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Cardiovascular Lability As A Potential New Predictor Of Post-Operative Patient Prognosis In The Intensive Care Unit

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CARDIOVASCULAR LABILITY AS A POTENTIAL NEW PREDICTOR OF POST-OPERATIVE PATIENT PROGNOSIS IN THE INTENSIVE CARE UNIT

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Measuring individual patient outcomes in the intensive care unit (ICU) has been a difficult task at best. Multiple ICU scoring systems have been developed which are best used for assessing overall ICU performance. Recently the APGAR score, a simple metric based on worst cardiovascular parameters in operating room, has been designed to determine morbidity and mortality in post-surgical ICU patients. Cardiovascular instability is very likely an important key to assessing and predicting poor outcomes. Beat-to-beat variability and blood pressure variability have been well characterized. The hypothesis for this study was that cardiovascular instability, as measured by lability in heart rate and blood pressure during the ICU stay, yields information that is different than the current ICU and APGAR scoring systems. This study captured ICU data on 10 post-operative patients at 5 minute intervals. Fluctuations over ICU stay in blood pressure and heart rate were measured as range, interquartile range, and coefficient of variation. These measures were analyzed to determine if they correlated with ICU and APGAR scores. Our results show that range, interquartile range, and coefficient of variation for heart rate, arterial systolic blood pressure, and diastolic blood pressure do not correlate with the scores and so provide different information that may better reflect a patient's instability and thus outcomes. From this work, we hope to develop more studies especially focused on morbidity and mortality outcomes.

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INTRODUCTION

I. The role of assessment of Intensive Care Unit Patients

The intensive care unit (ICU) houses the sickest patients in the hospital, however these patients are not otherwise uniform or alike. No specific guidelines or criteria exist that dictate which patients get admitted to the ICU – there is no standardization in the type of disease/pathology, organ(s) involved, extent of progression of disease, hemodynamic instability, length of illness (chronic or acute), age, or really any other factor. Patients may have anything from myocardial infarction to infection to renal failure. As such, ICU patients have a wide variety of morbidities/diagnoses and capacity for recovery, and as a result have a wide range of outcomes including prognosis, length of stay, and morbidity.

The ability to assess the severity of illness, prognosis of patients and outcomes in the intensive care unit can be helpful for multiple reasons. (1) These reasons are not limited to but include

1. Improving decision making for clinical management especially with respect to therapeutic intervention: The ability to assess the severity of illness and prognosis of the patient may help in determining the suitability of a patient to try novel therapies. This is currently done for trials of potential therapies for sepsis and ARDS. rhAPC is given in the case of sepsis for patients with a calculated APACHE score above a certain threshold based on the PROWESS trial. (2)Interestingly, in these models, patients are assigned either 0 or 1 (to receive an intervention or not) but the model predicts a risk in the range of 0-1. Therefore, it may not be perfect for each individual patient especially since these models do not factor in how strong a patient's response to the

therapy will be. Nevertheless, it does provide a cut-off in helping to decide whether to provide a certain intervention, especially if that intervention is very costly (see #2).

2. Optimizing resource allocation: This is linked to #1 but expands well beyond it. Evaluating and understanding an ICU's resource allocation requires a more long-term evaluation of a specific ICU's performance. Such an evaluation with severity scores could be used to triage patients with lower scores to less expensive inpatient settings. The Therapeutic Intervention Scoring System (TISS), for example, a severity of illness score, reports workload and costs to evaluate and measure nursing workload. This is well correlated to APACHE III and IV. (3-6)

Knowing certain factors can help optimize resource allocation. These include determining which patients are sicker via markers like mortality, ICU length of stay, and readmission rate. (1)

While it would be helpful to predict which patients are sicker to optimize resource allocation, studies have not been able to show a correlation with mortality and length of stay that are reliably predictable. (7, 8) It seems that inter-hospital variability in practice and as such geography may play a role in this and so one study, CALICO found that APACHE IV and MPM3 more accurate at predicting ICU length of stay in California where the population is more similar geographically and temporally to populations used for the newer models.(9)

Resource allocation can also be improved if ICU length of stay can be predicted. A weighted hospital days model was created based on four variables: mortality rate, percentage of unscheduled surgical patients, mechanical ventilation within 1 hour of

ICU admission and patient discharge to post acute care facility. (7) This is helpful in that this model can predict at an ICU level (not individual level) the predicted length of stay. Length of stay will be discussed in greater detail, as it is becoming more and more important in our cost-conscientious health care system.

It would also be useful to determine which patients are most likely to get readmitted; similar factors are used to predict readmission rates for ICU but no definitive model has emerged at this time. (10)

3. Evaluating ICU performance against peer units: This would allow for quality improvement and standardization of care and possibly outcomes in the ICU by comparing patients with similar baseline risks in the two (or more) ICU settings being evaluated side-by-side. Furthermore, it would allow for benchmarking, i.e. allowing for a comparison of one ICU to similar ICUs at other hospitals or within the same hospital or comparing the ICU to itself over a certain period of time. For example, studies have compared open and closed ICUs. Severity-of-illness scores have been helpful in evaluating ICU performance by explaining variation in resource utilization/costs and length of ICU stay. (11, 12) One must beware of referral bias in which ICUs that receive transfer patients will likely have worse outcomes. (13-15)

4. Stratifying patient by extent of illness can aid in research design. Risk stratification allows for easy identification of patients with similar risk who then can then be randomized for randomized controlled trials. (1)

Given so many potential uses, how to measure ICU outcomes and better evaluated performance? Potential outcomes that can be measured include mortality,

morbidity, disability, cognitive dysfunction, length of ICU stay, cost, duration of ICU therapy, nosocomial infection rates, and procedure complications(1). Outcomes such as morbidity and mortality are affected by multiple variables(15, 16), mean ICU length of stay is skewed by the long staying outliers(17), and of course long term resource use, return to work, quality of life, 1- or 5-year survival require intensive follow-up(18, 19). Some have suggested using retrospective data, i.e. insurance codes for billing to obtain diagnoses. However, in very ill patients, especially with multiple morbidities, this method will result in the loss of additional but important diagnoses that may not have been coded for(20).

II. Severity of Illness Scoring Systems: General concepts

For the purpose of measuring ICU outcomes, especially length of stay and mortality, predictive scoring systems evaluating specifically ICU patients have been developed. These systems take into account several clinical variables including physiologic parameters, laboratory values, chronic disease status, neurologic function, etc. and compiles it into a numerical score to quantify the severity of illness. In some models, these scores can be plotted to a regression that can give a prediction of an outcome, for example the outcome being the likelihood of mortality.

Four major predictive scoring systems currently exist – The Acute Physiologic and Chronic Health Evaluation (APACHE) systems, the Simplified Acute Physiologic Score (SAPS) the Mortality Prediction Model (MPM), and Sequential Organ Failure Assessment (SOFA). As a side note, other scoring systems were created to assess organ dysfunction, trauma cases, and burn victims but here the focus will be the severity of illness scoring systems.

