stream where gaps were noticed, likely due to poor signal capture. Gaps in the data stream were populated using linear interpolation between the points (Lehman, Nemati, Adams, & Mark, 2012), to make the data stream continuous, for each of the 3 variables. We employed the use of this strategy since linear interpolation assumes that the unknown value of any given physiologic variable lies on the line between the two known values, similar to that of normal physiological mechanisms.

Testing the stationarity of the VSTS individually for each of the variables

The time series data for each of the individual VS variables were first visualized by a graphical line plot of each of the variables to assess for any trends as well as to assess for stationarity. From a visual perspective, it verifies that the series looks flat, without any upward or downward trend and with no periodic fluctuations over time. To test stationarity mathematically, we used the most commonly employed test called the Augmented Dickey-Fuller test (Wai & Ismail, 2014). An autogregressive model can be represented as $Xt = \alpha + \rho Xt\text{-}1 + \dot{\epsilon}t$ or $\Delta Xt = \alpha + (\rho\text{-}1) Xt\text{-}1 + \dot{\epsilon}t$, where $\Delta Xt = Xt - Xt\text{-}1$. If $\delta = \rho\text{-}1$, then $\Delta Xt = \alpha + \delta Xt\text{-}1 + \dot{\epsilon}t$. The null hypothesis for the Augmented Dickey-Fuller (ADF) test is that the time series is non-stationary ($H0 : \rho=1$) and the alternative hypothesis ($H1 : \rho<1$) is that the series is stationary. In this case, if the null

hypothesis holds, then $\Delta Xt = \alpha + \dot{\epsilon}t$. Using the Dickey-Fuller table and a t-statistic on δ, if we can conclude that the t-value is less than the DFcritical, then we can reject the null hypothesis ($p<0.05$), thus proving that the series is stationary (Dickey, 2011). This test was performed individually for each of the 3 VS variables for each patient. If the VS time series was not stationary, the series was differenced and the ADF test applied again on the differenced time series to check for stationarity. Figure 1 illustrates the ADF test for differenced HR for a particular patient (Pt ID #1 in the sample).

Lag-length selection criteria

Once stationarity of a series was determined, we proceeded with lag-length selection criteria, using EViews® lag length selection criteria to identify the order of the lag to be chosen. An example illustrating a series of lags as well as the different selection criteria for a particular patient is shown in Figure 2. The most commonly employed criteria is the Akaike Information Criteria, which (similar to minimizing the error term in regression), chooses the lag order with the lowest value of AIC (Vrieze, 2012). In the example in Figure 2, the lowest AIC is starred (*) by Eviews®, and is shown in this example on the 12th lag, indicated with gray shading.

Building a VAR model with appropriate lags

The VAR model was next constructed in order to include the number of lags from 1 until the specified lag as described above. Figure 3 shows the example of a VAR model with lags from 1 to 12 for HR for one patient (Pt ID #1). The same was done correspondingly to represent RR as well as SpO2, and the significance of their coefficients assessed to decide whether another VAR model should be constructed so as to minimize the non-significant coefficients.

Assessing the residual autocorrelation with the LM test

We next applied the Lagrange Multiplier (LM) test to check for residual serial correlation, where the null hypothesis is that there is no serial correlation up to the specified lag order. If a proper VAR system is obtained from the previous step, then the coefficients of the LM-Stat are not significant, thus accepting the null hypothesis up to the specified lag. This means that the past values of a variable do not affect the future value of the variable until the specified lag value. This is illustrated in Figure 4 for one patient (Pt ID #1).

Assessing the stability of the VAR system with the autoregressive (AR) roots graph

As the next step, we assessed the stability of the VAR system by evaluating the roots of the characteristic polynomial with the endogenous variables of HR, RR and SpO2 and the lag specification as per above criteria. If no root lies outside the unit circle as shown in Figure 5 for one patient (Pt ID #1), then VAR system satisfies the stability condition, indicating model stability. This evaluation was performed on a patient-by-patient basis.

H.2.3 RESULTS

Granger causality is a commonly employed method for the investigation of dynamic interrelationships in multivariate time series (Eichler, 2013). It is based on the common-sense concept that causes precede their effects in time. Granger causality treats one of the VS variables as a dependent variable (DV) and the others as independent variables (IVs). It assesses for causality between the DV and the IV (including all significant lags of the IV) as shown in Figure 6. A p-value < .05 is suggestive of causality. Unidirectional causality is assumed if the IV Granger causes (<0.05) the DV. Figure 6 shows an example for one patient (Pt ID #1) where RR with all of its lags causes HR. This demonstrates that there is unidirectional causality running

from RR to HR, with changes in RR causing changes in HR in the patient's time series prior to CRI1. However, if both IV causes DV, and DV causes IV, then bidirectional causality with feedback effect among the variables is assumed. Table 1 contains three cases Pt ID # 8, 14 and 18 where bidirectional causality occurred.

The final results of the Granger Causality Test, as shown in Table 1, indicate that the first VS over threshold to begin the CRI epoch was SpO2 in 60% cases, followed by RR (30%) and HR (10%). Within CRI1 cases, Granger causality revealed that RR caused HR (21%) (i.e. RR changed before HR changed) more often than HR causing RR (15%). Similarly, RR caused SpO2 (15%) was more common than SpO2 causing RR (9%). For HR and SpO2, HR caused SpO2 (18%) and SpO2 caused HR (18%).

H.2.4 DISCUSSION

The purpose of this study was to develop a stable patient-specific multivariate time series VAR model using HR, RR and SpO2 in a sample of SDU patients in order to study the Granger casual dynamics among the monitored vital signs leading up to a first CRI. Our results suggest that using this information may be helpful to determine causality in VS threshold deviations, and determine a physiologic cause. For example in our 20 cases, SpO2 falling below threshold was the first indicator of CRI. SpO2 itself was generally not the cause for changed RR or HR, but rather RR and HR tended to be the cause for the fall in SpO2. This suggests that SpO2 is a later VS change, and is led by more subtle changes in other VS which in turn caused changes in SpO2.

From an analysis standpoint, there were 2 cases where the patient developed CRI1 before a 6-hour window period of his/her arriving on the SDU was complete. In such cases, we only considered the entire period back starting with the start time of CRI1. One patient (Pt ID # 6) had a 2-hour window period preceding CRI1, while another (Pt ID # 11) had a 4-hour window period prior to CRI1, Also, there were 2 cases where we could only obtain VSTS from two variables--HR and RR VSTS prior to CRI1 (Pt ID # 3) and HR and SpO2 prior to CRI1 (Pt ID # 8). We encountered few instances where patients were not monitored (the reasons for the patients being off the monitor were not known) for a brief window period of at least 3 hours, within the 6-hour period prior to CRI1. Fortunately, there were only 2 instances where the above was the case (Pt IDs #9 and #16). In such cases, we used the Markov Chain Monte Carlo (MCMC) approach to impute missing values to the dataset, since it was not possible to fill the data stream with linear interpolation. For a continuous variable with missing values, MCMC uses the non-missing values to find the variable's sample mean and standard deviation and then fills in the missing values with random draws from a normal distribution with mean and standard deviation equal to the sample values, limited within the range of the observed minimum and maximum values (Brooks, Gelman, Jones, & Meng, 2011; Young, Weckman, & Holland, 2011).

There were no smoothing or other filtering approaches used to remove artifacts in our dataset—this was done by prior expert review before data pre-processing. Florin et al. showed that filtering approaches disturb the information content, leading to spurious and missed causalities (Florin, Gross, Pfeifer, Fink, & Timmermann, 2010). Hence, no filtering approaches were used, but the series was differenced to maintain stationarity, a prerequisite for Granger causality. Finally, there were two cases (Pt ID #12 and #20) where the VAR model could not be stabilized for reasons that are unclear. Interestingly, both cases were those of HR crossed the

threshold first. It is possible that HR is less likely to induce compensatory changes than other VS, but this would require further exploration.

A major disadvantage of our study is the absence of continuous streaming data from these SDU patients for the entire 6-hour period, whereby we could avoid the use of linear interpolation or MCMC. We implemented these imputation procedures so as to maintain continuity of the VSTS for VAR modeling. Even though the VAR model is quite rich in capturing the temporal dynamics of highly complex hemodynamic responses, one must be careful not to over-interpret Granger causal relationships as truly causal.

H.2.5 FUTURE DIRECTIONS

Our study, the first to use patient-specific VAR modeling approach and the testing of Granger causality in multivariate VSTS in a small sample of SDU patients, has shown that the VAR modeling approach is able to expose Granger causal dynamics in evolving CRI. Future studies with much larger samples and longer VSTS monitoring to study casual dynamics are warranted. Such information could help target surveillance monitoring, enabling nurses to better recognize impending CRI.

REFERENCES

Brooks, S., Gelman, A., Jones, G., & Meng, X.-L. (2011). *Handbook of Markov Chain Monte Carlo*: CRC press.

Chester, J. G., & Rudolph, J. L. (2011). Vital signs in older patients: age-related changes. *J Am Med Dir Assoc, 12*(5), 337-343. doi: 10.1016/j.jamda.2010.04.009

Dickey, D. G. (2011). Dickey-Fuller Tests *International Encyclopedia of Statistical Science* (pp. 385-388): Springer.

Eichler, M. (2013). Causal inference with multiple time series: principles and problems. *Philosophical Transactions of the Royal Society of London A: Mathematical, Physical and Engineering Sciences, 371*(1997), 20110613.

Florin, E., Gross, J., Pfeifer, J., Fink, G. R., & Timmermann, L. (2010). The effect of filtering on Granger causality based multivariate causality measures. *NeuroImage, 50*(2), 577-588.

Granger, C. W. J., & Newbold, P. (2014). *Forecasting economic time series*: Academic Press.

Hravnak, M., Edwards, L., Clontz, A., Valenta, C., DeVita, M. A., & Pinsky, M. R. (2008). Defining the incidence of cardiorespiratory instability in patients in step-down units using an electronic integrated monitoring system. *Archives of internal medicine, 168*(12), 1300-1308.

Knobel, R. B., Levy, J., Katz, L., Guenther, B., & Holditch-Davis, D. (2013). A pilot study to examine maturation of body temperature control in preterm infants. *J Obstet Gynecol Neonatal Nurs, 42*(5), 562-574. doi: 10.1111/1552-6909.12240

Lehman, L.H., Nemati, S., Adams, R. P., & Mark, R. G. (2012). *Discovering shared dynamics in physiological signals: Application to patient monitoring in ICU.* Paper presented at the Engineering in Medicine and Biology Society (EMBC), 2012 Annual International Conference of the IEEE.

Lütkepohl, H. (2011). *Vector autoregressive models*: Springer-Verlag,Berlin.

Schulz, S., Adochiei, F. C., Edu, I. R., Schroeder, R., Costin, H., Bar, K. J., & Voss, A. (2013). Cardiovascular and cardiorespiratory coupling analyses: a review. *Philos Trans A Math Phys Eng Sci, 371*(1997), 20120191. doi: 10.1098/rsta.2012.0191

Tang, W., Bressler, S. L., Sylvester, C. M., Shulman, G. L., & Corbetta, M. (2012). Measuring Granger causality between cortical regions from voxelwise fMRI BOLD signals with LASSO. *PLoS Comput Biol, 8*(5), e1002513. doi: 10.1371/journal.pcbi.1002513

Tsai, S.-Y., Barnard, K. E., Lentz, M. J., & Thomas, K. A. (2010). Mother–infant activity synchrony as a correlate of the emergence of circadian rhythm. *Biological research for nursing.000(00)1-9.* doi:10.1177/1099800410378889

Vrieze, S. I. (2012). Model selection and psychological theory: a discussion of the differences between the Akaike information criterion (AIC) and the Bayesian information criterion (BIC). *Psychological methods, 17*(2), 228.

Wai, P. S., & Ismail, M. T. (2014). *Measuring nonlinear behavior in time series data.* Paper presented at the International Conference On Quantitative Sciences and Its Applications (ICOQSIA 2014): Proceedings of the 3rd International Conference on Quantitative Sciences and Its Applications.

Young, W., Weckman, G., & Holland, W. (2011). A survey of methodologies for the treatment of missing values within datasets: limitations and benefits. *Theoretical Issues in Ergonomics Science, 12*(1), 15-43.

