HHS Public Access

Author manuscript

J Intensive Care Med. Author manuscript; available in PMC 2016 October 01.

Published in final edited form as:

J Intensive Care Med. 2015 October ; 30(7): 420–425. doi:10.1177/0885066614523536.

Coefficient of Variation of Coarsely Sampled Heart Rate Is Associated with Early Vasopressor Independence in Severe Sepsis and Septic Shock

Samuel M. Brown, MD MS[1,2], **M. Quinn Tate, MS**[3], **Jason P. Jones, PhD**[4], **Kathryn G. Kuttler, PhD**[5], **Michael Lanspa, MD**[1,2], **Matthew T. Rondina, MD**[6], **Colin K. Grissom, MD**[1,2], and **V.J. Mathews, PhD**[3]

[1]Pulmonary and Critical Care, Intermountain Medical Center

[2]Pulmonary and Critical Care, University of Utah School of Medicine

[3]Electrical and Computer Engineering, University of Utah

[4]Research Division, Kaiser Permanente Southern California

[5]Medical Informatics, Intermountain Healthcare

[6]Internal Medicine, University of Utah Medical Center and School of Medicine

Abstract

Purpose—Determine whether variability of coarsely sample heart rate and blood pressure early in the course of severe sepsis and septic shock predicts successful resuscitation, defined as vasopressor independence at 24 hours after admission.

Methods—In an observational study of patients admitted with severe sepsis or septic shock from 2009 to 2011 to one of two ICUs at a tertiary-care hospital, in whom blood pressure was measured via an arterial catheter, we sampled heart rate and blood pressure every 30 seconds over the first six hours of ICU admission and calculated coefficient of variability of those measurements. Primary outcome was vasopressor independence at 24 hours; secondary outcome was 28-day mortality.

Results—We studied 165 patients, of which 97 (59%) achieved vasopressor independence at 24 hours. Overall 28-day mortality was 15%. Significant predictors of vasopressor independence at 24 hours included the coefficient of variation of heart rate, age, APACHE II, the number of increases in vasopressor dose, mean vasopressin dose, mean blood pressure, and time-pressure integral of mean blood pressure below 60mm Hg. Lower sampling frequencies (up to once every 5 minutes) did not affect the findings.

Conclusions—Increased variability of coarsely sampled heart rate was associated with vasopressor independence at 24 hours after controlling for possible confounders. Sampling frequencies of once in five minutes may be similar to once in 30 seconds.

Corresponding author: Samuel Brown, Intermountain Medical Center, Shock Trauma Intensive Care Unit, 5121 South Cottonwood Street, Murray, UT 84107, Telephone: 801-507-6556, Fax: 801-507-5578, samuel.brown@imail.org.

The authors declare that they have no conflict of interest.

Keywords

Sepsis; Shock; Physiological Variability; Hemodynamics; Vasopressor Agents

Introduction

Severe sepsis and septic shock, the life-threatening manifestations of severe infection, are significant public health problems, with an annual incidence of 750,000 in the USA and an associated mortality of 25–50%.[1, 2] While there is a mounting consensus that early intervention is most important in the management of sepsis,[3, 4] appropriate therapeutic endpoints and near-term predictors for hemodynamic resuscitation in severe sepsis and septic shock are still not well characterized.[5, 6] Which attributes of the cardiovascular system are most relevant is not clear. The regulation of beat-to-beat heart rate and blood pressure by the autonomic nervous system provides important input into severity of illness and prognosis in patients with cardiac dysfunction.[7, 8] Loss of normal variability is associated with more severe disease and worse prognosis in patients with systolic heart failure and coronary artery disease.[9] Analyses of heart-rate complexity, especially a version of sample entropy (which measures the unpredictability of a time series), have demonstrated efficacy in management of premature infants at risk for sepsis. Specifically, Moorman and colleagues monitored a version of sample entropy in a cohort of neonates in a controlled trial which demonstrated a mortality benefit among monitored infants.[10, 11] Although not yet validated in controlled trials, some early results suggest that measurements of heart-rate variability may also be useful in adult sepsis.[12–14] These advanced techniques require high-granularity data (125–500 samples per second), which can be resource-intensive to obtain, validate, and store. Such high-granularity data requires high-fidelity identification of each beat and large amounts of digital storage space, in addition to integration with other sources of clinical data. Whether coarsely sampled (i.e., a lower sampling frequency, as opposed to beat-to-beat) heart rate and blood pressure will be of use in the management of adult sepsis is not known. We hypothesized that patterns in heart rate and blood pressure, sampled as moving 8-beat median values every 30 seconds, would provide useful information about the probability of being liberated from vasopressor medications 24 hours after ICU admission, which we took as a measure of successful early resuscitation in severe sepsis and septic shock.