Generally speaking, there are a few basics to understanding predicative scoring systems. It is helpful to have a brief understanding of how to develop and assess the predictive scoring instrument.

The process by which to develop a strong and sensible severity of illness model is as follows(1):

1. define outcomes (usually long-term mortality or functional status)
2. Identify/define predictor variables: data versus expert opinions*
3. collect data: ensure accuracy with reabstraction/kappa analysis**
4. examine continuous variables and transform or dichotomize
5. univariate analysis against outcomes
6. multivariate analysis
7. consider interactions between variables***
8. develop score that relates variables to outcome
9. test calibration: Hosmer-Lemeshow method
10. test discrimination: ROC
11. validate model with independent data/split sample, jackknife techniques
12. external validation in new setting
13. publish

*Most of the scoring systems chose variables to include such as physiologic data, lab values, diagnoses (acute and chronic), age, requirement of ventilation and/or cardiopulmonary resuscitation, comorbidities/organ dysfunction (coma/cirrhosis, etc.) amongst others.

**Data collection requires large populations. Most of the scoring systems use patients of upwards of the tens of thousands.

***With respect to data analysis and making a regression, limit the number of terms to 10% of the number of patients having the outcome of interest to avoid over fitting the model to the developmental dataset. It is also helpful to recognize additive/cancelling or synergistic relationships between terms in the model.

The most common measure of ICU performance is the standardized mortality ratio (SMR), which is ratio of the observed mortality to expected mortality with a mean value +/- the 95% confidence interval. (1)

Once the data are collected and analysis done, it is important to determine whether the scoring system is actually a good one (see #9 and #10): one that is predictive and accurate. This is done by analyzing the regression and its discrimination and calibration. (21) Discrimination is defined as the accuracy of a given prediction from the regression. For example, if the predictive scoring system predicts a mortality of 85%, and the mortality is 85% then the discrimination is perfect. The most accepted and standard way to determine discrimination is to appreciate the area under the receiver operating characteristic (ROC) curve. An ROC of 0.5 is no better than chance; values > 0.7 are acceptable, 0.8 is excellent and 0.9 is outstanding. (22) Calibration is defined how precise the scoring system is over the entire range of values. For example, a highly predictive scoring system is one that is accurate at mortalities of 10% as well as mortality of 90% and everything in between. The Hosmer-Lemeshow C statistic is used for this.

A regression should calibrate and discriminate well when applied to a new population, i.e. it should be validated in a separate cohort(see #12). (23) Generally speaking, populations of ICU admissions for the creating a scoring system and thus regression should be diverse, not all low risk or specialized diagnosis. (24, 25) Not surprisingly, predictive scoring systems cannot predict outcomes for populations that were not included in the derivation data sets.

Calibration can be affected by different ICU types as mentioned above, admission diagnoses, with the passage of time, and by applying to different geographic regions. (26) First, admission diagnoses can make a tremendous difference and so some scores have been especially designed for specific diagnoses, for example the APACHE II score for pancreatitis. Second, models can deteriorate over time and drift out of calibration as interventions/populations change, so the models need to be constantly updated. (27)This is why updated models have been published for each of the major severity of illness scores every 10-15 years. (5, 6, 28-35) Third, location matters and so a model may only be applicable in certain geographic settings. New validation/recalibration may be necessary if applied to new geographic settings. (36) The reasons for differences in calibration with geography include regional differences in practices of care, differences in acuity mix, or differences in the age of the patient population. (26) To correct for this geographical factor, some European governments have used only patients from their country to better calibrate the severity of illness score that they are employing for their ICU patients.

Another interesting facet of interpreting severity of illness metrics is appreciating how one's individual ICU's operations and processes differ from the reference ICUs used to built the severity of illness models. (26) Some hospitals may easily be able to transfer patients to other hospitals, which would result in lower mortality rates. Conversely, tertiary care centers do not have that option and so may have higher mortality rates. Another issues may be that some hospitals may have better and easier access to alternative care sites, such as long-term acute care facilities, and so fewer of these patients will stay long enough in the ICU to pass away there. Most obviously, available resources within the ICU, quality of sign out and transition from shift-to-shift by the staff, and cooperation between different teams providing services for the same patient will also affect morbidity and mortality.

Current scoring systems are not perfect and there are many biases and problems to consider. For example, oftentimes physicians and nurses have better intuition in figuring out survivors and non-survivors than these scores and so the scores may not be actually helpful for individual patients. (37) Another issue is that ICU patients who come through the emergency department are stabilized by the emergency department physician so that they have lower ICU admission scores, although they may in fact be very sick. The converse is that ICU patients who do not come through an emergency department may in fact have very abnormal vital signs that may predict higher mortality predictions but these vital signs may correct with some basic treatments – this creating a lower actual-to-predicted mortality ratio) and improving the mortality and outcome statistics for that ICU. (38) And yet another example is that by the 24-hour point in the ICU, a treatment has usually already been given and the speed and

correctness with which the intervention was done will affect the patient's score and mortality/prognosis. (39) Finally, most of the scoring systems are specific but insensitive in predicting death.(1) In general they are excellent for assessing ICU performance by comparing outcomes within the treated population to reference population used to develop and validate the score. (26) However, there has been little utility for these scores with respect to managing individual patients and since physician/nursing intuition is as good as the score, there has been very little utility for it in predicting individual patient outcomes unless the scores are specific to a diagnosis, e..g APACHE II and acute pancreatitis.

Perhaps an even greater pitfall is misapplication of the scoring system by the user herself. Some of the pitfalls in the application of these systems include

1. data collection and entry error: the user may incorrectly include ineligible patients, forget or be missing certain variables, incorrectly transcribe the data, or select the wrong diagnosis. Miscommunication between hospital clinical and risk adjustment applications may also results in errors. (40)
2. Misapplication of the model: This can occur if there are case-mix differences, if the model is applied to only subsets of the populations used to develop the model, if certain variables are influenced by improvements in medical care, if there is lead time bias (transfers), and if small clinical changes correlate to large risks when continuous data are sorted into discrete data and categorized. (15, 24, 41)

3. Use of mortality as the sole criterion of outcome: This may be skewed by patients lost to follow-up, factors related to chance, the role of resources and costs, etc.
4. Failure to account for sample size and chance variability: This may occur with a small sample size, computational errors, misapplication of group data to the individual, and misinterpretation of statistical significance to suggest clinical significance. (42-44)

At this point in time, ICU scoring systems are currently used in approximately 10-15% of US ICU patients. (26)The belief is that this will increase as costs associated with manual data collection disappear as more and more health care systems adopt electronic charting. Although not perfect, ICU scoring systems are considered the best measure of outcome-focused ICU quality and performance that currently exists. It is continually calibrated and in our modern day emphasis on objective evidence of outcomes, it would be a failure not to employ the ICU scoring systems. (26)

III. Severity of Illness Scoring Systems: specifics

Each of the four major severity of illness scores is unique and a short discussion of each is merited to understand its application, strengths, flaws, and utility.