Table 1: Granger Causality—unidirectional indicated with (→) and bidirectional with (←→)

Patient ID (Pt. ID)	Data presence	First VS over Threshold in CRI_1	Granger Causality (GC)
1	All 3 VS, all 6 hours pre CRI	SpO_2	RR →HR
2	All 3 VS, all 6 hours pre CRI	SpO_2	RR →HR RR → SpO_2
3	Only HR and RR VS, all 6 hours pre CRI	RR	RR →HR
4	All 3 VS, all 6 hours pre CRI	SpO_2	HR←→ SpO_2 RR →HR RR → SpO_2
5	All 3 VS, all 6 hours pre CRI	RR	No causal structure noticed among the variables
6	All 3 VS, only 2 hours pre CRI	SpO_2	HR →RR
7	All 3 VS, all 6 hours pre CRI	SpO_2	RR→HR RR → SpO_2 HR→ SpO_2
8	Only HR and SPO2 VS, all 6 hours pre CRI	SpO_2	HR ←→SPO2
9	All 3 VS, all 6 hours pre CRI	RR	RR → SpO_2
10	All 3 VS, all 6 hours pre CRI	SpO_2	No causal structure noticed among the variables
11	All 3 VS, only 4 hours pre CRI	SpO_2	SpO_2 →RR HR → SpO_2
12	All 3 VS, all 6 hours pre CRI	HR	Unable to achieve a stable VAR model
13	All 3 VS, all 6 hours pre CRI	SpO_2	SpO_2→HR
14	All 3 VS, all 6 hours pre CRI	RR	HR ←→ RR
15	All 3 VS, all 6 hours pre CRI	RR	No causal structure noticed among the variables
16	All 3 VS, all 6 hours pre CRI	SpO_2	HR ←→ SpO_2 HR → RR SpO_2 → RR
17	All 3 VS, all 6 hours pre CRI	SpO_2	SpO_2 → HR
18	All 3 VS, all 6 hours pre CRI	RR	HR←→RR
19	All 3 VS, all 6 hours pre CRI	SpO_2	HR → RR SpO_2←→ RR SpO_2 ←→ HR
20	All 3 VS, all 6 hours pre CRI	HR	Unable to achieve a stable VAR model

Figure 1: Augmented Dickey Fuller test for assessing stationarity of the individual time series in one patient.

Null Hypothesis: D(IPHR) has a unit root
Exogenous: None
Lag Length: 5 (Automatic - based on SIC, maxlag=21)

		t-Statistic	Prob.*
Augmented Dickey-Fuller test statistic		-19.78943	0.0000
Test critical values:	1% level	-2.567115	
	5% level	-1.941118	
	10% level	-1.616501	

*MacKinnon (1996) one-sided p-values.

Augmented Dickey-Fuller Test Equation
Dependent Variable: D(IPHR,2)
Method: Least Squares

Sample (adjusted): 8 1082
Included observations: 1075 after adjustments

Variable	Coefficient	Std. Error	t-Statistic	Prob .
D(IPHR(-1))	-1.773697	0.089628	-19.78943	0.0000
D(IPHR(-1),2)	0.790138	0.077616	10.18009	0.0000
D(IPHR(-2),2)	0.508490	0.065739	7.735011	0.0000
D(IPHR(-3),2)	0.325283	0.051871	6.271053	0.0000
D(IPHR(-4),2)	0.168148	0.039054	4.305545	0.0000
D(IPHR(-5),2)	0.087524	0.028581	3.062339	0.0023

R-squared	0.522789	Mean dependent var	-0.000930
Adjusted R-squared	0.520557	S.D. dependent var	2.646465
S.E. of regression	1.832461	Akaike info criterion	4.054763
Sum squared resid	3589.609	Schwarz criterion	4.082558
Log likelihood	-2173.435	Hannan-Quinn criterion	4.065290
Durbin-Watson stat	2.013721		

Figure 2. VAR Lag Order Selection Criteria

VAR Lag Order Selection Criteria
Endogenous variables: HR RR
SPO2
Exogenous variables: C

Sample: 1 1082
Included observations: 1066

Lag	LogL	LR	FPE	AIC	SC	HQ
0	-4409.508	NA	0.790567	8.278627	8.292619	8.283928
1	-4058.505	699.3724	0.416170	7.636970	7.692936	7.658175
2	-3895.079	324.7059	0.311489	7.347240	7.445181	7.384348
3	-3845.196	98.83015	0.288490	7.270536	7.410452	7.323549
4	-3765.865	156.7268	0.252828	7.138583	7.320474	7.207500
5	-3729.862	70.92546	0.240339	7.087921	7.311786	7.172741
6	-3688.072	82.08909	0.226001	7.026402	7.292242*	7.127126
7	-3660.948	53.12992	0.218446	6.992397	7.300212	7.109025
8	-3635.782	49.15075	0.211922	6.962068	7.311857	7.094599*
9	-3622.142	26.56326	0.210087	6.953362	7.345126	7.101797
10	-3610.422	22.75931	0.209020	6.948258	7.381997	7.112597
11	-3598.588	22.91200	0.207915	6.942942	7.418656	7.123185
12	-3574.577	46.35551*	0.202145*	6.914779*	7.432467	7.110925
13	-3567.614	13.40285	0.202924	6.918601	7.478264	7.130651
14	-3562.765	9.307612	0.204516	6.926388	7.528026	7.154342
15	-3559.000	7.205468	0.206540	6.936210	7.579822	7.180067

* indicates lag order selected by the criterion
LR: sequential modified LR test statistic (each test at 5% level)
FPE: Final prediction error
AIC: Akaike information criterion
SC: Schwarz information criterion
HQ: Hannan-Quinn information criterion

Figure 3: Illustration of a VAR model with 12 lags for HR as the dependent variable for one patient.

VAR Model:
==========
HR = C(1,1)*HR(-1) + C(1,2)*HR(-2) + C(1,3)*HR(-3) + C(1,4)*HR(-4) + C(1,5)*HR(-5) + C(1,6)*HR(-6) + C(1,7)*HR(-7) + C(1,8)*HR(-8) + C(1,9)*HR(-9) + C(1,10)*HR(-10) + C(1,11)*HR(-11) + C(1,12)*HR(-12) + C(1,13)*RR(-1) + C(1,14)*RR(-2) + C(1,15)*RR(-3) + C(1,16)*RR(-4) + C(1,17)*RR(-5) + C(1,18)*RR(-6) + C(1,19)*RR(-7) + C(1,20)*RR(-8) + C(1,21)*RR(-9) + C(1,22)*RR(-10) + C(1,23)*RR(-11) + C(1,24)*RR(-12) + C(1,25)*SPO2(-1) + C(1,26)*SPO2(-2) + C(1,27)*SPO2(-3) + C(1,28)*SPO2(-4) + C(1,29)*SPO2(-5) + C(1,30)*SPO2(-6) + C(1,31)*SPO2(-7) + C(1,32)*SPO2(-8) + C(1,33)*SPO2(-9) + C(1,34)*SPO2(-10) + C(1,35)*SPO2(-11) + C(1,36)*SPO2(-12) + C(1,37)

Figure 4: VAR Residual Serial Correlation with LM Tests

VAR Residual Serial Correlation
LM Tests
Null Hypothesis: no serial correlation at lag order h

Sample: 1 1082
Included observations: 1069

Lags	LM-Stat	Prob
1	9.495643	0.3928
2	9.068058	0.4310
3	7.579804	0.5770
4	13.56391	0.1387
5	4.095677	0.9050
6	14.69532	0.0997
7	8.875476	0.4488
8	6.233729	0.7163
9	6.032959	0.7366
10	8.505331	0.4841
11	17.01417	0.0485
12	10.74452	0.2936

Probs from chi-square with 9 df.

Figure 5: VAR System Stability Condition check for one patient.

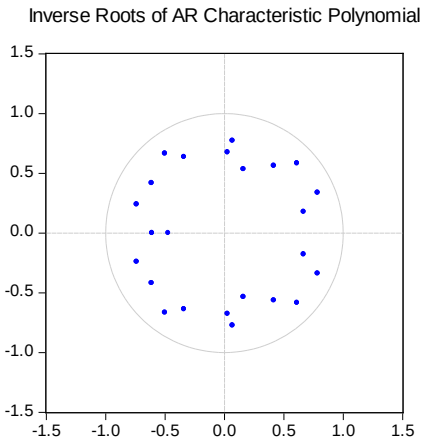

Figure 6: Granger causality after a stable VAR model in one patient

VAR Granger Causality/Block Exogeneity Wald Tests

Sample: 1 1082
Included observations: 1069

Dependent variable: HR

Excluded	Chi-sq	df	Prob.
RR	21.67892	12	0.0413
SPO2	17.56553	12	0.1295
All	42.08405	24	0.0126

Dependent variable: RR

Excluded	Chi-sq	df	Prob.
HR	16.74601	12	0.1594
SPO2	5.447528	12	0.9413
All	23.00000	24	0.5198

Dependent variable: SPO2

Excluded	Chi-sq	df	Prob.
HR	17.94254	12	0.1174
RR	20.26748	12	0.0622
All	37.59647	24	0.0381

APPENDIX I

MONITORING CARDIORESPIRATORY INSTABILITY: CURRENT STATUS AND IMPLICATIONS FOR NURSING PRACTICE

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I.1.1 ABSTRACT

Unrecognized in-hospital cardiorespiratory instability (CRI) risks negative or fatal patient outcomes. Even though step down unit patients have continuous non-invasive physiologic monitoring of vital signs and a ratio of 1 nurse to 4 or 6 patients, detection of CRI is still suboptimal. Nursing surveillance alone is unable to detect CRI. Telemedicine and rapid response teams have been tested as possible approaches to prevent CRI with mixed outcomes, while the problem still persists. Technology-enabled early warning scores, though rigorously studied, may not detect subtle instability. Existing monitoring systems hold the promise of better detection and recognition of CRI, but nursing surveillance still remains the key to reliable early detection. Research directed towards improving nursing surveillance and facilitating decision-making is needed to ensure safe patient outcomes and prevent CRI.

Keywords: Death, Sudden, Cardiac, Vital Signs, survival

I.1.2 Introduction

Unrecognized cardiorespiratory instability (CRI) risks negative or fatal patient outcomes. CRI, defined as abnormalities in heart rate (HR), respiratory rate (RR), blood pressure (BP), and/or peripheral oxygenation by pulse oximetry (SpO2) that precede an adverse event, may not be detected until late in the course of instability or until cardiopulmonary arrest. Nursing

surveillance alone has not been successful in detecting CRI early enough to prevent negative outcomes (Henneman, Gawlinski, & Giuliano, 2012). Telemedicine and rapid response systems have been advocated as possible approaches to prevent adverse events, with mixed outcomes (Kerlin et al., 2013; Venkataraman & Ramakrishnan, 2015; Winters et al., 2013). Utilization of early warning scoring systems, with or without automated calculation and notification, has resulted in improvement, but these systems also have deficiencies (Alam et al., 2014). Even mature rapid response systems, with track-and-trigger systems based on intermittent patient evaluation, miss avoidable cardiopulmonary arrests (Trinkle & Flabouris, 2011). The purpose of this review is to describe the current state-of-the science regarding approaches nurses may potentially use for detecting CRI and identify strategies that may lead to improved detection.

I.1.3 Unrecognized CRI risks negative or fatal patient outcomes

Over 80% of in-hospital cardiac arrests (IHCA) are preceded by serious vital sign (VS) abnormalities 6-8 hours before the arrest (Buist, Bernard, Nguyen, Moore, & Anderson, 2004; Rozen et al., 2014). Survival after IHCA is poor. In one report of 14,720 adult IHCA patients with evolving CRI, only 44% had return of spontaneous circulation and only 17% survived to discharge (Perberdy, Kaye, & Ornato, 2003). Long-term survival after IHCA with preceding CRI is also poor. In a study that reported outcomes following IHCA in 732 patients, 6.6% lived to discharge, 5.2% for 1 year, and 3% for 3 years (Bloom et al., 2007). These outcomes illustrate why it is crucial that nurses detect CRI early and initiate supportive or corrective action prior to progression to cardiopulmonary arrest.

I.1.4 Nursing surveillance alone is unable to detect CRI

Nursing surveillance, a process wherein nurses assess patients on a routine or as-needed basis to evaluate and act on emerging indicators of a status change, is a central nursing function that directly impacts patient outcomes (Bulechek, Butcher, Dochterman, & Wagner, 2013). Nursing surveillance includes assessment using sight, touch and hearing, or technological assistance, ranging from information acquired via thermometers, stethoscopes and sphygmomanometers to continuous physiologic data. Although technology can improve assessment sensitivity, failure to notice subtle changes in VS over time prevents nurses from intervening to reverse the process.

Several reasons have been posed to explain why subtle changes may go undetected. Patient mortality has been shown to be higher as a nurse's patient caseload increases (Aiken et al., 2011; Beaudoin & Edgar, 2003; Ebright, Patterson, Chalko, & Render, 2003; Needleman et al., 2011; Patrician et al., 2011). However, staffing level alone does not appear to influence CRI detection but, rather, staffing in combination with other nurse characteristics, such as education level and familiarity with the care required (Aiken et al., 2011; Blegen, Goode, Park, Vaughn, & Spetz, 2013). In one study, CRI was less likely to be detected when patients were admitted to units where nurses were less familiar with their care, e.g., agency or "pulled" staff (Schmid-Mazzoccoli, Hoffman, Wolf, Happ, & Devita, 2008). As well, frequent interruption of nurses during care provision negatively impacts ability to recognize a patient's changing condition (Page, 2004; Potter et al., 2005).