The Intermountain IRB approved this study with waiver of the requirement for informed consent. Early results from this work have been reported in abstract form.[15]

Materials and Methods

Setting

Two intensive-care units at a tertiary-care, academic hospital in Murray, Utah, USA. The hospital has 452 total beds, the Shock Trauma ICU has 24 beds, and the Respiratory ICU has 12 beds.

Patients

We prospectively identified patients with severe sepsis or septic shock admitted to study ICUs from our active sepsis screening logs, from September 2009 to May 2011. The study hospital employs a real-time, electronic sepsis screening tool for research and quality improvement applications, and a dedicated research coordinator focused on sepsis. This coordinator reviews output from the screening tool and performs active case-finding in real-time. Patients thus included in the sepsis screening logs must meet consensus criteria for severe sepsis or septic shock.[16] In our ICUs we routinely sample and store heart rate and arterial blood pressure values from the Philips Intellivue™ bedside monitors. These monitors provide moving 8-beat median values of heart rate and arterial blood pressure every 30 seconds, cleaned according to the standard Philips proprietary algorithms, which are stored in the hospital's enterprise data warehouse. We did not have the capacity to measure beat-to-beat values of heart rate and blood pressure for this study. We included patients with severe sepsis or septic shock in whom every-30-second vital signs data were available for at least 3 of the first 6 hours of ICU admission. We only included the initial ICU admission for sepsis patients admitted during the study period.

Clinical Data

We analyzed heart rate and blood pressure data for the first six hours after ICU admission for each study patient, sampled directly from the bedside monitor (which represents an 8-beat median value) at the given sampling interval, with every 30-second sampling as our default. We manually inspected the time series of heart rate and blood pressure data to identify and exclude noisy data. (Noisy data were of two types: 1) arterial blood pressure near 300mmHg related to blood draws from the arterial catheters; 2) rarely EKG-based heart rate failed to match the heart rate measured via simultaneous pulse oximetry, presumably from low voltage EKG or movement artifact.) APACHE II score[17] is calculated prospectively in all patients admitted to study ICUs. Infusion rates of vasopressors (namely norepinephrine, epinephrine, dopamine, phenylephrine, and vasopressin) are automatically uploaded (via a wireless uplink) in real-time to the hospital Electronic Medical Record (EMR) as part of routine clinical care. We analyzed all vasopressors administered during the first six hours after ICU admission, converting them to norepinephrine equivalent dosages according to pharmacological equivalencies.[18] The study hospital has implemented Surviving Sepsis guidelines for care of patients with sepsis.[4]

Outcomes

We chose as our primary outcome vasopressor independence at 24 hours after ICU admission, an *a priori* intermediate outcome we felt represented successful early resuscitation of sepsis. To meet criteria for vasopressor independence at 24 hours, a patient needed to be alive and free of vasopressor therapy from 24 to 48 hours after ICU admission. Secondary outcomes included all-cause mortality, vasopressor-free days and ICU-free days, all measured at 28 days after ICU admission. Mortality was determined from the Intermountain Master Death Record, which combines inpatient and Utah state vital statistics sources.[19]