The APACHE II score is the most commonly used score. Twelve variables go into creating the predictive score and the worst value for each variable is used from the initial 24 hours after admission to the ICU. (28) Thus a major drawback is that patients have, for the most part, already received an intervention by the time a score is calculated. The variables are weighted equally except those markers for neurologic and

renal function, specifically Glasgow coma score and serum creatinine, which are weighted higher. All twelve variables are necessary to calculate the score. The worst score is 71 and lower scores are better. The scores directly correlate to observed hospital death rate and broken into increments of 5 points. For patients with scores of 0-4, the death rate was 1.9% by hospital discharge. On the flip side, patients with scores of 30-34 have a 73% death rate and 84% and higher for patients with scores greater than 35. With respect to estimating individual death rates, the overall correct classification rate was 86% with decreasing false positive rates as scores increase. But clinicians do not use the APACHE II to accurate predict outcomes. Discrimination is excellent for this instrument but the calibration is not perfect and requires constant updating. While, APACHE II is the most frequently employed scoring system, the most recent is APACHE IV, which has more variables, a new logistical regression equation and a new statistical modeling. (45, 46) APACHE IV was determined by an observational study of 110, 588 ICU admissions and can more accurately predict mortality and ICU length of stay than previous models. (6)

The SAPS II scoring system uses 17 variables and calculates a severity score using the worst values measured during the first 24 hours after admission to the ICU. Some variables are continuous and assigned points based on which range set it falls into. Others are dichotomous, assigned 1 for present or 0 for absent. The scores can predict hospital mortality rate when input into a mathematical formula. The SAPS II is the most commonly used model of the SAPS series and was based on data from 8500 patients. ((34)It has excellent discrimination and calibration but is less accurate for patients who are admitted to the ICU for non-cardiovascular disease. (47, 48) The more recent

version, SAPS III, has been found in validation studies to have excellent discrimination but poor calibration. (30, 49)

The MPM II scoring system utilizes 15 variables and calculates a severity score using the value collected at the time of ICU admission for each variable. All the variables except for age are dichotomous and the score can be recalculated every 24 hours to provide an updated assessment of the patient and also to compare it to the SAPS and APACHE scores. The MPM II was based on data from over 12,500 patients and was shown to have excellent calibration and discrimination. (31)The updated version MPM0-III also has excellent calibration when validated over a cohort of 55,000 ICU patients. (50)

The SOFA utilizes measurements of organ function (respiratory, cardiovascular, hepatic, coagulation, neurologic, and renal) to calculate a severity score. Scores are calculated at 24 hours after admission to the ICU and every 24 hours after. The mean and the highest scores are most predictive of mortality. Scores that increase substantially (30% or more) are associated with a mortality rate of >50%. (20) This scoring system was derived from data gathered from 1449 patients admitted to 40 ICUs in 16 countries. (51)

IV. Comparison of the Severity of Illness Scores

Briefly, overall, the efficacy of the APACHE scoring system appears to be superior. (52) One retrospective study comparing MPM II, SAPS II and APACHE IV showed that APACHE IV was most accurate but the MPM III is a better instrument if cost and complexity of data collection are factored in. (44) A systematic review

comparing SOFA, SAPS II, and APACHE II and III found that the APACHE systems were better at predicting ICU mortality. (53) However, the APACHE III and IV systems require proprietary computer technology and substantial data collection. This extra cost makes the APACHE systems prohibitively expensive for most ICUs. The other scoring systems require less data collection and no technologic investment and are therefore more commonly used in the ICU setting. Interestingly, the variables for the APACHE II system were randomly chosen where as the variables for MPM II, SAPS II, and APACHE IV have all been shown to independently predict mortality. (6, 28, 30, 34)

Predicting ICU length of stay is of appreciable importance in today's health care system as there is growing interest in reducing health care costs. APACHE was the only scoring system that has been shown to have good discrimination and calibration in predicting ICU and hospital length of stay in US ICUs. (26) MPM was shown to predict ICU length of stay adequately in California hospitals. (9)

Additionally, the scores have been customized to fit a specific patient population. APACHE was fit to the Veteran Administration hospital system in the United States, California ICU Outcomes Study/CalHospitalCompare project worked with the MPM, APACHE, and SAPS scoring systems, the Netherlands used APACHE II, MPM-admit III, and SAPS2, and Great Britain adapted the APACHE II scoring. (9, 54-57) These adaptions were made by using either first-level customization or second-level customization. First level customization is the use of the same variable weights that were used in the original index but readjustment of the regression equation so that it better fits the patient population to which the user wishes to apply it. Second level

customization involves changing the weights of the variable as well readjusting the regression equation.

V. A prognostic score based on intraoperative data: the APGAR score

More recently, Gawande, et. al surmised that medical staffing could tremendously benefit from a more simple score than the current severity of illness scoring systems for surgical patients going to the ICU. (58)The current scores require too many data elements, the scores are too bulky to quickly calculate on the fly, oftentimes all the variables are not uniformly collected for each patient, rendering them useless., and most scores are not useful in predicting outcomes of individual patients. The goal was to create a simple score that could easily be calculated at the bedside and be used to predict which individual post-operative patients in the ICU might have complications and/or poor outcomes and thus require more monitoring, attention, and intervention by the medical staff in the ICU.

Rather than looking at data from the ICU, i.e. after the patient has already arrived in the unit, these studies focused on perioperative data to calculate a simple score that could then serve as an alert for staff before or just as the patient even arrives in the ICU. Patients undergoing major general or vascular surgery were enrolled in the study and 28 variables from the intraoperative anesthesia records were collected and analyzed with the primary outcomes measured as death or major complications (acute renal failure, bleeding requiring transfusion of 4 or more units of packed red blood cells within 72 hours after surgery, cardiac arrest requiring CPR, coma for 24 hours or longer, deep vein thrombosis, septic shock, myocardial infarction, unplanned intubation,

ventilator use for 48 hours or more, pneumonia, pulmonary embolism, stroke, wound disruption, deep or organ-space surgical site infection, sepsis, systemic inflammatory response syndrome, vascular graft failure, anastomotic leak, cystic duct leak after cholecystectomy, pericardial effusion requiring drainage, and gastric outlet obstruction requiring reoperation) within 30 days after the operation. Variables that were shown in univariate analysis to independently predict major complications or death were plugged into a regression equation that weighted the variable on a 10 point score, where each 1 point increase would produce an equivalent increase in the odds of complication. A multivariate analysis and logistical regression was derived and tested for calibration and discrimination. The end result was a 10 point score based on lowest heart rate, log estimated blood loss and lowest mean arterial pressure. (see table 3). Lower scores correlated to worse outcomes. The score was applied to a separate cohort of patients. Twenty percent of patients had scores of 9 or 10 and those patients experience a < 4%incidence of major complications and no deaths. In contrast 4% of patients, much fewer, had scores of < or = 4 but they had a >50% risk of major complications and a 14% mortality rate. Even with the low prevalence at the high risk end, the c-statistic was 0.72 suggesting good discrimination.