An additional factor that may contribute to unrecognized CRI lies within the very nature of the evolving CRI process. Unless due to an abrupt catastrophic event, such as pulmonary

embolism, stroke, or sudden arrhythmia, CRI is more commonly due to processes that evolve slowly over time, such as sepsis, respiratory insufficiency, or hypovolemia. In these cases, patients demonstrate VS changes that wax and wane between normal and abnormal (Figure 1). With only intermittent evaluation, patients may be seen by a nurse during periods of seeming stability when, in fact, CRI is present and progressing. This waxing and waning may also contribute to nurses feeling unsure that the patient is truly unstable and in need of care escalation. Although it is crucial that nursing surveillance provide timely recognition of VS changes signaling deterioration, current mechanisms for nursing surveillance and decision-making may not be sufficient (Dresser, 2012; Henneman, Gawlinski, & Giuliano, 2012; Hillman et al., 2005).

I.1.5 Telemedicine and Rapid Response Terms

Attempts to provide earlier treatment of CRI focus on two approaches. The first--telemedicine--provides continuous monitoring, teleconferencing, quick-consultation and advice from experienced physicians and advanced practice nurses around the clock to sites without specialized resources, with the goal of more promptly and appropriately managing any acute change in patient status. To date, this model of surveillance has most commonly been deployed in intensive care units (ICUs). Adoption of ICU telemedicine increased rapidly within US hospitals at an average of 101% per year from 2002 to 2005, but then slowed to 8.1% per year from 2006 to 2010. Hospitals adopting this system were typically large (> 400 beds), teaching and urban (Kahn, Cicero, Wallace, & Iwashyna, 2014). However, telemedicine is expensive, with start-up costs ranging from $45,000-$50,000 per bed and annual costs between $28,000-

$32,000 per bed (Ries, 2009) that may not be reimbursed by insurance (Alverson et al., 2004; Kumar et al., 2013). Benefits of ICU telemedicine are conflicting (Wootton, 2012) with some experts positing that expenditures are regained by reductions in ICU length of stay and in-hospital complications (Breslow, 2007) and others reporting no cost offset. Additional concerns relate to medical liability (Hoffmann & Rowthorn, 2011; Sao, Gupta, & Gantz, 2012; Whitten & Mackert, 2005), loss of privacy (Sao et al., 2012), lack of control over remote physician practices (Alverson et al., 2004), and unclear investment return (Moehr et al., 2006). To date, telemedicine continuous surveillance is generally not used in patient wards or other areas where patient to nurse ratios are higher than in ICUs and instability is more likely to be unrecognized.

A second option involves utilizing a rapid response system (RRS) and medical emergency team (MET) to address needs of unstable non-ICU patients (DeVita et al., 2010). The MET is usually a multidisciplinary team composed of medical, nursing, and respiratory therapy staff who can be summoned immediately to the patient's bedside at any time and regardless of location for prompt evaluation, triage, and treatment of clinical deterioration (Chan, Jain, Nallmothu, Berg, & Sasson, 2010). The RRS consists of an "afferent arm" consisting of some system for "track and trigger," meaning an established set of conditions or rules whereby unstable patients can be identified (tracked) and then an organized system whereby the clinician (or family member) can place a call for help (trigger) as shown in Table 1. This component is accompanied by the "efferent arm", i.e., MET deployment, organization, membership, systems, equipment, and protocols. The MET can assess and treat patients in whom respiratory, neurologic, or cardiac deterioration is in process (Jones, DeVita, & Bellomo, 2011) versus a "code team" whose goal is to resuscitate patients once a cardiopulmonary arrest has developed (Litvak & Pronovost, 2010).

In the most comprehensive evaluation of benefit, a multicenter cluster-randomized controlled trial called the Medical Early Response Intervention and Therapy (MERIT) study failed to demonstrate a reduction in mortality (Hillman et al., 2005) with MET use. However, post-hoc analysis (Chen et al., 2009) showed that the study reported deaths associated with all RRS calls, some of which occurred after cardiopulmonary arrest had developed. When these patients were excluded and only unstable patients prior to an arrest state were included, there was a benefit.

Notably, a MET team can only be deployed when called to help. In one setting with a long-standing RRS and clear call guidelines, of 108 MET calls on medical-surgical units, 44% were delayed (documented evidence that pre-established criteria for a MET call were present for > 30 minutes) (Schmid-Mazzoccoli et al., 2008). In a second study conducted on a SDU in the same institution, of 326 continuously monitored patients, MET activation criteria were achieved in 59 patients, but the MET was activated in only 7 cases (Hravnak et al., 2008). Several reasons have been posed for failure to recognize CRI, including episodic or abbreviated recording of VS, e.g., RR monitored for 15 seconds and multiplied by 4 (Ludikhuize, Smorenburg, de Rooij, & de Jonge, 2012), failure to recognize the significance of VS changes, and the belief that the problem can be managed without additional support (Galhotra, DeVita, Simmons, & Dew, 2007; Ludikhuize, Dongelmans, et al., 2012; Trinkle & Flabouris, 2011).

I.1.6 Technology enabled early warning scores

Early warning scoring (EWS) systems and modified early warning scores (MEWS) have been developed and utilized to calculate a single composite score from multiple noninvasively acquired VS parameters which are then weighted and summed to identify patients who pass a "concern threshold" that designates possible CRI. EWS objectively quantify concern to intervene or request additional support and are therefore less influenced by individual opinion (DeVita et al., 2010; Gardner-Thorpe, Love, Wrightson, Walsh, & Keeling, 2006; Sharpley & Holden, 2004; Subbe, Gao, & Harrison, 2007). EWS are typically designed to be bedside scoring systems for use by nurses or other clinicians who collect data via handwritten score cards or, more recently, personal digital assistants (PDAs). Technologically assisted EWS, also known as aggregate weighted track and trigger systems (AWTTS), are available from a variety of manufacturers,e.g.VitalPACTM,The Learning Clinic (http://www.thelearningclinic.co.uk/vitalpac.html). PDA-based applications allow VS data to be linked by a wireless network to the hospital's information system. When this system is used, data is integrated with other patient information, e.g., lab results, and programmed to make direct contact with the MET team through an automated alerting system (Smith et al., 2006).

Since 2012, the National Health Service in the United Kingdom has been mandated to use the National Early Warning Score (NEWS), a commercially available EWS, nationally. Prior to making this decision, NEWS was tested to discriminate patients at risk of IHCA and various other outcomes with 33 other AWTTS (excluding ViEWS described below) using a database of 198,755 observations. Data (RR, HR, SpO2, supplemental oxygen [Yes/No], temperature [oC], systolic blood pressure [mmHg] and level of consciousness using the Alert-Verbal-Painful-

Unresponsive [AVPU] system), were entered whereupon VitalPAC® software automatically computed the score as shown in Table 2. The NEWS was then assessed to determine its ability to derive scores that identified patients with or without cardiac arrest. In order to perform this comparison, they used a measurement process termed area under receiving operator characteristics (AUROC) curves. AUROCs plot the false positive rate of a score (1-specificity) on the x-axis against the true positive rate (sensitivity) on the y-axis. In terms of discrimination, an AUROC value between 0.7 and 0.8 indicates fair, a value between 0.8 and 0.9 indicates good and a value > 0.9 is excellent. When assessed in this manner, NEWS achieved an AUROC value of 0.722 (95% CI 0.685-0.759) for cardiac arrest discrimination which was better than any other EWS system evaluated. (Smith, Prytherch, Meredith, Schmidt, & Featherstone, 2013).

Another EWS--VitalPACTM EWS—(ViEWS) has been tested in a similar manner. ViEWS is used to enter data that includes HR, RR, temperature, systolic BP, SpO2, fraction of inspired oxygen (FiO2), and level of consciousness (AVPU scale), as recommended by the National Institute for Health and Clinical Excellence (Armitage, Eddleston, & Stokes, 2007). Using ViEWS, the authors were able to predict in-hospital death within 24 h of a given observation with a much higher AUROC (0.888) compared to 33 other AWTTS whose AUROCs ranged from 0.803 to 0.850 (Prytherch, Smith, Schmidt, & Featherstone, 2010).

This literature is rapidly evolving. Churpek et al. reported upon a cardiac arrest risk triage score (CART) was more accurate than ViEWS for predicting cardiac arrest (CART AUROC 0.88 vs. ViEWS 0.78, $p<0.001$) (Churpek, Yuen, Park, Gibbons, & Edelson, 2014). Ludikhuize et al. evaluated use of a three-times-a-day protocolized measurement of EWS and reported that it resulted in better (90 MET calls intervention vs. 9 MET calls control) detection of physiological abnormalities and more reliable MET activation (Ludikhuize et al., 2014). However, in a

randomized trial, Kollef et al. (Kollef et al., 2014) reported that alerts calculated by EWS and sent to the RRS did not reduce in-hospital mortality (odds ratio = 0.944, 95% CI: 0.509-1.764). Although EWS tools can amalgamate intermittently determined VS data and determine when a threshold value is reached, such systems do not interface with continuous monitoring and therefore may not detect subtle instability, a factor that may explain conflicting study findings. Romero-Brufau et al. concluded that the most widely used AWTTS do not offer good predictive capabilities and called for better criteria to be developed and validated (Romero-Brufau et al., 2014). A more ideal goal would be a system that could continuously and in "real-time" predict patients likely to become unstable in the future allowing for preemptive, rather than reactive, intervention. In addition, there may be benefit to adding "static" patient information, such as demographics and comorbid conditions, to EWS to improve assessment (DeVita et al., 2010). Smith et.al showed that adding age to a single VS parameter tracking system improved mortality prediction (Smith et al., 2008). Possibly incorporating more variables such as gender, comorbidities, diagnoses and procedures could further improve CRI-model prediction capabilities.

I.1.7 Future directions

Collecting continuous physiologic monitoring data in SDUs opens the door for refining systems at the bedside that can more sensitively and specifically detect overt CRI or, ideally, predict its occurrence without caregiver presence. Cao et al. analyzed the MIMIC II database of ICU patients, which consists of capture of minute-by-minute heart rate (HR) and arterial blood pressure (BP) monitoring data, in over 1875 adult ICU patients. They reported that entering

continuous and streaming input of HR and invasive BP measurements into a logistic regression model allowed prediction of CRI, defined as patients needing vasopressor augmentation to maintain normal blood pressure at least two hours before its overt manifestation (Cao et al., 2008). Although this and other models and clinical algorithms have been developed to predict CRI in the ICU (Eshelman et al., 2008), tools have not been adapted for SDU patients, in part due to only intermittent recording of vital signs (VS), and use of noninvasive monitoring parameters.

Hravnak et al. used an integrated monitoring system (IMS) which continuously integrates HR, RR, BP and SpO2 using a previously trained neural network (Tarassenko, Hann, & Young, 2006) which generated a single-parameter IMS index value (INDEX) ranging from 0 (no CRI) to 10 (severe CRI) to determine if use of such a system was able to decrease the length of time that patients were in an unstable state on an SDU (Hravnak et al., 2008). An alert was generated if the INDEX was > 3.2 which, per their implementation algorithm, called for the nurse to go immediately to the bedside and evaluate the patient. Nurses could then decide whether they should activate the MET, perform further evaluation and nursing interventions, or call upon the provider. This IMS INDEX correlated significantly with CRI concern criteria, usually occurring before overt instability and demonstrated use of the IMS resulted in a 60% decrease in the overall duration of SDU patient instability and decreased the number of patients progressing from mild instability to serious instability by 58% (Hravnak et al., 2011).

I.1.8 Implications for Clinical Practice

Newly developed technology and EWS offer the promise of better detection and recognition of CRI, but are imperfect. MET activation presents the advantage of bringing a skilled team immediately to the bedside to assist in care triage, but can only act when summoned. Despite a vast literature devoted to identifying ways to detect CRI sooner, and extensive resources dedicated to developing technology designed to reliably detect CRI, problems continue to persist. Absent a "perfect" solution, nurse surveillance continues to be a critical factor. To encourage best practices in recognizing CRI at the bedside, the following are recommended:

Establish clear guidelines for initiating a MET call: METs have been driven by the belief that they make hospitals safer by preventing adverse events that lead to CRI. To fully embrace this system, nurses need clear and established unit-based guidelines for initiating a MET. Nurses within a particular unit can develop a form to record and organize information about the patient's condition prior to every MET activation, as well as interventions needed. Such information could be used for quality-improvement team-based interventions as well as a repository for staff education.

Provide education regarding adverse outcomes: Staff must be educated about the importance of accurate VS measurements and adverse outcomes. There must be proper training and strict adherence to standards especially by care technicians and early notification of the primary nurse or other care providers (or MET activation) when CRI is detected.

Avoid behaviors that discourage prompt notification: Since nurses value access to MET activation and RRS, barriers to MET activation such as criticism of actions, their expertise in providing care, etc. should be avoided. Nurses who believe their actions positively impact patient outcomes are more likely to implement them.

Share positive outcomes following CRI detection with the team as a way of promoting best practices. Staff nurses need verification of the positive results of their actions. Too often, the focus is on what did not succeed, rather than success.

Regardless of the approach used, nursing surveillance is critically important in detecting CRI. Research directed towards improving and enhancing the ability of nurses to monitor caseloads of patients and recognize evolving CRI earlier in SDUs will ensure better patient outcomes.