Statistical Methods

We calculated basic descriptors of blood pressure and its variability across the first 6 hours of data, beginning at the time of ICU admission. We assessed heart rate and blood pressure variability primarily with the coefficient of variation (variance divided by mean). We also incorporated a measure of the burden of time above (area above the curve, bpAOC) or below (area under the curve, bpAUC) standard cutoffs (60mmHg for mean blood pressure, 90mmHg for systolic blood pressure)—in essence, time-pressure integrals above or below a reference blood pressure. These statistical descriptors were incorporated as predictors into multivariate naïve Bayesian models of binary study outcome (vasopressor independence at 24 hours). For classification models after assessing univariate associations, we employed an iterative Bayesian method for feature selection that incorporated a predictor if, on 2000 bootstrap iterations, it statistically significantly improved the out-of-bag area under the receiver operating characteristic curve (AUC) of the regression model.[20, 21] We employed a similar strategy, optimizing R^2, for linear regression models of ventilator- and ICU-free days. All calculations were performed within the R statistical package (version 2.13).[22] Because this was an exploratory study we did not make a formal adjustment of p values for multiple comparisons.

In an exploratory analysis, we evaluated whether similar findings obtained when under-sampling the physiological data at intervals of 1, 2, and 5 minutes (i.e., obtaining 8-beat median values from the bedside monitor at 1, 2, and 5 minute intervals). In additional sensitivity analyses, we measured the proportion of heart rates that were in the normal range (60–90 min^{-1}), proportion of arterial blood pressure readings within normal range (60mmHg ≤ mean arterial pressure ≤ 100mmHg) and whether the patient was in atrial fibrillation at any point during the first 6 hours of ICU admission (as determined from review of EKGs and the medical record).

Results

We studied 165 patients who met inclusion criteria. Figure 1 depicts the flow of patients through screening and analysis. Ninety-seven (59%) study patients were vasopressor-independent at 24 hours. Demographics, severity predictors, and outcomes for study patients are displayed in Table 1. Median APACHE II was 22 (Interquartile Range [IQR] 17–28). Mortality at 28 days was 15%. We display the central tendencies of the measures of variability during the first 6 hours of ICU admission in Table 2.

Coefficient of variation of systolic blood pressure (p=0.05) predicted vasopressor independence at 24 hours when controlling for mean systolic blood pressure (p<0.01), an effect that became non-significant on multivariate Bayesian modeling. In the best multivariate model of vasopressor independence (out-of-bag AUC 0.8), the coefficient of variation of the heart rate was predictive of outcome, as was the AUC of the mean blood pressure, the number of increases in vasopressor dose over the first 6 hours, and the mean vasopressin dose. A higher coefficient of variation of heart rate was associated with a higher probability of being vasopressor independent at 24 hours. We present effect plots, a more informative depiction of parameter estimates from regression/classification models than the usual beta coefficient, for the predictors in Figure 2. The other predictors listed in Table 2

were not associated with outcomes at a statistically significant level (data not shown). Models of vasopressor- and ICU- free days had relatively poor fit, with an adjusted $R^2 < 0.2$. Age, APACHE II, and mean heart rate were retained in those regression models (data not shown).

Vasopressor independence at 24 hours was significantly associated with 28-day mortality (Odds Ratio 0.36, p = 0.02 by Fisher's exact test), although the association became non-significant on multivariate analysis. The final Bayesian classification model of 28-day mortality (out-of-bag AUC 0.8) included age, APACHE II, mean heart rate, and whether the patient met the transfusion standards incorporated into early goal directed therapy.

When we calculated predictors from under-sampled data (every 1 min, 2 min, or 5 min), there was no statistically significant difference in the models: the models and the distribution of coefficient of variation of heart rate are displayed in Table 3. Inclusion of proportion of heart rates within the normal range (mean for all patients, 53%), proportion of arterial blood pressure within the normal range (mean for all patients, 86%) and the presence of atrial fibrillation during the first 6 hours of ICU admission (affecting 20 patients, 12%) did not affect the primary classification model of vasopressor independence or the secondary classification model of 28-day mortality.

Discussion

Measures of variation of heart rate and blood pressure calculated from coarsely sampled hemodynamic data appear to be associated with successful early resuscitation of severe sepsis and septic shock. The coefficient of variation of heart rate was statistically significantly associated with vasopressor independence at 24 hours on multivariate analysis: increased variability of heart rate was associated with increased probability of successful resuscitation.