	Odds ratio	95% Confidence interval	P value
Lowest heart rate	1.06	1.03-1.08	<0.0001
Log estimated blood loss	1.82	1.08-3.07	0.002
Lowest mean arterial pressure	0.96	0.93-0.99	0.002

Table 1. APGAR score: characteristics associated with major complications and death for 303 colectomy patients: multivariable analysis

The initial study was expanded to 4119 general and vascular surgery patients. Of those, 1441 patients had scores of 9-10 with a major complication rate of 5% and death rate of 0.1%. of the 128 patients with scores of 4 or less, the relative risk of major complication was 56.3% (11.3 95% confidence interval) and the a relative risk of death was 19.5% (140.7 95% confidence interval). (59)The C statistics were 0.73 for major complications and 0.81 for deaths.

Further studies by the same group accounted for fixed preoperative risk, secondary to patients' acute conditions, comorbidities, or the complexity of the operation. Even in patients with equivalent preoperative predictions, higher surgical Apgar scores still predicted lower odds of major complications and lower scores higher odds. (60) Gawande, et al also expanded the use of the score to other surgical sub-specialties and found some utility in this for many other surgical services. It has additionally be expanded and validated in a global patient population –in 8 other countries. (61)

The Surgical Apgar score has several major benefits and purposes. It is useful in backing up a team's "gut feeling" about how well the operation went and how well the patient faired through the operation. It is simple to calculate, available immediately, objective, and easy to communicate by the teams, and helpful in decision making for management and increasing monitoring. (59)In the future, it may be helpful in decision-making for which patients should be admitted to the ICU post-operatively as well as for quality monitoring.

Of note, there are a few shortcomings and criticisms of the score. This score cannot be used for the comparison of quality between different institutions or practitioners since each of the variables is influenced by both the patient's prior condition but also the interventions of the medical/surgical teams. Of course, estimated blood loss is not exact and so the anesthesiologist is relied upon to avoid any bias on the part of the surgical team. Even so, it is an estimate and therefore imprecise. The hemodynamic variables are also subject to being affected by anesthetic medications and how reactive the anesthesiologist is to certain hemodynamic thresholds. Moreover transient hypotension and prolonged hypotension result in the same score although one may actually be worse than the other. The risk of intra operative hypotension is higher in patients who have a preoperative mean arterial pressure (MAP) > or = to 110, a walking distance of less than 400 m, plasma volume of less than 3000 cc, having intra-abdominal or vascular surgery, surgery that is longer than 2 hours, and elderly with reduced plasma volume. (62) Regardless the cause, hypotension persistently elevated heart rates and are associated with poorer outcomes. (63)

VI. Cardiovascular stability: better marker of prognosis?

How then can we improve on this surgical Apgar score? Thus far, all of the ICU severity scores and APGAR metric consider either admission data or worst score over a 24-hour period and do not comment on variability or lability. We would like to explore beyond this norm and assess what sort of effect fluctuations in physiologic factors, specifically cardiovascular vital signs, in the intraoperative and postoperative setting has with respect to patient outcomes.

Variability in beat-to-beat interval of the heart rate has been well-studied. Physiologically, the sinoatrial node has its own intrinsic rate and is modulated by the autonomic system especially the vagal nerve and catecholamines as well as the baroreflex, thermoregulation, hormones, respiration, physical activity, stress, meals and the sleep-wake cycle. Decreased parasympathetics or increased sympathetic activity will result in reduced heart rate variation. Measuring variability can be difficult because of artifact especially with motion, muscle contraction, vocalization, and electrode movement. Endurance athletes have higher heart rate variability (HRV), possibly due to exercise or perhaps due to a genetic component. (64)It has been shown that heart rate variability has some genetic component. Also of note, many drugs can affect heart rate variability and these include anticholinergics, beta blockers, calcium channel blockers, digoxin, ACE inhibitors, and antiarrhythmics.

There are a number of measures of heart rate variability, which do not need to be discussed in great depth for this project. (Please refer to the appendix)

Measures of heart rate variability are clinically useful in many settings and the most commonly uses are 1. For the prediction of the risk of cardiac death or arrhythmia

after myocardial infarction and 2. To detect and assess the extent of autonomic neuropathy in patients with diabetes. (65)

In post myocardial infarction patients, the beat-to-beat (RR) variability is significant depressed. (66) Moreover, it may be associated with sympathetic state that could result in arrhythmogenesis. Beat-to-beat variability is not useful in predicting recurrent infarction nor is it predictive of poor outcomes in patients with angina. (67)

In the general population, low RR variability is associated with mortality and the risk of cardiac events (68). Studies have confirmed this in healthy patients and in patients referred for 24-hour Holter monitor recordings. Patients with lower RR variability have been shown to have a higher risk of coronary heart disease when adjusted for other cardiovascular risk factors. (69, 70) Limited data suggest that beat-to-beat variability may be of predictive value in heart failure specifically in patients with dilated cardiomyopathy and congestive heart failure. (71-76) Abnormal heart rate variability may also predict early recurrence of atrial fibrillation after cardio version. (77)

In the SICU, depressed HRV have been associated with worse outcomes. (78) Studies have shown that HRV parameters are predictive of ICU length of stay post coronary artery bypass surgery and following abdominal aortic surgery (79, 80). Poor outcomes of neurological injury especially stroke are correlated with heart rate and blood pressure variability both in children (81) and adults (82) perhaps indicative of the extent of injury to the autonomic nervous system. (83) In sepsis, HRV indices have

been shown to be helpful in diagnostically as well as to monitor improvement and recovery (84, 85).

Thus, beat-to-beat variability has been well studied and characterized. In our study we are interested in studying variations of heart rate of longer periods of time. Heart rate over longer periods adjusts to maintain cardiac output as cardiac output is the product of heart rate and stroke volume. As demand increases, cardiac output also increases. We expect that in our ICU patients that large variations in heart rate over hours and days (not beat-to-beat variability) will be an important factor in predicting poor patient outcomes.

Variability in blood pressure has not been studied as thoroughly. Broadly, night time dipping of blood pressure, defined as a reduction in the mean nighttime blood pressure to levels <90% of mean day time levels, is not concerning and in fact is considered favorable in cardiovascular prognosis. (86) Therefore, when studying shorter-term variability in blood pressure it is important to note this type of variation is physiologic. Higher than normal blood pressure variability is seen in essential hypertension. (87) In animal models, increases in short term blood pressure variability (BPVar) is associated with poor outcomes such as biventricular hypertrophy, atherosclerosis, structural damage to heart and kidneys and adverse arterial remodeling. (88, 89) Data in humans shows that for higher than base-line BPVar is associated with higher rates of cardiovascular morbidity, stroke, target organ damage scores, progression of carotid intima to medial wall thickness and left ventricular hypertrophy. (90-93) One large sample of the general population showed that a higher than average standard deviation of systolic and diastolic blood pressure was associated

with greater cardiovascular mortality at mean follow-up of 8.5 years. (94) No data exist on short-term consequences of increased blood pressure variability/lability in the ICU. Of note, studies use both arterial lines and non-invasive monitoring to access variability in blood pressure. (87)

While studies on beat-to-beat heart rate variability and blood pressure variability have been reported in the literature, we wish to formally study longer periods of lability (minutes to hours) in cardiovascular parameter. Physiologically, the mechanisms are well understood.