References

Aiken, L. H., Cimiotti, J. P., Sloane, D. M., Smith, H. L., Flynn, L., & Neff, D. F. (2011). The effects of nurse staffing and nurse education on patient deaths in hospitals with different nurse work environments. *Medical care, 49*(12), 1047.

Alam, N., Hobbelink, E., van Tienhoven, A., van de Ven, P., Jansma, E., & Nanayakkara, P. (2014). The impact of the use of the Early Warning Score (EWS) on patient outcomes: A systematic review. *Resuscitation, 85*(5), 587-594.

Alverson, D. C., Shannon, S., Sullivan, E., Prill, A., Effertz, G., Helitzer, D., . . . Preston, A. (2004). Telehealth in the trenches: reporting back from the frontlines in rural America. *Telemedicine Journal & e-Health, 10*(Supplement 2), S-95-S-109.

Armitage, M., Eddleston, J., & Stokes, T. (2007). NICE guidelines: Recognising and responding to acute illness in adults in hospital: Summary of NICE guidance. *BMJ: British Medical Journal, 335*(7613), 258.

Beaudoin, L. E., & Edgar, L. (2003). Hassles: their importance to nurses' quality of work life. *Nurs Econ, 21*(3), 106-113.

Blegen, M. A., Goode, C. J., Park, S. H., Vaughn, T., & Spetz, J. (2013). Baccalaureate education in nursing and patient outcomes. *Journal of Nursing Administration, 43*(2), 89-94.

Bloom, H. L., Shukrullah, I., Cuellar, J. R., Lloyd, M. S., Dudley, S. C., & Zafari, A. M. (2007). Long-term survival after successful inhospital cardiac arrest resuscitation. *American heart journal, 153*(5), 831-836.

Breslow, M. J. (2007). Remote ICU care programs: current status. *Journal of critical care, 22*(1), 66-76.

Buist, M., Bernard, S., Nguyen, T. V., Moore, G., & Anderson, J. (2004). Association between clinically abnormal observations and subsequent in-hospital mortality: a prospective study. *Resuscitation, 62*(2), 137-141.

Bulechek, G. M., Butcher, H. K., Dochterman, J. M. M., & Wagner, C. (2013). *Nursing interventions classification (NIC)*: Elsevier Health Sciences.

Cao, H., Eshelman, L., Chbat, N., Nielsen, L., Gross, B., & Saeed, M. (2008). *Predicting ICU hemodynamic instability using continuous multiparameter trends.* Paper presented at the

Engineering in Medicine and Biology Society, 2008. EMBS 2008. 30th Annual International Conference of the IEEE.

Chan, P. S., Jain, R., Nallmothu, B. K., Berg, R. A., & Sasson, C. (2010). Rapid response teams: a systematic review and meta-analysis. *Archives of internal medicine, 170*(1), 18-26.

Chen, J., Bellomo, R., Flabouris, A., Hillman, K., Finfer, S., Centre, M. S. I. f. t. S., & Group, A. C. T. (2009). The relationship between early emergency team calls and serious adverse events. *Critical care medicine, 37*(1), 148-153.

Churpek, M. M., Yuen, T. C., Park, S. Y., Gibbons, R., & Edelson, D. P. (2014). Using electronic health record data to develop and validate a prediction model for adverse outcomes in the wards. *Crit Care Med, 42*(4), 841-848. doi: 10.1097/ccm.0000000000000038

DeVita, M. A., Smith, G. B., Adam, S. K., Adams-Pizarro, I., Buist, M., Bellomo, R., . . . Winters, B. (2010). "Identifying the hospitalised patient in crisis"--a consensus conference on the afferent limb of rapid response systems. *Resuscitation, 81*(4), 375-382. doi: 10.1016/j.resuscitation.2009.12.008

Dresser, S. (2012). The role of nursing surveillance in keeping patients safe. *Journal of Nursing Administration, 42*(7/8), 361-368.

Ebright, P. R., Patterson, E. S., Chalko, B. A., & Render, M. L. (2003). Understanding the complexity of registered nurse work in acute care settings. *Journal of Nursing Administration, 33*(12), 630-638.

Eshelman, L. J., Lee, K., Frassica, J. J., Zong, W., Nielsen, L., & Saeed, M. (2008). *Development and evaluation of predictive alerts for hemodynamic instability in ICU patients.* Paper presented at the AMIA Annual Symposium Proceedings.

Galhotra, S., DeVita, M. A., Simmons, R. L., & Dew, M. A. (2007). Mature rapid response system and potentially avoidable cardiopulmonary arrests in hospital. *Quality and Safety in Health Care, 16*(4), 260-265.

Gardner-Thorpe, J., Love, N., Wrightson, J., Walsh, S., & Keeling, N. (2006). The value of Modified Early Warning Score (MEWS) in surgical in-patients: a prospective observational study. *Annals of The Royal College of Surgeons of England, 88*(6), 571.

Henneman, E. A., Gawlinski, A., & Giuliano, K. K. (2012). Surveillance: a strategy for improving patient safety in acute and critical care units. *Critical Care Nurse, 32*(2), e9-e18.

Hillman, K., Chen, J., Cretikos, M., Bellomo, R., Brown, D., Doig, G., . . . Investigators, M. S. (2005). Introduction of the medical emergency team (MET) system: a cluster-randomised controlled trial. *Lancet, 365*(9477), 2091-2097.

Hoffmann, D., & Rowthorn, V. (2011). Legal impediments to the diffusion of telemedicine. *J. Health Care L. & Pol'y, 14*, 1.

Hravnak, M., DeVita, M. A., Clontz, A., Edwards, L., Valenta, C., & Pinsky, M. R. (2011). Cardiorespiratory instability before and after implementing an integrated monitoring system. *Critical care medicine, 39*(1), 65.

Hravnak, M., Edwards, L., Clontz, A., Valenta, C., DeVita, M. A., & Pinsky, M. R. (2008). Defining the incidence of cardiorespiratory instability in patients in step-down units using an electronic integrated monitoring system. *Archives of internal medicine, 168*(12), 1300-1308.

Jones, D. A., DeVita, M. A., & Bellomo, R. (2011). Rapid-response teams. *New England Journal of Medicine, 365*(2), 139-146.

Kahn, J. M., Cicero, B. D., Wallace, D. J., & Iwashyna, T. J. (2014). Adoption of ICU telemedicine in the United States. *Critical care medicine, 42*(2), 362-368.

Kerlin, M. P., Small, D. S., Cooney, E., Fuchs, B. D., Bellini, L. M., Mikkelsen, M. E., . . . Harhay, M. O. (2013). A randomized trial of nighttime physician staffing in an intensive care unit. *New England Journal of Medicine, 368*(23), 2201-2209.

Kollef, M. H., Chen, Y., Heard, K., LaRossa, G. N., Lu, C., Martin, N. R., . . . Bailey, T. (2014). A randomized trial of real-time automated clinical deterioration alerts sent to a rapid response team. *J Hosp Med, 9*(7), 424-429. doi: 10.1002/jhm.2193

Kumar, G., Falk, D. M., Bonello, R. S., Kahn, J. M., Perencevich, E., & Cram, P. (2013). The costs of critical care telemedicine programs: a systematic review and analysis. *Chest Journal, 143*(1), 19-29.

Litvak, E., & Pronovost, P. J. (2010). Rethinking rapid response teams. *Jama, 304*(12), 1375-1376.

Ludikhuize, J., Dongelmans, D. A., Smorenburg, S. M., Gans-Langelaar, M., de Jonge, E., & de Rooij, S. E. (2012). How nurses and physicians judge their own quality of care for deteriorating patients on medical wards: Self-assessment of quality of care is suboptimal. *Critical care medicine, 40*(11), 2982-2986.

Ludikhuize, J., Smorenburg, S. M., de Rooij, S. E., & de Jonge, E. (2012). Identification of deteriorating patients on general wards; measurement of vital parameters and potential effectiveness of the Modified Early Warning Score. *Journal of critical care, 27*(4), 424. e427-424. e413.

Ludikhuize, J., Borgert, M., Binnekade, J., Subbe, C., Dongelmans, D., & Goossens, A. (2014). Standardized measurement of the Modified Early Warning Score results in enhanced implementation of a Rapid Response System: a quasi-experimental study. *Resuscitation, 85*(5), 676-682. doi: 10.1016/j.resuscitation.2014.02.009

Moehr, J. R., Schaafsma, J., Anglin, C., Pantazi, S. V., Grimm, N. A., & Anglin, S. (2006). Success factors for telehealth—a case study. *International Journal of Medical Informatics, 75*(10), 755-763.

Needleman, J., Buerhaus, P., Pankratz, V. S., Leibson, C. L., Stevens, S. R., & Harris, M. (2011). Nurse staffing and inpatient hospital mortality. *New England Journal of Medicine, 364*(11), 1037-1045.

Page, A. (2004). *Keeping Patients Safe:: Transforming the Work Environment of Nurses*: National Academies Press.

Patrician, P. A., Loan, L., McCarthy, M., Fridman, M., Donaldson, N., Bingham, M., & Brosch, L. R. (2011). The association of shift-level nurse staffing with adverse patient events. *Journal of Nursing Administration, 41*(2), 64-70.

Potter, P., Wolf, L., Boxerman, S., Grayson, D., Sledge, J., Dunagan, C., & Evanoff, B. (2005). Understanding the cognitive work of nursing in the acute care environment. *Journal of Nursing Administration, 35*(7-8), 327-335.

Prytherch, D. R., Smith, G. B., Schmidt, P. E., & Featherstone, P. I. (2010). ViEWS—towards a national early warning score for detecting adult inpatient deterioration. *Resuscitation, 81*(8), 932-937.

Ries, M. (2009). Tele-ICU: a new paradigm in critical care. *International anesthesiology clinics, 47*(1), 153-170.

Romero-Brufau, S., Huddleston, J. M., Naessens, J. M., Johnson, M. G., Hickman, J., Morlan, B. W., . . . Santrach, P. J. (2014). Widely used track and trigger scores: are they ready for automation in practice? *Resuscitation, 85*(4), 549-552. doi: 10.1016/j.resuscitation.2013.12.017

Rozen, T. H., Mullane, S., Kaufman, M., Hsiao, Y.-F. F., Warrillow, S., Bellomo, R., & Jones, D. A. (2014). Antecedents to cardiac arrests in a teaching hospital intensive care unit. *Resuscitation, 85*(3), 411-417.

Sao, D., Gupta, A., & Gantz, D. A. (2012). Legal and regulatory barriers to telemedicine in the United States: public and private approaches toward health care reform. *The Globalization of Health Care: Legal and Ethical Issues (I. Glenn Cohen ed., Oxford University Press 2013), Forthcoming*.

Schmid-Mazzoccoli, A., Hoffman, L., Wolf, G., Happ, M., & Devita, M. (2008). The use of medical emergency teams in medical and surgical patients: impact of patient, nurse and organisational characteristics. *Quality and Safety in Health Care, 17*(5), 377-381.

Sharpley, J. T., & Holden, J. C. (2004). Introducing an early warning scoring system in a district general hospital. *Nursing in critical care, 9*(3), 98-103.

Smith, G. B., Prytherch, D. R., Meredith, P., Schmidt, P. E., & Featherstone, P. I. (2013). The ability of the National Early Warning Score (NEWS) to discriminate patients at risk of early cardiac arrest, unanticipated intensive care unit admission, and death. *Resuscitation, 84*(4), 465-470.

Smith, G. B., Prytherch, D. R., Schmidt, P., Featherstone, P. I., Knight, D., Clements, G., & Mohammed, M. A. (2006). Hospital-wide physiological surveillance–a new approach to the early identification and management of the sick patient. *Resuscitation, 71*(1), 19-28.

Smith, G. B., Prytherch, D. R., Schmidt, P. E., Featherstone, P. I., Kellett, J., Deane, B., & Higgins, B. (2008). Should age be included as a component of track and trigger systems used to identify sick adult patients? *Resuscitation, 78*(2), 109-115.

Subbe, C. P., Gao, H., & Harrison, D. A. (2007). Reproducibility of physiological track-and-trigger warning systems for identifying at-risk patients on the ward. *Intensive care medicine*, *33*(4), 619-624.

Tarassenko, L., Hann, A., & Young, D. (2006). Integrated monitoring and analysis for early warning of patient deterioration. *British Journal of Anaesthesia*, *97*(1), 64-68.

Trinkle, R. M., & Flabouris, A. (2011). Documenting Rapid Response System afferent limb failure and associated patient outcomes. *Resuscitation*, *82*(7), 810-814.

Venkataraman, R., & Ramakrishnan, N. (2015). Outcomes Related to Telemedicine in the Intensive Care Unit: What We Know and Would Like to Know. *Critical Care Clinics*.

Whitten, P. S., & Mackert, M. S. (2005). Addressing telehealth's foremost barrier: provider as initial gatekeeper. *International journal of technology assessment in health care*, *21*(04), 517-521.