Disease severity as estimated by APACHE II, age, how often clinicians increased the vasopressor dose, whether clinicians administered vasopressin, how long the patient's mean blood pressure was below 60 mm Hg were generally most predictive of independence from vasopressor therapy at 24 hours. The coefficient of variation of heart rate remained, however, predictive of successful early resuscitation in multivariate models.

Substantial research on the autonomic nervous system, including especially its baroreflex control system, has suggested that increased variability denotes relative health, while a loss of variability is associated with pathologic or imbalanced states.[9, 23, 24] Almost all of these analyses have been based on beat-to-beat measures of instantaneous heart rate. In our study population, a simple measure of increased variability was associated with improved short-term outcome. Whether the same physiological mechanisms are at play at both beat-to-beat and coarsely sampled levels of scale is unknown. We acknowledge that our study design does not allow us to draw inferences about the relationships between coarsely sampled hemodynamic data and autonomic modulation. Further studies should investigate relationships between beat-to-beat and coarsely sampled data, particularly with regard to suitability for targeted therapies.

Determining the optimal sampling frequency in data-rich environments is an ongoing area of research and discussion. In our study, there was no significant difference between every-30-second and every-5-minute sampling and the coefficient of variability of heart rate remained predictive of successful resuscitation across those time scales. Further research should characterize the sampling frequencies requisite for particular applications.

Our study is of reasonable size and has the advantage of incorporating highly detailed information about vital signs and therapies, taking advantage of the data-rich environment in study ICUs. We identified patients prospectively as part of our sepsis screening, and the clinical data we employed are routinely acquired.

Limitations of our study include its overall retrospective design, use of an intermediate clinical outcome, use of the Philips proprietary data cleaning algorithms, and the multiple comparisons problem. The prospective data acquisition within the Intermountain EMR and the pattern of sepsis screening in study ICUs substantially ameliorates the risks of retrospective study design. We felt that use of an intermediate outcome was important given constraints of sample size and relevance to clinical outcomes in complex, dynamic disease processes. In clinical resuscitation, in which many components interrelate, the effects of a particular predictor or intervention may be difficult to assess with regard to broad clinical outcomes like mortality, which will be confounded by factors unrelated to resuscitation of sepsis. We analyzed heart rate and blood pressure results derived from the Philips monitoring systems; our results may not generalize to settings where substantially different data cleaning algorithms are employed. Although we were primarily interested in simple measures of variability, we investigated several possible measures of variability. Because of susceptibility to the multiple comparisons problem (in which Type 1 statistical error becomes an important risk when several associations are tested in the same data set), the associations we identified merit further validation to be sure they are not due to chance alone.

Conclusions

Increased variability of heart rate measured at 30-second intervals was associated with increased probability of successful early resuscitation of severe sepsis and septic shock after controlling for covariates. Sampling at 5-minute intervals, as opposed to 30-second intervals, did not appear to change this association.

Acknowledgments

Financial Support: This study was funded by National Institute of General Medical Sciences (K23GM094465), Intermountain Research and Medical Foundation, and the Easton Fund.

References

1. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. Jul; 2001 29(7):1303–1310. [PubMed: 11445675]
2. Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. Crit Care Med. May; 2007 35(5):1244–1250. [PubMed: 17414736]

3. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. Nov 8; 2001 345(19):1368–1377. [PubMed: 11794169]
4. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med. Jan; 2008 36(1):296–327. [PubMed: 18158437]
5. Dellinger RP. Cardiovascular management of septic shock. Crit Care Med. Mar; 2003 31(3):946–955. [PubMed: 12627010]
6. Russell JA. Management of sepsis. N Engl J Med. Oct 19; 2006 355(16):1699–1713. [PubMed: 17050894]
7. Nolan J, Batin PD, Andrews R, et al. Prospective study of heart rate variability and mortality in chronic heart failure: results of the United Kingdom heart failure evaluation and assessment of risk trial (UK-heart). Circulation. Oct 13; 1998 98(15):1510–1516. [PubMed: 9769304]
8. La Rovere MT, Pinna GD, Maestri R, et al. Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. Circulation. Feb 4; 2003 107(4):565–570. [PubMed: 12566367]
9. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation. Mar 1; 1996 93(5):1043–1065. [PubMed: 8598068]
10. Moorman JR, Delos JB, Flower AA, et al. Cardiovascular oscillations at the bedside: early diagnosis of neonatal sepsis using heart rate characteristics monitoring. Physiological measurement. Nov; 2011 32(11):1821–1832. [PubMed: 22026974]
11. Moorman JR, Carlo WA, Kattwinkel J, et al. Mortality reduction by heart rate characteristic monitoring in very low birth weight neonates: a randomized trial. The Journal of pediatrics. Dec; 2011 159(6):900–906. e901. [PubMed: 21864846]
12. Ahmad S, Ramsay T, Huebsch L, et al. Continuous multi-parameter heart rate variability analysis heralds onset of sepsis in adults. PLoS ONE. 2009; 4(8):e6642. [PubMed: 19680545]
13. Chen WL, Chen JH, Huang CC, Kuo CD, Huang CI, Lee LS. Heart rate variability measures as predictors of in-hospital mortality in ED patients with sepsis. Am J Emerg Med. May; 2008 26(4):395–401. [PubMed: 18410805]
14. Buchman TG. Nonlinear dynamics, complex systems, and the pathobiology of critical illness. Current opinion in critical care. Oct; 2004 10(5):378–382. [PubMed: 15385755]
15. Tate Q, Brown SM, Jones J, et al. Predicting Early Vasopressor Independence with Coarsely Sampled Arterial Blood Pressure in Severe Sepsis and Septic Shock [Abstract]. Shock. Jun; 2011 35(7):1–2. 2011. [PubMed: 21160386]
16. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. Jun; 1992 101(6):1644–1655. [PubMed: 1303622]
17. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. Oct; 1985 13(10):818–829. [PubMed: 3928249]
18. Brown SM, Lanspa MJ, Jones JP, et al. Survival after Shock Requiring High-Dose Vasopressor Therapy. Chest. Aug 13.2012 in press.
19. Francis DP, Willson K, Georgiadou P, et al. Physiological basis of fractal complexity properties of heart rate variability in man. J Physiol. Jul 15; 2002 542(Pt 2):619–629. [PubMed: 12122157]
20. Efron B, Tibshirani R. Improvements on cross-validation: The .632+ bootstrap method. Journal of the American Statistical Association. 1997; 92(438):548–560.
21. Harrell, F. Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis. New York: Springer; 2001.
22. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2009. [computer program]. Version
23. Gang Y, Malik M. Heart rate variability in critical care medicine. Curr Opin Crit Care. Oct; 2002 8(5):371–375. [PubMed: 12357103]

24. Tsuji H, Venditti FJ Jr, Manders ES, et al. Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham Heart Study. Circulation. Aug; 1994 90(2):878–883. [PubMed: 8044959]