Changes in heart rate reflect the cardiovascular system's ability to adjust cardiac output. (95)Classically, heart rate multiplied by the stroke volume determines cardiac output. Cardiac output is determined by workload and oxygen consumption, and heart rate correlates linearly with both of these. Heart rate at any workload is higher in an unfit person than a fit person because the workload uses a greater capacity of muscle power of the unfit person. (96)Similarly, females have a higher heart rate at the same workload because the average maximum oxygen consumption is higher in males as a result of larger muscle mass. Thus, if workload is normalized to the maximum capacity, then heart rate can be determined as a percentage of that maximum capacity. Thus cardiac output is regulated by absolute workload and heart rate by relative workload. The theoretical application here is that heart rate, a much easier measure than cardiac output, can determine in a patient the relative workload demands and how these are fluctuating in the ICU patient.

Note, heart rate cannot compensate for factors that affect stroke volume, such as poor venous return (Frank-Starling mechanism) or contractility and function. However,

heart rate can affect ejection fraction measurements because as heart rate increases in the setting of cardiac muscle dysfunction, end diastolic volumes will appear to be lower although there is no change in contractility. (95)

Physiologically, heart rate itself is regulated by hypothalamic and medullary centers which increase sympathetic output, vagal input, baroreceptors which respond to changes in peripheral resistance, and from afferent fibers that carry metabolic signals from peripheral tissues. (95) Interestingly, heart rate does not appear to respond well to isolated hypovolemia, as studied in healthy volunteers where 20% of blood volume was removed. (97) In this study, the patients did not respond with reflexive tachycardia. Therefore, most likely, tachycardia that seen alongside hypovolemia is a response that occurs primarily due heightened sensitivity to pain, anxiety, or inflammatory process that is associated with the underlying cause of the patient's hypovolemia.

Numerous causes of tachycardia exist: the main differential being arrhythmias versus sinus tachycardia. Arrhythmias like supraventricular tachycardia (atrial fibrillation or junctional tachycardia) and ventricular tachycardias are more likely to be suggestive of poorer outcomes. Sinus tachycardias involve feedback mechanisms that will results from an affected blood pressure. This is known as reflex tachycardia and occurs in response to hypotension, especially in distributive shock or severe hypovolemia. This hypotension produces a sympathetic response where there is a simultaneous increase in blood pressure and heart rate. In the operating room, many of the anesthetic agents may induce tachycardia. Other causes to consider include physiologic response such as exercise, stress, fear, anxiety OR drug induced, namely

from beta adrenergic stimulation with isoproterenol, epinephrine, dobutamine or anticholinergic medications, usually atropine.

The major causes of hypotension include hypovolemia (due to increased diuresis, insensible loss poor intake, etc.), cardiogenic shock and distributive etiology (sepsis, neurogenic, anaphylactic). Except for neurogenic and possibly cardiogenic (depending on the exact mechanism) shock, the other conditions result in reflex tachycardia as the body attempts to compensate to maintain perfusion. Hypotension can also be induced by several of the anesthetic agents including the sedation gases and Propofol, commonly used at induction.

VII. Goals of our study

Given the dearth of literature, our study presents an excellent opportunity to look more closely at how short-term variations and swings in blood pressure might play a role in assessing a patient's severity of illness and prognosis.

As aforementioned, we are designing a study with the hope and intent of improving upon the current surgical APGAR score, which only measures static heart rate and blood pressure. As such we are pursuing a pilot study gathering retrospective data on post-op SICU patient to see if incorporating physiologic variability will be at least as good in discrimination and calibration to the current scale, the surgical APGAR score.

Heart rate is the body's ability to maintain cardiac output and perfusion in the event of low stroke volume. Thus, fluctuations of the heart rate reflect the body being in disequilibrium with swings of workloads and oxygen consumption over a short period of time. This disequilibrium may be due to stressors, cardiac problems,

autonomic instability. Whether exogenous or endogenous causes, in order to keep up with this hemodynamic instability, the heart rate fluctuates to maintain cardiac output which is what we expect to find in sicker patients.

In the APGAR studies, several different variables were analyzed in the initial study but only heart rate, blood pressure and estimated blood loss intra-operatively were considered relevant. Therefore, we felt that it would be best to focus on these variables in our study rather than reinvent the wheel and look at all the other variables again. Our hope and goal is to maintain simplicity while providing some improvement on current scores.

Our group has previously published an abstract looking closely at variation in intraoperative heart rate and blood pressure. Ten colectomy and vascular surgeries cases were randomly selected and intraoperative physiologic data was collected for each. Variation in the data was analyzed and the results were converted to a simple, user-friendly scale, which was subsequently compared to the APGAR score. The abstract clearly demonstrates that the APGAR score and our proposed scale are very different in terms of the underlying premise and the data collected. Given that we have this technique and have developed this scale for intra-operative studies, we hope to apply this to our post-operative, ICU data. We believe that this emphasis on the patient's hemodynamic status and lability will yield a different point of reference and invaluable information about that patient's stability and prognosis.

Ideally, our study would like to compare this new scoring system with actual outcomes however given that this is a preliminary study with just 10 patients, we wanted to compare to a more standardized measure of outcome. Thus we focused on

comparing our new scale to those well-studied markers of patient outcomes, i.e. the severity of illness scales such as APACHE II, MPM, and SAPS II.

STATEMENT OF PURPOSE

Our purpose in this study is to study heart rate and blood pressure variation in 10 post-operative patients in the ICU and correlate this variation to current prognostic scores, using the APGAR are the current standard and the severity of illness scores as proxy markers of outcomes.

METHODS

All patients used for this study were in the Surgical Intensive Care Unit at Yale New Haven Hospital from October 20-Dec 31, 2011. HIC approval was obtained to collect de-identified data during the length of stay in the ICU. Patients were candidates for this study if they had undergone any general surgical, vascular, ENT, transplant, or orthopedic procedure leading to admission to the SICU. Most cases were elective. The main inclusion criterion was that the patient should have had an arterial line placed in the operating room so that we could get real-time blood pressure readings at frequent (5 min) intervals.