Winters, B. D., Weaver, S. J., Pfoh, E. R., Yang, T., Pham, J. C., & Dy, S. M. (2013). Rapid-response systems as a patient safety strategy: a systematic review. *Annals of internal medicine*, *158*(5_Part_2), 417-425.

Wootton, R. (2012). Twenty years of telemedicine in chronic disease management–an evidence synthesis. *Journal of telemedicine and telecare*, *18*(4), 211-220.

Table 1: Example of thresholds of vital sign abnormalities of changes in patient condition used to "track" for instability and the "trigger" deployment of the Medical Emergency Team (Hravnak et al., 2008)

Cardiorespiratory system
Respirations < 8/min or > 36/min
New onset of breathing difficulty
New pulse oximeter reading < 85% for > 5 minutes, unless patient is known to have chronic hypoxemia
Heart rate < 40 beats/min or >140 beats/min with new symptoms or any rate > 160 beats/min
Blood pressure: systolic < 80 or >200 mm Hg or diastolic 110 mm Hg with symptoms (neurologic change, chest pain, or breathing difficulty)
Neurologic system
Acute loss of consciousness
New onset of lethargy or difficulty in waking
Sudden collapse
Seizure (outside of seizure monitoring unit)
Sudden loss of mobility (or weakness) of face, arm, or leg
Other criteria
More than 1 stat page required to assemble MET needed to respond to a crisis
Patient report of (cardiac) chest pain (unresponsive to nitroglycerine or physician unavailable)
Color change in patient or extremity to pale, dusky, gray or blue
Unexplained agitation for > 10 min
Suicide attempt
Uncontrolled bleeding
Bleeding into airway
Naloxone hydrochloride use without immediate response
Large volume of short-term blood loss
Crash cart must be used for rapid delivery of medications

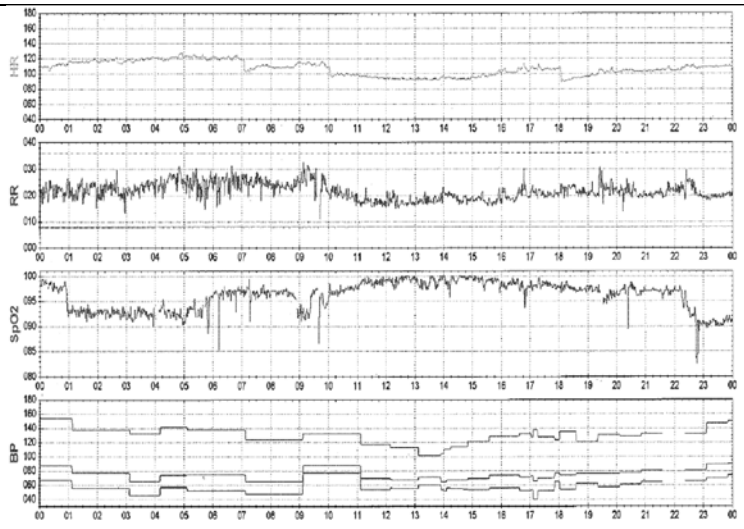
Table 2: The National Early Warning Score (NEWS) (adapted from Smith et al., 2013)

Physiological Parameters	3	2	1	0	1	2	3
Respiration Rate (bpm)	≤ 8		9-11	12-20		21-24	≥ 25
Oxygen Saturation (%)	≤ 91	92-93	94-95	≥96			
Any Supplemental Oxygen		Yes		No			
Temperature (^{o}C)	< 35.0		35.1-36.0	36.1-38.0	38.1-39.0	≥ 39.1	
Systolic BP (mm Hg)	≤ 90	91-100	101-110	111-219			≥ 220
Heart Rate	≤ 40		41-50	51-90	91-110	111-130	≥ 131
Level of Consciousness				A			V,P,U

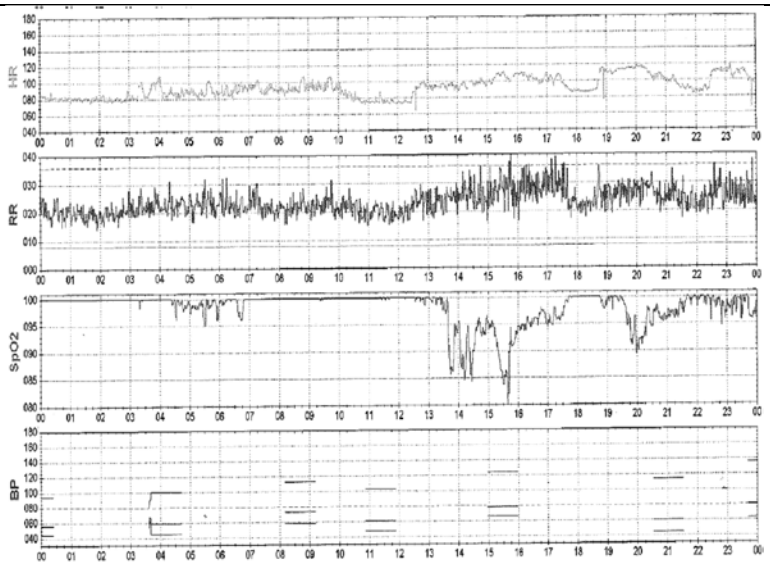
Definition of abbreviations: A = alert; V = responds to voice; P = responds to pain; U = unresponsive

Figure 1: Waxing and waning of vital signs over time between normal and abnormal as patients proceed to overt cardiorespiratory instability (CRI).

Patient 1: This patient's CRI evolves progressively over 23 hours. Between 0300 and 0500, there is increasing respiratory rate(RR) with mild changes in pulse oximetry(SpO_2). Patient remains stable from 1100 to 1630, after which increasing RR is accompanied by low SpO_2. Around 1930 patient develops increasing RR with drop in SpO_2. An hour later, at 2030, there is a significant drop in both RR and SpO_2 until past 2230, the patient developed overt CRI.



Patient 2: This patient is stable until 1200, after which there is increasing heart rate (HR), increasing RR and a drop in SpO_2. Between 1330 and 1430, the patient experienced waxing and waning of SpO_2 with increasing RR, until finally around 1530, the patient developed overt CRI.



BIBLIOGRAPHY

Aksoy, Olcay, & Rodriguez, Leonardo. (2013). Tamponade *Cardiovascular Hemodynamics* (pp. 181-196): Springer.

Alizadeh, Ash A, Eisen, Michael B, Davis, R Eric, Ma, Chi, Lossos, Izidore S, Rosenwald, Andreas, . . . Yu, Xin. (2000). Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature, 403*(6769), 503-511.

Alon, Uri, Barkai, Naama, Notterman, Daniel A, Gish, Kurt, Ybarra, Suzanne, Mack, Daniel, & Levine, Arnold J. (1999). Broad patterns of gene expression revealed by clustering analysis of tumor and normal colon tissues probed by oligonucleotide arrays. *Proceedings of the National Academy of Sciences, 96*(12), 6745-6750.

Alousi, AA, & Johnson, DC. (1986). Pharmacology of the bipyridines: amrinone and milrinone. *Circulation, 73*(3 Pt 2), III10-24.

Andreopoulos, Bill, An, Aijun, Wang, Xiaogang, & Schroeder, Michael. (2009). A roadmap of clustering algorithms: finding a match for a biomedical application. *Briefings in Bioinformatics, 10*(3), 297-314.

Antman, Elliott M, Anbe, Daniel T, Armstrong, Paul Wayne, Bates, Eric R, Green, Lee A, Hand, Mary, . . . Lamas, Gervasio A. (2004). ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summaryA report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). *Journal of the American College of Cardiology, 44*(3), 671-719.

Barnett, Lionel, & Seth, Anil K. (2014). The MVGC multivariate Granger causality toolbox: A new approach to Granger-causal inference. *Journal of neuroscience methods, 223*, 50-68.

Bellomo, R., Chapman, M., Finfer, S., Hickling, K., & Myburgh, J. (2000). Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. *Lancet, 356*(9248), 2139-2143.

Bellomo, Rinaldo, Kellum, John, & Ronco, Claudio. (2001). Acute renal failure: time for consensus. *Intensive care medicine, 27*(11), 1685-1688.

Berman, Marius, Tsui, Steven, Vuylsteke, Alain, Klein, Andrew, & Jenkins, David P. (2008). Life-threatening right ventricular failure in pulmonary hypertension: RVAD or ECMO? *The Journal of Heart and Lung Transplantation, 27*(10), 1188-1189.

Bleyer, Anthony J, Vidya, Sri, Russell, Gregory B, Jones, Catherine M, Sujata, Leon, Daeihagh, Pirouz, & Hire, Donald. (2011). Longitudinal analysis of one million vital signs in patients in an academic medical center. *Resuscitation, 82*(11), 1387-1392.

Blow, Osbert, Magliore, Lissa, Claridge, Jeffrey A, Butler, Kathy, & Young, Jeffrey S. (1999). The golden hour and the silver day: detection and correction of occult hypoperfusion within 24 hours improves outcome from major trauma. *Journal of Trauma and Acute Care Surgery, 47*(5), 964.

Bouachour, G, Tirot, P, Varache, N, Gouello, JP, Harry, P, & Alquier, PH. (1994). Hemodynamic changes in acute adrenal insufficiency. *Intensive care medicine, 20*(2), 138-141.

Boulain, Thierry, Runge, Isabelle, Bercault, Nicolas, Benzekri-Lefevre, Dalila, Wolf, Manuel, & Fleury, Christian. (2009). Dopamine therapy in septic shock: Detrimental effect on survival? *Journal of critical care, 24*(4), 575-582.

Box, George EP, Jenkins, Gwilym M, & Reinsel, Gregory C. (2013). *Time series analysis: forecasting and control*: John Wiley & Sons.

Boyd, Owen, Grounds, R Michael, & Bennett, E David. (1993). A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. *Jama, 270*(22), 2699-2707.

Buist, Michael, Bernard, Stephen, Nguyen, Tuan V, Moore, Gaye, & Anderson, Jeremy. (2004). Association between clinically abnormal observations and subsequent in-hospital mortality: a prospective study. *Resuscitation, 62*(2), 137-141.

Chan, Paul S, Jain, Renuka, Nallmothu, Brahmajee K, Berg, Robert A, & Sasson, Comilla. (2010). Rapid response teams: a systematic review and meta-analysis. *Archives of Internal Medicine, 170*(1), 18-26.

Chen, Jonathan M, Levin, Howard R, Rose, Eric A, Addonizio, Linda J, Landry, Donald W, Sistino, Joseph J, . . . Oz, Mehmet C. (1996). Experience with right ventricular assist devices for perioperative right-sided circulatory failure. *The Annals of thoracic surgery, 61*(1), 305-310.

Chertow, MD, Glenn, M, Levy, MD, Elliott, M, Hammermeister, MD, Karl, E, . . . Daley, MD. (1998). Independent association between acute renal failure and mortality following cardiac surgery. *The American journal of medicine, 104*(4), 343-348.

Claridge, Jeffrey A, Crabtree, Traves D, Pelletier, Shawn J, Butler, Kathy, Sawyer, Robert G, & Young, Jeffrey S. (2000). Persistent occult hypoperfusion is associated with a significant increase in infection rate and mortality in major trauma patients. *Journal of Trauma-Injury, Infection, and Critical Care, 48*(1), 8.

Claussen, Mark S, Landercasper, Jeffrey, & Cogbill, Thomas H. (1992). Acute adrenal insufficiency presenting as shock after trauma and surgery: three cases and review of the literature. *Journal of Trauma-Injury, Infection, and Critical Care, 32*(1), 94-100.

Cretikos, Michelle, Chen, Jack, Hillman, Ken, Bellomo, Rinaldo, Finfer, Simon, & Flabouris, Arthas. (2007). The objective medical emergency team activation criteria: a case–control study. *Resuscitation, 73*(1), 62-72.

Crouser, Elliott D. (2004). Mitochondrial dysfunction in septic shock and multiple organ dysfunction syndrome. *Mitochondrion, 4*(5), 729-741.

Crump, Cindy, Saxena, Sunil, Wilson, Bruce, Farrell, Patrick, Rafiq, Azhar, & Silvers, Christine Tsien. (2009). *Using Bayesian Networks and Rule-Based Trending to Predict Patient*

Status in the Intensive Care Unit. Paper presented at the AMIA Annual Symposium Proceedings.

D'Alonzo, Gilbert E, Barst, Robyn J, Ayres, Stephen M, Bergofsky, Edward H, Brundage, Bruce H, Detre, Katherine M, . . . Kernis, Janet T. (1991). Survival in patients with primary pulmonary hypertensionResults from a national prospective registry. *Annals of internal medicine, 115*(5), 343-349.

Damiano, RJ, La Follette, P, Cox, JL, Lowe, JE, & Santamore, WP. (1991). Significant left ventricular contribution to right ventricular systolic function. *American Journal of Physiology-Heart and Circulatory Physiology, 261*(5), H1514-H1524.

De Backer, Daniel, Biston, Patrick, Devriendt, Jacques, Madl, Christian, Chochrad, Didier, Aldecoa, Cesar, . . . Vincent, Jean-Louis. (2010). Comparison of dopamine and norepinephrine in the treatment of shock. *New England Journal of Medicine, 362*(9), 779-789.