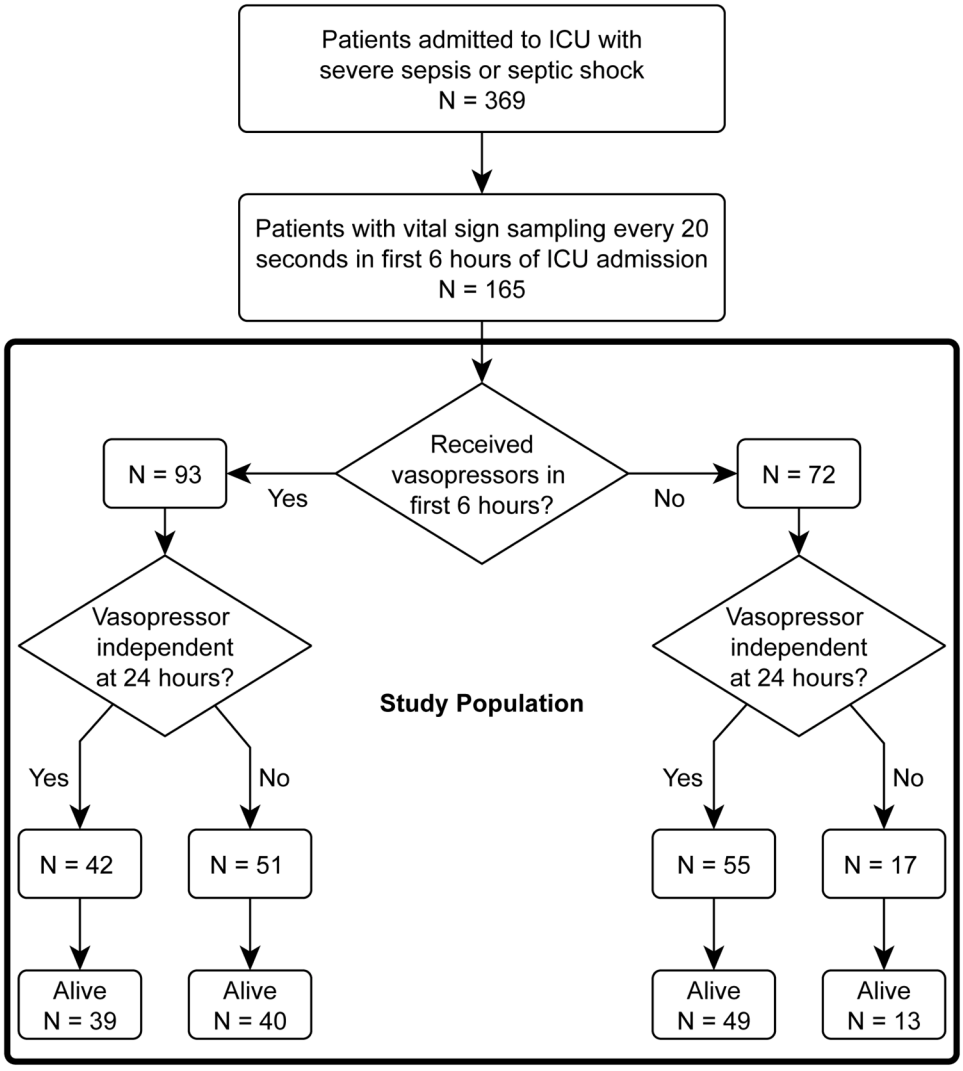

Figure 1.
Schematic of Patient Selection and Outcomes

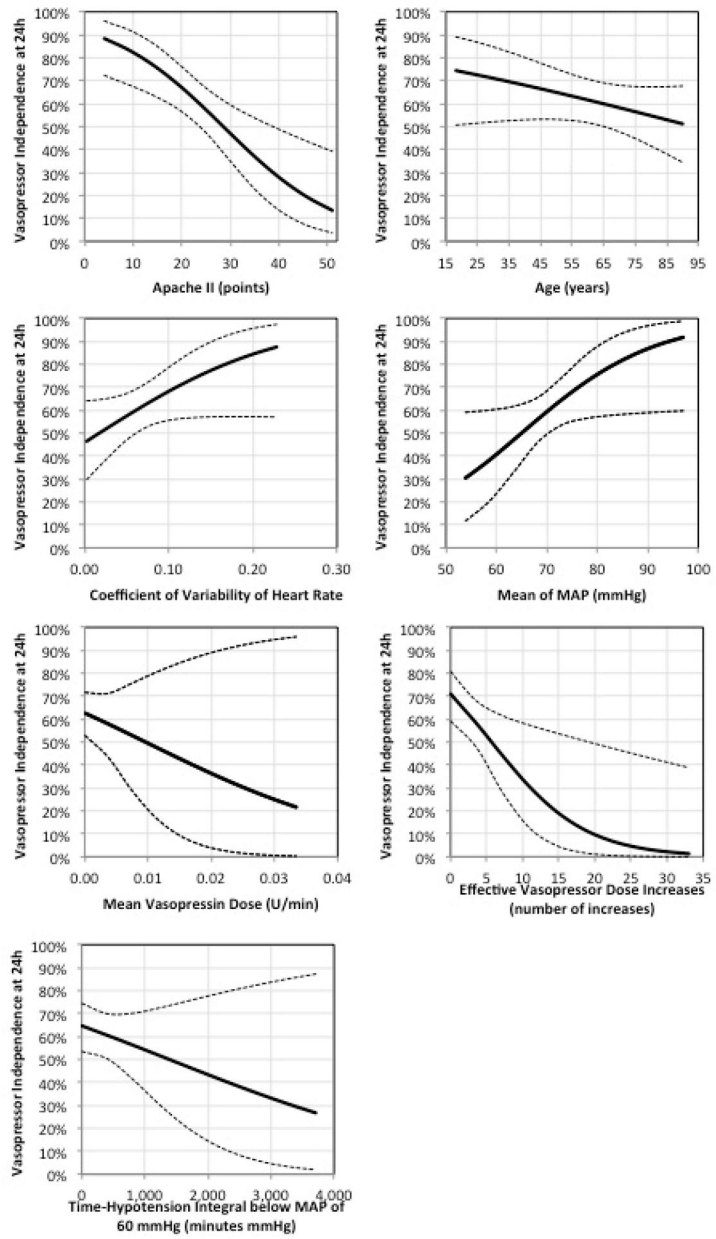

Figure 2. Effect plots of predictors of vasopressor independence at 24 hours

These effect plots represent the relationship between a given predictor and the outcome at different values of the predictor, with all other predictors held constant. These plots represent a more detailed view of what has been represented historically by regression "parameter estimates", commonly called beta coefficients.

Table 1

Patient Characteristics

Characteristic	Central Tendency
Age (years)	64 (IQR 48–77)
Female sex (%)	59
Admission APACHE II score (points)	22 (IQR 17–28)
Received vasopressors in first 6 hours (%)	56
Vasopressor independent at 24 hours (%)	59
28-day mortality (%)	15
ICU-free days at 28 days (days)	25 (IQR 20–26)
Vasopressor-free days at 28 days (days)	27 (IQR 26–28)

APACHE II: Acute Physiology and Chronic Health Evaluation; ICU: Intensive care unit; IQR: Interquartile range

Table 2

Baseline measures of heart rate and blood pressure (first 6 hours)

Characteristic	Central Tendency*
Heart rate (beats/min)	98.75 (19.2)
Coefficient of variation for heart rate	0.06 (0.04–0.09)
Total vasopressor dose (norepinephrine equivalent, mcg/kg)	3.62 (0–30)
Systolic blood pressure (SBP, mm Hg)	103.47 (11.5)
Diastolic blood pressure (DBP, mm Hg)	53.77 (49–58)
Mean blood pressure (MBP, mm Hg)	70.13 (66–75)
Coefficient of variation for SBP	0.1 (0.08–0.13)