Data were obtained for each patient from admission until as close to discharge from the ICU as feasible or until the arterial line was discontinued. Data were printed to reflect readings for every 5 minutes during this time period. The variables included were heart rate, blood pressure, O_2 saturation, and respiratory rate. ST segments were

collected on a few patients. The data could only be printed from the ICU monitors and not electronically saved. I was designated to print these data. Along with the help of multiple research assistants in the Anesthesiology Department, I then manually input these data into an excel file for manipulation and data analysis. The data was subsequently sent to our biostatistician who calculated measures of variation of the data and the measures of variation that we chose were range, interquartile range, and coefficient of variation.

The outcome measured was severity of illness scores as a proxy of measuring mortality outcomes. Severity and illness scores were calculated by going through the electronic medical record and obtaining the relevant laboratory and vital signs data. These values were plugged into online calculators to calculate the scores. APGAR scores were calculated by electronically downloading the operating room anesthesia record and subsequently using the minimum heart rate and mean arterial pressure for the score. Additionally, the estimated blood loss (EBL), also a component of the APGAR score calculation, was found by looking into the surgical operative note in the patient's electronic chart.

The scores studied were the APACHE II, MPM2 at admission and at 24 hours, SAPS 2, and SOFA. The APGAR scores were correlated to these scores as were measures of variation for heart rate, systolic blood pressure and diastolic blood pressure data from the ICU. For additional analysis, we also correlated the minimum, 25% quartile, median, 75% quartile, and maximum values.

RESULTS

DIASTOLIC BLOOD PRESSURE	Sample Correlation	P value
ArtDBP Range- APACHE II	0.42683	0.2276
ArtDBP Range - SAPS2	0.37657	0.3320
ArtDBP Range - MPM2 24 hr	-0.28338	0.6767
ArtDBP Range - SOFA	0.24316	0.5115
ArtDBP Range – APGAR(intraop)	0.27867	0.4489
ArtDBP Interquartile range- APACHE II	-0.14154	0.7062
ArtDBP Interquartile Range - SAPS2	0.27615	0.4874
ArtDBP Interquartile Range - MPM2 24 hr	-0.44801	0.2020
ArtDBP Interquartile Range - SOFA	0	1
ArtDBP Interquartile Range - APGAR(intraop)	0.40001	0.2623
ArtDBP CV*- APACHE II	0.43769	0.2143
ArtDBP CV - SAPS2	0.55000	0.1298
ArtDBP CV - MPM2 24 hr	-0.36775	0.3074
ArtDBP CV - SOFA	0.21335	0.5665
ArtDBP CV - APGAR(intraop)	0.69765	0.0225

Table 2. Correlation of arterial Diastolic Blood Pressure measures of variation with the APGAR score and severity of illness scores.

*CV is the coefficient of variation.

No strong correlations were noted with the measures of variation to the arterial diastolic blood pressure. The strongest correlation was the coefficient of variation with the APGAR score (r^2=0.69765, p=0.0225) which is not surprising given that a large component of the APGAR score is calculated by using the mean arterial pressure (MAP).

SYSTOLIC BLOOD PRESSURE	Sample Correlation	P value
ArtSBP Range- APACHE II	0.47417	0.2276
ArtSBP Range - SAPS2	0.73333	0.3320
ArtsBP Range - MPM2 24 hr	0.24309	0.6767
ArtSBP Range - SOFA	0.25860	0.5115
ArtSBP Range - APGAR(intraop)	0.09261	0.4489
ArtSBP Interquartile range- APACHE II	0.10976	0.7706
ArtSBP Interquartile Range - SAPS2	0.41841	0.2749
ArtSBP Interquartile Range - MPM2 24 hr	0.08753	0.6171
ArtSBP Interquartile Range - SOFA	0.05836	0.8771
ArtSBP Interquartile Range - APGAR(intraop)	0.00310	0.9935
ArtSBP CV- APACHE II	0.41945	0.2369
ArtSBP CV - SAPS2	0.43333	0.2557
ArtSBP CV - MPM2 24 hr	0.20569	0.5809
ArtSBP CV - SOFA	0.14870	0.6918
ArtSBP CV - APGAR(intraop)	0.00617	0.9870

Table 3. Correlation of arterial Systolic Blood Pressure measures of variation with the APGAR score and severity of illness scores.

No strong correlations were noted with the measures of variation to the arterial systolic blood pressure. The strongest correlation was the range with the SAPS2 score (r^2=0.73333, p=0.3320) but the correlation not statistically significant.

HEART RATE	Sample Correlation	P value
HR Range- APACHE II	-0.00610	0.1727
HR Range - SAPS2	0.34310	0.0219
HR Range - MPM2 24 hr	-0.32823	0.5116
HR Range - SOFA	0.07133	0.4839
HR Range - APGAR(intraop)	0.72455	0.8059
HR Interquartile range- APACHE II	-0.31783	0.3837
HR Interquartile Range - SAPS2	0.53629	0.1424
HR Interquartile Range - MPM2 24 hr	0.42173	0.2340
HR Interquartile Range - SOFA	0.18558	0.6194
HR Interquartile Range - APGAR(intraop)	-0.14557	0.6981
HR CV- APACHE II	0.34651	0.3389
HR CV - SAPS2	0.56667	0.1155
HR CV - MPM2 24 hr	-0.11219	0.7656
HR CV - SOFA	0.07112	0.8505
HR CV - APGAR(intraop)	0.54948	0.1022

Table 4. Correlation of heart rate measures of variation with the APGAR score and severity of illness scores.

The range of heart rate did correlate well with the APGAR score but not to any statistical significance (r^2=0.72455, p=0.8059).

	Sample Correlation	P value
APACHE II-APGAR(intraop)	-0.00929	0.9804
APACHE II-MPM2 24 hr	0.44389	0.2069
APACHE II-SAPS2	0.85356	0.0019
APACHE II-SOFA	0.55120	0.1009
APGAR(intraop)-MPM2 24 hr	-0.70162	0.0213
APGAR(intraop)-SAPS2	0.11815	0.7712
APGAR(intraop)-SOFA	-0.06915	0.8546
MPM2-24hr – SAPS2	0.42749	0.2631
MPM2-24hr - SOFA	0.33910	0.3502
SAPS2-SOFA	0.44333	0.2433

Table 5. Correlation of each severity of illness score to the other scores

The strong correlations were noted here. An inverse relationship between APGAR and MPM at 24 hours (r^2 = -0.70162, p = 0.0213) was found to be is statistically

significant. APACHE II and SAPS2 were also found to be well correlated and the relationship was statistically significant ($r^2 = 0.85356$, $p = 0.0019$).

DISCUSSION

The APGAR score, which is advantageous in many ways as describe above, we believe is not the best possible measure for cardiovascular instability in the operative room or post-operative setting. Moreover, the severity of illness indices do not weigh hemodynamic parameters heavily into their calculations. Our group, however, feels that cardiovascular status is an important consideration in post-operative course and a major cause of mortality and possibly morbidity as well. We believe that a scoring system developed exclusively from these parameters may be useful in determining prognosis, resource allocation, and length of stay in the ICU.