De Backer, Daniel, Hollenberg, Steven, Boerma, Christiaan, Goedhart, Peter, Büchele, Gustavo, Ospina-Tascon, Gustavo, . . . Ince, Can. (2007). How to evaluate the microcirculation: report of a round table conference. *Critical Care, 11*(5), R101.

Dei Cas, L, Metra, M, & Visioli, O. (1989). Clinical pharmacology of inodilators. *Journal of cardiovascular pharmacology, 14*, S60-S71.

Dellinger, R Phillip, Levy, Mitchell M, Carlet, Jean M, Bion, Julian, Parker, Margaret M, Jaeschke, Roman, . . . Beale, Richard. (2008). Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Intensive care medicine, 34*(1), 17-60.

DeVita, Michael A, Bellomo, Rinaldo, Hillman, Kenneth, Kellum, John, Rotondi, Armando, Teres, Dan, . . . Kenward, Gary. (2006). Findings of the first consensus conference on medical emergency teams*. *Critical care medicine, 34*(9), 2463-2478.

Dresser, Susan. (2012). The role of nursing surveillance in keeping patients safe. *Journal of Nursing Administration, 42*(7/8), 361-368.

Earl, CQ, Linden, J, & Weglicki, WB. (1985). Biochemical mechanisms for the inotropic effect of the cardiotonic drug milrinone. *Journal of cardiovascular pharmacology, 8*(4), 864-872.

Emery, Robert W, & Joyce, Lyle D. (1991). Directions in cardiac assistance. *Journal of cardiac surgery, 6*(3), 400-414.

Everitt, BS, Landau, S, & Leese, M. (2001). Cluster Analysis Arnold. *A member of the Hodder Headline Group, London*.

Farrar, David J, Hill, J Donald, Pennington, D Glenn, McBride, Lawrence R, Holman, William L, Kormos, Robert L, . . . Schoettle, G Phillip. (1997). Preoperative and postoperative comparison of patients with univentricular and biventricular support with the Thoratec ventricular assist device as a bridge to cardiac transplantation. *The Journal of thoracic and cardiovascular surgery, 113*(1), 202-209.

Fiddian-Green, Richard G, Haglund, Ulf, Gutierrez, Guillermo, & Shoemaker, William C. (1993). Goals for the resuscitation of shock. *Critical care medicine, 21*(2), S25-31.

Fieselmann, John F, Hendryx, Michael S, Helms, Charles M, & Wakefield, Douglas S. (1993). Respiratory rate predicts cardiopulmonary arrest for internal medicine inpatients. *Journal of general internal medicine, 8*(7), 354-360.

Figueiredo, Mário AT, Cheng, Dong Seon, & Murino, Vittorio. (2007). Clustering under prior knowledge with application to image segmentation. *Advances in Neural Information Processing Systems, 19*, 401.

Fink, Mitchell P, Abraham, Edward, Vincent, Jean-Louis, & Kochanek, Patrick. (2005). *Textbook of critical care: with e-dition*: Elsevier Saunders.

Fink, MP. (1996). Does tissue acidosis in sepsis indicate tissue hypoperfusion? *Intensive care medicine, 22*(11), 1144-1146.

Follath, F, Cleland, JGF, Just, H, Papp, JGY, Scholz, H, Peuhkurinen, K, . . . Sandell, EP. (2002). Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. *The Lancet, 360*(9328), 196-202.

Fonger, JD, Borkon, AM, Baumgartner, WA, Achuff, SC, Augustine, S, & Reitz, BA. (1985). Acute right ventricular failure following heart transplantation: improvement with prostaglandin E1 and right ventricular assist. *The Journal of heart transplantation, 5*(4), 317-321.

Frazier, OH, Rose, Eric A, Macmanus, Quentin, Burton, Nelson A, Lefrak, Edward A, Poirier, Victor L, & Dasse, Kurt A. (1992). Multicenter clinical evaluation of the HeartMate 1000 IP left ventricular assist device. *The Annals of thoracic surgery, 53*(6), 1080-1090.

Gao, Haiyan, McDonnell, Ann, Harrison, David A, Moore, Tracey, Adam, Sheila, Daly, Kathleen, . . . Rashidian, Arash. (2007). Systematic review and evaluation of physiological track and trigger warning systems for identifying at-risk patients on the ward. *Intensive care medicine, 33*(4), 667-679.

Garber, Mitchell E, Troyanskaya, Olga G, Schluens, Karsten, Petersen, Simone, Thaesler, Zsuzsanna, Pacyna-Gengelbach, Manuela, . . . Whyte, Richard I. (2001). Diversity of gene expression in adenocarcinoma of the lung. *Proceedings of the National Academy of Sciences, 98*(24), 13784-13789.

Gelman, Simon, & Mushlin, Phillip S. (2004). Catecholamine-induced changes in the splanchnic circulation affecting systemic hemodynamics. *Anesthesiology, 100*(2), 434-439.

Giesler, Gregory M, Gomez, Jaime S, Letsou, George, Vooletich, Mary, & Smalling, Richard W. (2006). Initial report of percutaneous right ventricular assist for right ventricular shock secondary to right ventricular infarction. *Catheterization and cardiovascular interventions, 68*(2), 263-266.

Goebel, Rainer, Roebroeck, Alard, Kim, Dae-Shik, & Formisano, Elia. (2003). Investigating directed cortical interactions in time-resolved fMRI data using vector autoregressive modeling and Granger causality mapping. *Magnetic resonance imaging, 21*(10), 1251-1261.

Goldhill, DR, & McNarry, AF. (2004). Physiological abnormalities in early warning scores are related to mortality in adult inpatients†. *British Journal of Anaesthesia, 92*(6), 882-884.

Goldhill, DR, McNarry, AF, Mandersloot, G, & McGinley, A. (2005). A physiologically-based early warning score for ward patients: the association between score and outcome*. *Anaesthesia, 60*(6), 547-553.

Goldstein, Daniel J, Oz, Mehmet C, & Rose, Eric A. (1998). Implantable left ventricular assist devices. *New England Journal of Medicine, 339*(21), 1522-1533.

Goodwin, Linda, VanDyne, Michele, Lin, Simon, & Talbert, Steven. (2003). Data mining issues and opportunities for building nursing knowledge. *Journal of Biomedical Informatics, 36*(4), 379-388.

Granger, Clive William John, & Newbold, Paul. (2014). *Forecasting economic time series*: Academic Press.

Gruen, Russell L, Jurkovich, Gregory J, McIntyre, Lisa K, Foy, Hugh M, & Maier, Ronald V. (2006). Patterns of errors contributing to trauma mortality: lessons learned from 2594 deaths. *Annals of Surgery, 244*(3), 371.

Gupta, Dilip, Saul, Melissa, & Gilbertson, John. (2004). Evaluation of a deidentification (De-Id) software engine to share pathology reports and clinical documents for research. *American journal of clinical pathology, 121*(2), 176-186.

Hack, C Erik, & Zeerleder, Sacha. (2001). The endothelium in sepsis: source of and a target for inflammation. *Critical care medicine, 29*(7), S21-S27.

Haikala, Heimo, Kaheinen, Petri, Levijoki, Jouko, & Lindén, Inge-Britt. (1997). The role of cAMP-and cGMP-dependent protein kinases in the cardiac actions of the new calcium sensitizer, levosimendan. *Cardiovascular research, 34*(3), 536-546.

Haikala, Heimo, Kaivola, Juha, Nissinen, Erkki, Wall, Pŵi, Levijoki, Jouko, & Lindén, Inge-Britt. (1995). Cardiac troponin C as a target protein for a novel calcium sensitizing drug, levosimendan. *Journal of molecular and cellular cardiology, 27*(9), 1859-1866.

Haikala, Heimo, Nissinen, Erkki, Etemadzadeh, Ehsan, Levijoki, Jouko, & Lindén, Inge-Britt. (1995). Troponin C-mediated calcium sensitization induced by levosimendan does not impair relaxation. *Journal of cardiovascular pharmacology, 25*(5), 794-801.

Hakim, Raymond M, Wingard, Rebecca L, & Parker, Robert A. (1994). Effect of the dialysis membrane in the treatment of patients with acute renal failure. *New England Journal of Medicine, 331*(20), 1338-1342.

Hansen, Mark H, & Yu, Bin. (2001). Model selection and the principle of minimum description length. *Journal of the American Statistical Association, 96*(454), 746-774.

Hayes, Michelle A, Timmins, Andrew C, Yau, Ernest, Palazzo, Mark, Hinds, Charles J, & Watson, David. (1994). Elevation of systemic oxygen delivery in the treatment of critically ill patients. *New England Journal of Medicine, 330*(24), 1717-1722.

Hennein, Hani A, Ebba, Hailu, Rodriguez, Jorge L, Merrick, Scot H, Keith, Fraser M, Bronstein, Merrill H, . . . Rankin, J Scott. (1994). Relationship of the proinflammatory cytokines to myocardial ischemia and dysfunction after uncomplicated coronary revascularization. *The Journal of thoracic and cardiovascular surgery, 108*(4), 626-635.

Henneman, Elizabeth A, Gawlinski, Anna, & Giuliano, Karen K. (2012). Surveillance: a strategy for improving patient safety in acute and critical care units. *Critical Care Nurse, 32*(2), e9-e18.

Hernandez, G., Bruhn, A., Luengo, C., Regueira, T., Kattan, E., Fuentealba, A., . . . Ince, C. (2013). Effects of dobutamine on systemic, regional and microcirculatory perfusion parameters in septic shock: a randomized, placebo-controlled, double-blind, crossover study. *Intensive Care Med, 39*(8), 1435-1443. doi: 10.1007/s00134-013-2982-0

Hillman, Ken, Chen, Jack, Cretikos, Michelle, Bellomo, Rinaldo, Brown, Daniel, Doig, Gordon, . . . Investigators, MERIT Study. (2005). Introduction of the medical emergency team (MET) system: a cluster-randomised controlled trial. *Lancet, 365*(9477), 2091-2097.

Hodgetts, Timothy J, Kenward, Gary, Vlachonikolis, Ioannis G, Payne, Susan, & Castle, Nicolas. (2002). The identification of risk factors for cardiac arrest and formulation of activation criteria to alert a medical emergency team. *Resuscitation, 54*(2), 125-131.

Hollenberg, Steven M, Ahrens, Tom S, Annane, Djillali, Astiz, Mark E, Chalfin, Donald B, Dasta, Joseph F, . . . Susla, Gregory M. (2004). Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update. *Critical care medicine, 32*(9), 1928-1948.

Honda, Katsuhiro, Notsu, Akira, & Ichihashi, Hidetomo. (2010). Fuzzy PCA-Guided Robust-Means Clustering. *Fuzzy Systems, IEEE Transactions on, 18*(1), 67-79.

Hravnak, Marilyn, DeVita, Michael A, Clontz, Amy, Edwards, Leslie, Valenta, Cynthia, & Pinsky, Michael R. (2011). Cardiorespiratory instability before and after implementing an integrated monitoring system. *Critical care medicine, 39*(1), 65.

Hravnak, Marilyn, Edwards, Leslie, Clontz, Amy, Valenta, Cynthia, DeVita, Michael A, & Pinsky, Michael R. (2008). Defining the incidence of cardiorespiratory instability in patients in step-down units using an electronic integrated monitoring system. *Archives of internal medicine, 168*(12), 1300-1308.

Hravnak, Marilyn, Schmid, Andrea, Ott, Lora, & Pinsky, Michael R. (2011). Causes of failure to rescue *Textbook of Rapid Response Systems* (pp. 141-150): Springer.

Imhoff, M, & Bauer, M. (1996). Time series analysis in critical care monitoring. *New horizons (Baltimore, Md.), 4*(4), 519-531.

Imhoff, Michael, Bauer, Marcus, Gather, Ursula, & Löhlein, Dietrich. (1998). Time series analysis in intensive care medicine: Technical Report, SFB 475: Komplexitätsreduktion in Multivariaten Datenstrukturen, Universität Dortmund.

Iyer, Vishwanath R, Eisen, Michael B, Ross, Douglas T, Schuler, Greg, Moore, Troy, Lee, Jeffrey CF, . . . Boguski, Mark S. (1999). The transcriptional program in the response of human fibroblasts to serum. *Science, 283*(5398), 83-87.

Jain, Anil K. (2010). Data clustering: 50 years beyond K-means. *Pattern Recognition Letters, 31*(8), 651-666.

Jain, Anil K, & Dubes, Richard C. (1988). *Algorithms for clustering data*: Prentice-Hall, Inc.

James, J Howard, Luchette, Fred A, McCarter, Freda D, & Fischer, Josef E. (1999). Lactate is an unreliable indicator of tissue hypoxia in injury or sepsis. *The lancet, 354*(9177), 505-508.

Jones, D., & Bellomo, R. (2005). Renal-dose dopamine: from hypothesis to paradigm to dogma to myth and, finally, superstition? *J Intensive Care Med, 20*(4), 199-211. doi: 10.1177/0885066605276963

Jones, Daryl, Duke, Graeme, Green, John, Briedis, Juris, Bellomo, Rinaldo, Casamento, Andrew, . . . Way, Margaret. (2006). Medical emergency team syndromes and an approach to their management. *Critical care, 10*(1), R30.