Coefficient of variation for DBP	0.1 (0.08–0.13)
Coefficient of variation for MBP	0.1 (0.07–0.12)
Variance of SBP	97.26 (60–163)
Variance of DBP	25.72 (16–50)
Variance of MBP	45.57 (25–72)
Time-pressure integral of MBP under 60 mm Hg (minute-mm Hg)	101 (14–338)

* Interquartile range or standard deviation follow central tendency in parenthesis, depending on normality of the data.

Table 3

Effect of different sampling frequencies on main findings

	Attribute
Every 30-seconds sampling	
Optimal regression model "out of bag" AUC (95% CI)*	0.797 (0.702–0.875)
Median (IQR) of coefficient of variation of heart rate	0.056 (0.039–0.088)
Every 1-minute sampling	
Optimal regression model "out of bag" AUC (95% CI)	0.799 (0.703–0.876)
Median (IQR) of coefficient of variation of heart rate	0.055 (0.039–0.087)
Every 2-minutes sampling	
Optimal regression model "out of bag" AUC (95% CI)	0.793 (0.699–0.874)
Median (IQR) of coefficient of variation of heart rate	0.055 (0.039–0.086)
Every 5-minutes sampling	
Optimal regression model "out of bag" AUC (95% CI)	0.794 (0.697–0.877)
Median (IQR) of coefficient of variation of heart rate	0.057 (0.039–0.086)

*Naïve Bayesian model of vasopressor independence; all models included the same predictors: coefficient of variation of heart rate, AUC of mean arterial blood pressure, number of increases of vasopressor doses in first six hours, mean vasopressin dose.

AUC: area under the curve; SD: standard deviation