As such, this preliminary study closely analyzed the measures of heart rate, systolic blood pressure, and diastolic blood pressure variation in the post-operative setting in the intensive care unit. We however did not find any correlation with our proxy outcome measures of the severity of illness scores or the APGAR score. While disappointing, it is not surprising., As mentioned before, the other scores do not heavily utilize these parameters and so our findings verify and confirm this.

We recognize that a major limitation to our study is that we had a very small sample size. However, our goal was not to get a definitive answer but explore this as a potential new index of cardiovascular variation that could possibly be applied to a

larger cohort and/or database of patient information and outcomes to develop a new scoring system and validate it.

Of note, we did not see any correlations of our cardiovascular data with the established scoring systems but we also did not find any strong correlations between the established scoring systems either. This finding was initially surprising but rather logical given that the different scoring measures incorporate vastly different input parameters and apply completely different weighting systems for those parameters in an attempt to predict similar outcomes, i.e. provide the same output in their calculation, for the studied patients. Moreover, each established scoring system was developed in its own cohort, population study, as well as within a specific temporal frame. As mentioned, geography and time can profoundly affect the calibration of the scoring system and most likely these established scoring systems are not well calibrated for our patient population in New Haven CT at the time the data was collected (2012).

Several limitations exist in this study. First off, we did not directly measure outcomes and this is discussed above. Secondly, patients in the study were in the ICU for different lengths of time and this was not controlled for or factored into the analysis. Obviously, patients in the ICU for longer periods of time may have an increased likelihood of outliers that may skew the data. Thirdly, in our preliminary analysis we did not factor in night-time dipping of blood pressures as normal variation in our analysis of blood pressure lability. This is a major flaw and will have to be redressed in further analysis. We also introduced a significant bias because we did not include all ICU patients but instead took a sample of them for this study. Sampling of ICU patients for prognostic scoring systems instead of including all patients has been shown to

create skewed results (41). Finally, secondary endpoints cannot be valid if the primary endpoint is not statistically significant. (98) The POISE PeriOperative Ischemic Evaluation trial showed that surrogate endpoints do not accurately predict mortality and therefore not recommended for studies in which the aim is to reduce mortality. (99) We have attempted to use a surrogate endpoint to compare scores but cannot make extrapolations or conclusions about the utility of our score in assessing other outcomes such as morbidity, mortality, length of ICU stay, etc. Finally, we may have had some bias and data entry errors as part of our study. Given that it was not feasible to electronically capture the physiologic data from the monitors in the ICU, we had no choice but to manually enter the data by hand into an excel sheet which may result in potential data entry errors.

As mentioned earlier, this project is just a beginning, an initial investigation, into the possibility of using hemodynamic parameters as a means to stratify patients. We hope that cardiovascular status as measured by heart rate and blood pressure lability will ultimately be useful in predicting prognosis for individual patients and thus stratify which patients will ultimately require greater ICU resources.

The group has multiple ideas for future projects that can stem and branch out from this initial study. One such idea is to go back to these charts and find out what exactly the outcomes were for the 10 patients. If this is done, then we no longer need to rely on the severity of illness scores as a proxy for the outcomes. A second idea is to build off our previous abstract for intraoperative hemodynamic lability and apply the scoring system that was developed in that abstract to assess patients in the ICU. We

could then expand to a larger sample size to attempt to calibrate our scoring system well and later validate it in a different population.

A third idea is to compare our scoring system the Therapeutic Intervention Scoring System (TISS). (100) The TISS measures severity of illness based on type and amount of treatment given to the patient and so is very useful in determining how many resources a patient consumes. Using this scoring system, it can be determined whether a patient can go to the floor, step down, or the ICU based on the level of nursing care the patient would require. Elements incorporated into the scoring system (updated in 1983) include cardiac arrest in the last 48 hours, ventilation, arterial infusion, dialysis, catheters/monitoring (pulmonary artery, intraarterial infusion, arterial line, chest tubes), and a variety of emergency procedures. (101) This ICU index may provide a more meaningful comparison for our scoring system since it is focused on acute events. Our scoring system is more aligned to the purpose of determining how to stratify individual patient prognosis and resource allocation and the TISS is more oriented to this purpose than the APACHE II, SOFA, MPM2, SAPS2, and APGAR scores.

The fourth idea was to simply study the correlation between severity of illness scores. Comparisons of the scores have been made in numerous studies with the intention of determining which is the best prognostic score, best predictor of ICU length of stay, and overall ICU performance. However, no study could be found via a Pubmed search showing how the scores correlate with each other. We would like to find out what the exact correlations are between the severity of illness indices by calculating and correlating the scores for a large sample of ICU patients. This correlation would be helpful, especially for small studies, like this one. The reason is that if the same

correlation is found in the small study as is found in the large population, then one can be relatively sure that in fact the power of the small study is quite good and results more promising.

Yet another idea is to compare our score to the Rothman Index, which is currently in use at Yale New Haven Hospital. This index is found on the nursing tab of our electronic medical record and was introduced as recently as late-fall of 2011. With further investigation, it can be determined if this score has been calibrated geographically, i.e. specifically for the patients seen within Connecticut or within the Yale New Haven Hospital System. If this is true, then we can compare our hemodynamic-based score to the Rothman Index to assess what sort of information each provides and what the best applications for each would be, if any.

Another question that arises from this work is whether the interquartile range correlates with the range. The range itself contains outliers as does the APGAR score, whereas the interquartile range may be a better measure of real instability. If morbidity outcomes could be measured, an interesting question would be whether the interquartile range better correlates to outcomes vs. the range and/or the APGAR score.

Finally, as mentioned earlier, blood pressure is known to dip at night and this is considered fairly normal. In the ICU, sleep patterns are disturbed and circadian rhythms out of sync. An interesting question for future work would be to see if nighttime dipping of blood pressures occurs in the ICU at all.

APPENDIX

Table 6. PREOPERATIVE CHARACTERISTICS

	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7	Pt 8	Pt 9	Pt 10
age	77	74	43	57	53	57	83	59	68	71
female	Y	N	Y	Y	N	N	Y	Y	Y	Y
non caucasian	no	?		?	?	?	no	?	?	?
BMI (>35 vs < 18.5)	19.2	26.9	33.6	24.7	28.0	25.0	30.3	32.9	26.1	25.6
Cardiovascular disease	no	no	no	no	no	no	yes	no	no	no
pulm disease)	no	no	yes	no	no	no	no	no	no	no
DM	No	no	no	no	yes	no	no	no	no	no
preoperative sepsis	No	no	no	no	no	no	no	no	no	no
wound contaminated or dirty	No	no	no	no	no	no	no	no	no	no
procedure for malignancy	No	yes	no	no	yes	no	yes	yes	yes	yes
bleeding disorder/transfusion > 4 U PRBC preop	No		no	no	no	no	no	no		no

emergency procedure	No	no	no	yes	no	no	no	no	no	no
ASA class >=3	Yes	yes	yes	yes	no	yes	yes	no	yes	yes
HTN	Yes	yes	no	yes	no	no	yes	no	yes	yes
dyspnea	No	no	no	no	no	yes	no	no	no	no
renal failure	No	no	no	no	no	no	no	no	no	no
hx of stroke or TIA	No	no	no	no	no	no	no	no	no	no
current smoker	No	no	no	no	yes	yes	no	no	no	no
disseminated cancer	No	no	no	no	no	no	yes	no	yes	yes
weight loss > 10% in 6 months	?	yes	no	no	?	?	yes	no	yes	?
oral or parenteral corticosteroid use	No	no	yes	no	no	no	no	no	no	no
ascites	no	no	no	yes	no	no	no	no	no	no
esophageal varices	no	no	no	no	no	no	no	no	no	no
rest pain or gangrene	no	no	no	no	no	no	no	no	no	no
coma	no	no	no	yes	no	no	no	no	no	no
DNR status	no	no	no	no	no	no	no	yes	yes	no