Jubran, Amal. (1999). Pulse oximetry. *Crit Care, 3*(2), R11-R17.

Jun, Min, Heerspink, Hiddo J Lambers, Ninomiya, Toshiharu, Gallagher, Martin, Bellomo, Rinaldo, Myburgh, John, . . . Perkovic, Vlado. (2010). Intensities of renal replacement therapy in acute kidney injury: a systematic review and meta-analysis. *Clinical Journal of the American Society of Nephrology, 5*(6), 956-963.

Kaufman, Leonard, & Rousseeuw, Peter J. (2009). *Finding groups in data: an introduction to cluster analysis* (Vol. 344): John Wiley & Sons.

Kellum, John A, & Pinsky, Michael R. (2002). Use of vasopressor agents in critically ill patients. *Current opinion in critical care, 8*(3), 236-241.

Kenward, Gary, Castle, Nicolas, Hodgetts, Timothy, & Shaikh, Loua. (2004). Evaluation of a medical emergency team one year after implementation. *Resuscitation, 61*(3), 257-263.

Kern, Jack W, & Shoemaker, William C. (2002). Meta-analysis of hemodynamic optimization in high-risk patients*. *Critical care medicine, 30*(8), 1686-1692.

Kersten, Judy R, Montgomery, Matthew W, Pagel, Paul S, & Warltier, David C. (2000). Levosimendan, a new positive inotropic drug, decreases myocardial infarct size via activation of KATP channels. *Anesthesia & Analgesia, 90*(1), 5.

Kiss, Zelma HT, & Tator, Charles H. (1993). Neurogenic shock. *Shock and Resuscitation. New York, NY: McGraw-Hill*, 421-440.

Klein, Neal A, Siskind, Steve J, Frishman, William H, Sonnenblick, Edmund H, & Lejemtel, Thierry H. (1981). Hemodynamic comparison of intravenous amrinone and dobutamine in patients with chronic congestive heart failure. *The American journal of cardiology, 48*(1), 170-175.

Kwon, Steve, Thompson, Rachel, Florence, Michael, Maier, Ronald, McIntyre, Lisa, Rogers, Terry, . . . Flum, David R. (2012). β-blocker continuation after noncardiac surgery: a report from the surgical care and outcomes assessment program. *Archives of Surgery, 147*(5), 467-473.

Landesberg, G, Luria, MH, Cotev, S, Eidelman, LA, Anner, H, Mosseri, M, . . . Berlatzky, Y. (1993). Importance of long-duration postoperative ST-segment depression in cardiac morbidity after vascular surgery. *The Lancet, 341*(8847), 715-719.

Lee, A, Bishop, G, Hillman, KM, & Daffurn, K. (1995). The medical emergency team. *Anaesthesia and intensive care, 23*(2), 183-186.

Lipskaia, Larissa, Chemaly, Elie R, Hadri, Lahouaria, Lompre, Anne-Marie, & Hajjar, Roger J. (2010). Sarcoplasmic reticulum Ca2+ ATPase as a therapeutic target for heart failure. *Expert opinion on biological therapy, 10*(1), 29-41.

Loeb, Henry S, Winslow, Edward BJ, Rahimtoola, Shahbudin H, Rosen, Kenneth M, & Gunnar, Rolf M. (1971). Acute hemodynamic effects of dopamine in patients with shock. *Circulation, 44*(2), 163-173.

Lucas, Peter. (2004). Bayesian analysis, pattern analysis, and data mining in health care. *Current opinion in critical care, 10*(5), 399-403.

Ludikhuize, Jeroen, Dongelmans, Dave A, Smorenburg, Susanne M, Gans-Langelaar, Miranda, de Jonge, Evert, & de Rooij, Sophia E. (2012). How nurses and physicians judge their own quality of care for deteriorating patients on medical wards: Self-assessment of quality of care is suboptimal*. *Critical care medicine, 40*(11), 2982-2986.

Lund, Lars H, Matthews, Jennifer, & Aaronson, Keith. (2010). Patient selection for left ventricular assist devices. *European journal of heart failure, 12*(5), 434-443.

Luz, Paula M, Mendes, Beatriz VM, Codeço, Claudia T, Struchiner, Claudio J, & Galvani, Alison P. (2008). Time series analysis of dengue incidence in Rio de Janeiro, Brazil. *The American journal of tropical medicine and hygiene, 79*(6), 933-939.

Lynn, L. A., & Curry, J. P. (2011). Patterns of unexpected in-hospital deaths: a root cause analysis. *Patient Saf Surg, 5*(1), 3. doi: 10.1186/1754-9493-5-3

Maas, Jacinta J, Pinsky, Michael R, de Wilde, Rob B, de Jonge, Evert, & Jansen, Jos R. (2013). Cardiac Output Response to Norepinephrine in Postoperative Cardiac Surgery Patients:

Interpretation With Venous Return and Cardiac Function Curves*. *Critical care medicine, 41*(1), 143-150.

Martin, Claude, Viviand, Xavier, Leone, Marc, & Thirion, Xavier. (2000). Effect of norepinephrine on the outcome of septic shock. *Critical care medicine, 28*(8), 2758-2765.

McLaughlin, Vallerie V, Archer, Stephen L, Badesch, David B, Barst, Robyn J, Farber, Harrison W, Lindner, Jonathan R, . . . Rosenson, Robert S. (2009). ACCF/AHA 2009 Expert Consensus Document on Pulmonary HypertensionA Report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association Developed in Collaboration With the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *Journal of the American College of Cardiology, 53*(17), 1573-1619.

Mehta, Navdeep K, & Pinsky, Michael R. (1998). Pharmacologic support of the hemodynamically unstable patient *Critical Care Nephrology* (pp. 43-50): Springer.

Menon, Venu, White, Harvey, LeJemtel, Thierry, Webb, John G, Sleeper, Lynn A, & Hochman, Judith S. (2000). The clinical profile of patients with suspected cardiogenic shock due to predominant left ventricular failure: a report from the SHOCK Trial Registry. *Journal of the American College of Cardiology, 36*(3s1), 1071-1076.

Michard, Frederic, Boussat, Sandrine, Chemla, Denis, Anguel, Nadia, Mercat, Alain, Lecarpentier, Yves, . . . Teboul, Jean-Louis. (2000). Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. *American Journal of Respiratory and Critical Care Medicine, 162*(1), 134-138.

Miura, Masahito, Hattori, Taiki, Murai, Naomi, Nagano, Tsuyoshi, Nishio, Taichi, Boyden, Penelope A, & Shindoh, Chiyohiko. (2012). Regional increase in extracellular potassium can be arrhythmogenic due to nonuniform muscle contraction in rat ventricular muscle. *American Journal of Physiology-Heart and Circulatory Physiology, 302*(11), H2301-H2309.

Moiseyev, VS, Poder, P, Andrejevs, N, Ruda, MY, Golikov, AP, Lazebnik, LB, . . . Nieminen, Markku S. (2002). Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction. A randomized, placebo-controlled, double-blind study (RUSSLAN). *European heart journal, 23*(18), 1422-1432.

Moore, Frederick A, McKinley, Bruce A, & Moore, Ernest E. (2004). The next generation in shock resuscitation. *The Lancet, 363*(9425), 1988-1996.

Moreau, Yves, De Smet, Frank, Thijs, Gert, Marchal, Kathleen, & De Moor, Bart. (2002). Functional bioinformatics of microarray data: from expression to regulation. *Proceedings of the IEEE, 90*(11), 1722-1743.

Müllner, M, Urbanek, B, Havel, C, Losert, H, Waechter, F, & Gamper, G. (2004). Vasopressors for shock. *Cochrane Database Syst Rev, 3*.

Nagarsheth, Nimesh P, Pinney, Sean, Bassily-Marcus, Adel, Anyanwu, Anelechi, Friedman, Lynn, & Beilin, Yaakov. (2008). Successful placement of a right ventricular assist device for treatment of a presumed amniotic fluid embolism. *Anesthesia & Analgesia, 107*(3), 962-964.

Nattel, Stanley. (2011). From guidelines to bench: implications of unresolved clinical issues for basic investigations of atrial fibrillation mechanisms. *Canadian Journal of Cardiology, 27*(1), 19-26.

Nieminen, Markku S, Akkila, Juha, Hasenfuss, Gerd, Kleber, Franz X, Lehtonen, Lasse A, Mitrovic, Veselin, . . . Remme, Willem J. (2000). Hemodynamic and neurohumoral effects of continuous infusion of levosimendan in patients with congestive heart failure. *Journal of the American College of Cardiology, 36*(6), 1903-1912.

O'Connor, Christopher M, Gattis, Wendy A, Uretsky, Barry F, Adams Jr, Kirkwood F, McNulty, Steven E, Grossman, Steven H, . . . Gheorghiade, Mihai. (1999). Continuous intravenous dobutamine is associated with an increased risk of death in patients with advanced heart failure: insights from the Flolan International Randomized Survival Trial (FIRST). *American heart journal, 138*(1), 78-86.

Oddis, Carmine V, & Finkel, Mitchell S. (1997). Cytokines and nitric oxide synthase inhibitor as mediators of adrenergic refractoriness in cardiac myocytes. *European journal of pharmacology, 320*(2), 167-174.

Pae, WE, & Pierce, WS. (1981). Temporary left ventricular assistance in acute myocardial infarction and cardiogenic shock: rationale and criteria for utilization. *CHEST Journal, 79*(6), 692-695.

Parissis, John T, Farmakis, Dimitrios, & Nieminen, Markku. (2007). Classical inotropes and new cardiac enhancers. *Heart failure reviews, 12*(2), 149-156.

Parks, Jennifer K, Elliott, Alan C, Gentilello, Larry M, & Shafi, Shahid. (2006). Systemic hypotension is a late marker of shock after trauma: a validation study of Advanced Trauma Life Support principles in a large national sample. *The American journal of surgery, 192*(6), 727-731.

Paterson, R, MacLeod, DC, Thetford, D, Beattie, A, Graham, C, Lam, S, & Bell, D. (2006). Prediction of in-hospital mortality and length of stay using an early warning scoring system: clinical audit. *Clinical Medicine, 6*(3), 281-284.

Pennington, DG, Reedy, JE, Swartz, MT, McBride, LR, Seacord, LM, Naunheim, KS, & Miller, LW. (1990). Univentricular versus biventricular assist device support. *The Journal of heart and lung transplantation: the official publication of the International Society for Heart Transplantation, 10*(2), 258-263.

Perdue, Philip W, Balser, Jeffrey R, Lipsett, Pamela A, & Breslow, Michael J. (1998). " Renal dose" dopamine in surgical patients: dogma or science? *Annals of surgery, 227*(4), 470.

Pinsky, Michael R. (1998). Applied cardiovascular physiology *Critical Care Nephrology* (pp. 1-8): Springer.

Pinsky, Michael R. (1998a). Rationale and application of physiologic monitoring *Critical Care Nephrology* (pp. 33-42): Springer.

Pinsky, Michael R. (2005). Assessment of indices of preload and volume responsiveness. *Current opinion in critical care, 11*(3), 235-239.

Pinsky, Michael R. (2006). Clinical significance of pulmonary artery occlusion pressure *Applied Physiology in Intensive Care Medicine* (pp. 53-56): Springer.

Pinsky, Michael R. (2007). CHEST Postgraduate Education Corner. *CHEST, 132*, 2020-2029.

Pinsky, Michael R. (2007). Heart–lung interactions. *Current opinion in critical care, 13*(5), 528-531.

Pinsky, Michael R. (2007). Hemodynamic evaluation and monitoring in the ICU. *CHEST Journal, 132*(6), 2020-2029.
Pinsky, Michael R. (2012). Pulmonary artery occlusion pressure *Applied Physiology in Intensive Care Medicine 1* (pp. 83-86): Springer.
Pinsky, Michael R, & Payen, Didier. (2005). Functional hemodynamic monitoring. *Critical Care, 9*(6), 566.
Pinsky, Michael R, & Rico, Phillipe. (2000). Cardiac contractility is not depressed in early canine endotoxic shock. *American journal of respiratory and critical care medicine, 161*(4), 1087-1093.
Pinsky, MR. (2002). Functional hemodynamic monitoring: applied physiology at the bedside *Intensive Care Medicine* (pp. 537-552): Springer.
Pinsky, MR. (2005). Protocolized cardiovascular management based on ventricular-arterial coupling *Functional hemodynamic monitoring* (pp. 381-395): Springer.
Pinsky, MR. (2009). Functional Hemodynamic Monitoring: A Personal Perspective *Intensive Care Medicine* (pp. 306-310): Springer.
Piper, Greta L, & Kaplan, Lewis J. (2012). Fluid and electrolyte management for the surgical patient. *Surgical Clinics of North America, 92*(2), 189-205.
Potapov, Evgenij V, Stepanenko, Alexander, Krabatsch, Thomas, & Hetzer, Roland. (2011). Managing long-term complications of left ventricular assist device therapy. *Current opinion in cardiology, 26*(3), 237-244.
Rabuel, C, & Mebazaa, A_. (2006). Septic shock: a heart story since the 1960s. *Intensive care medicine, 32*(6), 799-807.
Ragaller, Maximilian JR, Theilen, Hermann, & Koch, Thea. (2001). Volume replacement in critically ill patients with acute renal failure. *Journal of the American Society of Nephrology, 12*(suppl 1), S33-S39.
Rahbari, N. N., Zimmermann, J. B., Schmidt, T., Koch, M., Weigand, M. A., & Weitz, J. (2009). Meta-analysis of standard, restrictive and supplemental fluid administration in colorectal surgery. *Br J Surg, 96*(4), 331-341. doi: 10.1002/bjs.6552
Reichert, Thomas A, Simonsen, Lone, Sharma, Ashutosh, Pardo, Scott A, Fedson, David S, & Miller, Mark A. (2004). Influenza and the winter increase in mortality in the United States, 1959–1999. *American Journal of Epidemiology, 160*(5), 492-502.
Rivers, Emanuel P, Ander, Douglas S, & Powell, Doris. (2001). Central venous oxygen saturation monitoring in the critically ill patient. *Current opinion in critical care, 7*(3), 204-211.
Rivers, Emanuel P, Nguyen, H Bryant, Huang, David T, & Donnino, Michael. (2004). Early goal-directed therapy. *Critical care medicine, 32*(1), 314-315.
Roebroeck, Alard, Formisano, Elia, & Goebel, Rainer. (2005). Mapping directed influence over the brain using Granger causality and fMRI. *Neuroimage, 25*(1), 230-242.
Ronco, Claudio, Bellomo, Rinaldo, & Ricci, Zaccaria. (2001). Continuous renal replacement therapy in critically ill patients. *Nephrology Dialysis Transplantation, 16*(suppl 5), 67-72.
Sabharwal, MD, Paramjeet, Fishel, MD, Rhonda S, & Breslow, MD, Michael J. (1998). Adrenal Insufficiency--An Unusual Cause of Shock in postoperative patients. *Endocrine Practice, 4*(6), 387-390.
Sakr, Yasser, Reinhart, Konrad, Vincent, Jean-Louis, Sprung, Charles L, Moreno, Rui, Ranieri, V Marco, . . . Payen, Didier. (2006). Does dopamine administration in shock influence

outcome? Results of the Sepsis Occurrence in Acutely Ill Patients (SOAP) Study. *Crit Care Med, 34*(3), 589-597.

Sander, Olaf, Welters, Ingeborg D, Foëx, Pierre, & Sear, John W. (2005). Impact of prolonged elevated heart rate on incidence of major cardiac events in critically ill patients with a high risk of cardiac complications*. *Critical care medicine, 33*(1), 81-88.

Sapolsky, Robert M, Romero, L Michael, & Munck, Allan U. (2000). How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions 1. *Endocrine reviews, 21*(1), 55-89.

Scherf, Uwe, Ross, Douglas T, Waltham, Mark, Smith, Lawrence H, Lee, Jae K, Tanabe, Lorraine, . . . Andrews, Darren T. (2000). A gene expression database for the molecular pharmacology of cancer. *Nature genetics, 24*(3), 236-244.

Schmid-Mazzoccoli, A, Hoffman, LA, Wolf, GA, Happ, MB, & Devita, MA. (2008). The use of medical emergency teams in medical and surgical patients: impact of patient, nurse and organisational characteristics. *Quality and Safety in Health Care, 17*(5), 377-381.

Sear, J. W. (2005). Kidney dysfunction in the postoperative period. *Br J Anaesth, 95*(1), 20-32. doi: 10.1093/bja/aei018

Shoemaker, William C. (1996). Oxygen transport and oxygen metabolism in shock and critical illness: invasive and noninvasive monitoring of circulatory dysfunction and shock. *Critical care clinics, 12*(4), 939-969.

Silber, Jeffrey H, Williams, Sankey V, Krakauer, Henry, & Schwartz, J Sanford. (1992). Hospital and patient characteristics associated with death after surgery: a study of adverse occurrence and failure to rescue. *Medical care*, 615-629.

Silva, Eliézer, De Backer, Daniel, Creteur, Jacques, & Vincent, Jean-Louis. (2004). Effects of fluid challenge on gastric mucosal PCO2 in septic patients. *Intensive care medicine, 30*(3), 423-429.

Simon, Marc A, & Pinsky, Michael R. (2011). Right ventricular dysfunction and failure in chronic pressure overload. *Cardiology research and practice, 2011*.

Skomedal, Tor, Borthne, Kjell, Aass, Halfdan, Geiran, Odd, & Osnes, Jan-Bjørn. (1997). Comparison between alpha-1 adrenoceptor-mediated and beta adrenoceptor-mediated inotropic components elicited by norepinephrine in failing human ventricular muscle. *Journal of Pharmacology and Experimental Therapeutics, 280*(2), 721-729.

Slawsky, Mara T, Colucci, Wilson S, Gottlieb, Stephen S, Greenberg, Barry H, Haeusslein, Ernest, Hare, Joshua, . . . Loh, Evan. (2000). Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. *Circulation, 102*(18), 2222-2227.

Smith, AD. (1973). Mechanisms involved in the release of noradrenaline from sympathetic nerves. *British Medical Bulletin, 29*(2), 123-129.

Smith, Gary B, Prytherch, David R, Schmidt, Paul E, & Featherstone, Peter I. (2008). Review and performance evaluation of aggregate weighted 'track and trigger'systems. *Resuscitation, 77*(2), 170-179.

Smith, Gary B, Prytherch, David R, Schmidt, Paul E, Featherstone, Peter I, & Higgins, Bernie. (2008). A review, and performance evaluation, of single-parameter "track and trigger" systems. *Resuscitation, 79*(1), 11-21.

Smith, Gary B, Prytherch, David R, Schmidt, Paul E, Featherstone, Peter I, Kellett, John, Deane, Breda, & Higgins, Bernie. (2008). Should age be included as a component of track and trigger systems used to identify sick adult patients? *Resuscitation, 78*(2), 109-115.

Spodick, David H. (1998). Pathophysiology of cardiac tamponade. *CHEST Journal, 113*(5), 1372-1378.

Stein, Phyllis K, Barzilay, Joshua I, Chaves, Paulo HM, Mistretta, Stephanie Q, Domitrovich, Peter P, Gottdiener, John S, . . . Kleiger, Robert E. (2008). Novel measures of heart rate variability predict cardiovascular mortality in older adults independent of traditional cardiovascular risk factors: the Cardiovascular Health Study (CHS). *Journal of cardiovascular electrophysiology, 19*(11), 1169-1174.

Su, Ting, & Dy, Jennifer. (2004). *A deterministic method for initializing k-means clustering.* Paper presented at the Tools with Artificial Intelligence, 2004. ICTAI 2004. 16th IEEE International Conference on.

Subbe, CP, Davies, RG, Williams, E, Rutherford, P, & Gemmell, L. (2003). Effect of introducing the Modified Early Warning score on clinical outcomes, cardio-pulmonary arrests and intensive care utilisation in acute medical admissions*. *Anaesthesia, 58*(8), 797-802.

Subbe, CP, Kruger, M, Rutherford, P, & Gemmel, L. (2001). Validation of a modified Early Warning Score in medical admissions. *Qjm, 94*(10), 521-526.

Tang, W., Bressler, S. L., Sylvester, C. M., Shulman, G. L., & Corbetta, M. (2012). Measuring Granger causality between cortical regions from voxelwise fMRI BOLD signals with LASSO. *PLoS Comput Biol, 8*(5), e1002513. doi: 10.1371/journal.pcbi.1002513

Theodoridis, Sergios, & Koutroumbas, Konstantinos. (2008). Pattern recognition. *IEEE TRANSACTIONS ON NEURAL NETWORKS, 19*(2), 376.

Torbicki, Adam, Perrier, Arnaud, Konstantinides, Stavros, Agnelli, Giancarlo, Galiè, Nazzareno, Pruszczyk, Piotr, . . . Janssens, Uwe. (2008). Guidelines on the diagnosis and management of acute pulmonary embolism The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). *European heart journal, 29*(18), 2276-2315.

Trzeciak, Stephen, McCoy, Jonathan V, Dellinger, R Phillip, Arnold, Ryan C, Rizzuto, Michael, Abate, Nicole L, . . . Hollenberg, Steven M. (2008). Early increases in microcirculatory perfusion during protocol-directed resuscitation are associated with reduced multi-organ failure at 24 h in patients with sepsis. *Intensive care medicine, 34*(12), 2210-2217.

Tsukui, Hiroyuki, Teuteberg, Jeffrey J, Murali, Srinivas, McNamara, Dennis M, Buchanan, Julianne R, Winowich, Stephen, . . . Kormos, Robert L. (2005). Biventricular assist device utilization for patients with morbid congestive heart failure A justifiable strategy. *Circulation, 112*(9 suppl), I-65-I-72.

Ungar, Andrea, Fumagalli, Stefano, Marini, Maurizio, Di Serio, Claudia, Tarantini, Francesca, Boncinelli, Lorenzo, . . . Olianti, Catia. (2004). Renal, but not systemic, hemodynamic effects of dopamine are influenced by the severity of congestive heart failure*. *Critical care medicine, 32*(5), 1125-1129.

Unverferth, Donald V, Blanford, Marvin, Kates, Robert E, & Leier, Carl V. (1980). Tolerance to dobutamine after a 72 hour continuous infusion. *The American journal of medicine, 69*(2), 262-266.

Van Der Linden, P., James, M., Mythen, M., & Weiskopf, R. B. (2013). Safety of modern starches used during surgery. *Anesth Analg, 116*(1), 35-48. doi: 10.1213/ANE.0b013e31827175da

Vincent, Jean-Louis, Abraham, Edward, Kochanek, Patrick, Moore, Frederick A, & Fink, Mitchell P. (2011). *Textbook of Critical Care: Expert Consult Premium*: Elsevier Health Sciences.

Voelkel, Norbert F, Quaife, Robert A, Leinwand, Leslie A, Barst, Robyn J, McGoon, Michael D, Meldrum, Daniel R, . . . Smart, Frank W. (2006). Right Ventricular Function and Failure Report of a National Heart, Lung, and Blood Institute Working Group on Cellular and Molecular Mechanisms of Right Heart Failure. *Circulation, 114*(17), 1883-1891.

Weil, Max Harry, & Shubin, Herbert. (1968). Shock following acute myocardial infarction current understanding of hemodynamic mechanisms. *Progress in cardiovascular diseases, 11*(1), 1-17.

Westfall, Thomas C, & Westfall, David P. (2006). Adrenergic agonists and antagonists. *Goodman and Gilman's The Pharmacological Basis of Therapeutics, 11th ed. Edited by Brunton LL, Lazo JS, Parker KL. New York, McGraw-Hill*, 237-315.

Westphal, M., James, M. F., Kozek-Langenecker, S., Stocker, R., Guidet, B., & Van Aken, H. (2009). Hydroxyethyl starches: different products--different effects. *Anesthesiology, 111*(1), 187-202. doi: 10.1097/ALN.0b013e3181a7ec82

Wild, Beate, Eichler, Michael, Friederich, Hans-Christoph, Hartmann, Mechthild, Zipfel, Stephan, & Herzog, Wolfgang. (2010). A graphical vector autoregressive modelling approach to the analysis of electronic diary data. *BMC medical research methodology, 10*(1), 28.

Winslow, Edward J, Loeb, Henry S, Rahimtoola, Shahbudin H, Kamath, Savitri, & Gunnar, Rolf M. (1973). Hemodynamic studies and results of therapy in 50 patients with bacteremic shock. *The American journal of medicine, 54*(4), 421-432.

Xu, Rui, & Wunsch, Don. (2008). *Clustering* (Vol. 10): John Wiley & Sons.

Xu, Rui, & Wunsch, Donald. (2005). Survey of clustering algorithms. *Neural Networks, IEEE Transactions on, 16*(3), 645-678.

Yi, J, Du, CT, Wang, RH, & Liu, L. (2007). [Applications of multiple seasonal autoregressive integrated moving average (ARIMA) model on predictive incidence of tuberculosis]. *Zhonghua yu fang yi xue za zhi [Chinese journal of preventive medicine], 41*(2), 118-121.

Yokoshiki, Hisashi, Katsube, Yasuhiro, Sunagawa, Masanori, & Sperelakis, Nicholas. (1997). Levosimendan, a novel Ca< sup> 2+</sup> sensitizer, activates the glibenclamide-sensitive K< sup>+</sup> channel in rat arterial myocytes. *European journal of pharmacology, 333*(2), 249-259.

Yousef, Khalil, Pinsky, Michael R, DeVita, Michael A, Sereika, Susan, & Hravnak, Marilyn. (2012). Characteristics of Patients With Cardiorespiratory Instability in a Step-down Unit. *American Journal of Critical Care, 21*(5), 344-350.