*cardiovascular disease: (MI, CHF, PVD, stroke, prior revascularization)

Pulm: (PNA, COPD, ventilator dependent

Table 7. Severity of Illness Scores for each patient

	Pt 1	Pt 2 Day 1	Pt 2 Day 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7	Pt 8 Day 1	Pt 8 Day 2	Pt 9	Pt 10 Day 1	Pt 10 Day 2
APACHE 2	9	30	25	13	8	13	14	16	27	18	7	11	11
MPM2 admit	3	3		1	1	1	2	2	2		3	3	
MPM 24 hr	2	5	3	0	0	0	1	2	2	2	1	3	0
SAPS2		76	59	24	13	35	18	28	44	46	12	21	21
SOFA	1	14	12	2	2	1	2	1	3	3	1	2	0
APGAR	3	3		9	5	6	3	4	6		5	2	

Table 8. ICU data: HR

	range	25-75	dev/mean
Pt 1	31	12	0.071477595
Pt 2	26	15	0.092931121
Pt 3	37	6	0.087646547
Pt 4	22	6	0.05167474
Pt 5	49	12	0.14348662
Pt 6	21	9	0.055801647
Pt 7	20	6	0.053633026
Pt 8	55	12	0.113093198
Pt 9	32	11	0.091789625
Pt 10	21	7	0.04650648

Table 9. ICU: ARTSBP

	range	25-75	dev/mean
Pt 1	74	22.8	0.106590442

Pt 2	80	22	0.138370415
Pt 3	179	21.2	0.124940845
Pt 4	70	27	0.148722988
Pt 5	84	14	0.136169782
Pt 6	39	12	0.064906996
Pt 7	64	22.05	0.179590251
Pt 8	98	18	0.145854159
Pt 9	16	4.5	0.037878148
Pt10	58	13.5	0.086114274

Table 10. ICU: ARTDBP

	range	25-75	dev/mean
Pt 1	35	10	0.090968845
Pt 2	32	7	0.108374084
Pt 3	81	10	0.163213223
Pt 4	26	10	0.113161428
Pt 5	43	14.5	0.16103766
Pt 6	53	6.75	0.093563437
Pt 7	28	5.75	0.113586684
Pt 8	46	8	0.159668827

Pt 9	27	4.5	0.08618326
Pt10	32	7.5	0.095327599

Figure 1. Various measures of beat-to-beat variability

Definitions for time and frequency domain measures of heart period variability

Variable	Units	Definition
Time Domain - Statistical measures		
Night-day difference	ms	Difference between the average of all the normal RR intervals at night (24:00 to 05:00) and the average of all the normal RR intervals during the day (07:30 to 21:30).
SDNN	ms	Standard deviation of all normal RR intervals in the entire 24-hour ECG recording.
SDANN	ms	Standard deviation of the average normal RR intervals for all 288 5-minute segments of a 24-hour ECG recording (each average is weighted by the fraction of the 5 minutes that has normal RR intervals).
ASDNN	ms	Average of the standard deviations of normal RR intervals for all 288 5-minute segments of a 24-hour EGC recording.
r-MSSD	ms	Root mean square successive difference, the square root of the mean of the squared differences between adjacent normal RR intervals over the entire 24-hour ECG recording.
pNN50	percent	Percent of differences between adjacent normal RR intervals that are greater than 50 ms computed over the entire 24-hour ECG recording.
NN50	none	Number of adjacent normal RR intervals that are greater than 50 ms counted over the entire 24-hour ECG recording.
Time Domain - Geometric measures		
HRV triangular index	none	Total number of NN intervals divided by the number of NN intervals in the modal bin of a histogram of all NN intervals with a bin width of 7.8125 msec (for a sampling rate of 128/sec).
TINN	msec	Baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of all NN intervals.
Frequency Domain Measures		
Total power	ms^2	The energy in the heart period power spectrum up to 0.40 Hz.
Ultra low frequency (ULF) power	ms^2	The energy in the heart period power spectrum up to 0.0033 Hz.
Very low frequency (VLF) power	ms^2	The energy in the heart period power spectrum between 0.0033 and 0.04 Hz.
Low frequency (LF) power	ms^2	The energy in the heart period power spectrum between 0.04 and 0.15 Hz.
High frequency (HF) power	ms^2	The energy in the heart period power spectrum between 0.15 and 0.40 Hz.
LF/HF ratio	none	THe ratio of low to high frequency power.
beta	none	Slope of log (power) on log (frequency) between 0.01 and 0.0001 Hz on a log-log plot.

Table 11. Variables used to calculate each of the severity of illness score

SCORES	VARIABLES
APACHE II	Temperature, respiratory rate, serum bicarbonate or arterial pH, serum potassium, hematocrit, age, mean arterial pressure, A-a gradient if FiO_2> or = 50% OR PaO_2 if FiO2< 50%, serum creatinine, white blood cell count, heart rate, serum sodium, Glasgow coma scale (GCS) score, chronic organ insufficiency or immune-compromised.
SAPS 2	Type of admission, age, temperature, BUN, Serum sodium, chronic diseases, Systolic Blood pressure, PaO2/FiO2 mmHg if mechanically ventilated or CPAP, white blood cell count, serum bicarbonate, GCS score, heart rate, urine output, serum potassium, bilirubin
MPM-admit II	Medical or unscheduled surgery admission, metastatic neoplasm, cirrhosis, chronic renal insufficiency, CPR prior to admission, GCS score, heart rate, systolic blood pressure, acute renal failure, cardiac dysrhythmia, cerebrovascular incident, gastrointestinal bleeding, intracranial mass effect, mechanical ventilation, age
MPM-24 hr II	Medical or unscheduled surgery admission, metastatic neoplasm, cirrhosis, creatinine > 2.0, urine output, GCS score, confirmed infection, intracranial mass effect, mechanical ventilation, vasoactive drugs > or = 1 hour, paO2< 60 mmHg, Prothrombin time > standard+ 3 sec, age
SOFA	PaO2/FiO2, pressors, bilirubin, coagulation studies, GCS score, creatinine OR urine output.

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