**Supplemental Materials**

**Temporal trends and clinical outcomes associated with vasopressor and inotrope use in the cardiac intensive care unit**

Jacob C. Jentzer1,2; Brandon Wiley1,2; Courtney Bennett1,2; Dennis H. Murphree3; Mark T. Keegan4; Kianoush B. Kashani2,5; Malcolm R. Bell1; Gregory W. Barsness1

1 Department of Cardiovascular Medicine

2 Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine

3 Department of Health Sciences Research

4 Department of Anesthesiology and Perioperative Medicine

5 Division of Nephrology and Hypertension, Department of Internal Medicine

All from the Mayo Clinic, 200 First Street SW, Rochester MN 55905

**Supplemental Figure 1:** Flow diagram of patients excluded from and included in the final study population.

H:\Courtney Bennett\Catecholamines paper\Jentzer vasoactives in CICU Supplemental Figure 1.tif

**Supplemental Figure 2:** Short-term mortality in the study population as a function of peak cardiovascular SOFA sub-score. CICU, cardiac intensive care unit, SOFA, Sequential Organ Failure Assessment.

H:\Courtney Bennett\Catecholamines paper\Jentzer vasoactives in CICU Supplemental Figure 2.tif

**Supplemental Figure 3:** Unadjusted short-term mortality as a function of VIS quartile among patients receiving vasoactive drugs. Median VIS among patients receiving vasoactive drugs was 9 (interquartile range 4, 21.66). P <0.01 between groups by pairwise comparison. CICU, cardiac intensive care unit; VIS, Vasoactive-Inotropic Score.

**H:\Courtney Bennett\Catecholamines paper\Jentzer vasoactives in CICU Supplemental Figure 3.tif**

**Supplemental Table 1a.** Calculation of the cardiovascular SOFA sub-score. From Jentzer, JAHA 2018.5

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Score 0** | **Score 1** | **Score 2** | **Score 3** | **Score 4** |
| **Cardiovascular SOFA sub-score**  Mean arterial pressure (MAP, mmHg) and use of vasopressors (mcg/kg/min) | MAP ≥70 | MAP <70 without vasopressors | Dopamine ≤5 or any dobutamine | Dopamine >5, epinephrine ≤0.1 or norepinephrine ≤0.1 | Dopamine >15, epinephrine >0.1 or norepinephrine >0.1 |

**Supplemental Table 1b.** Conversion of other vasopressors into norepinephrine-equivalents (NEE). From Jentzer, Chest 2018.3

|  |  |  |
| --- | --- | --- |
| Drug | **Equivalent dose** | **Norepinephrine equivalents (NEE)** |
| **Norepinephrine** | 0.1 mcg/kg/min | 0.1 mcg/kg/min |
| **Epinephrine** | 0.1 mcg/kg/min | 0.1 mcg/kg/min |
| **Dopamine** | 15 mcg/kg/min | 0.1 mcg/kg/min |
| **Phenylephrine** | 1 mcg/kg/min | 0.1 mcg/kg/min |
| **Vasopressin** | 0.04 U/min | 0.1 mcg/kg/min |

**Supplemental Table 1c.** Calculation of the Cumulative Vasopressor Index (CVI); points given based on doses of each vasopressor. From Trceziak, Intensive Care Medicine 2008.21

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Vasopressor** | **1 point** | **2 points** | **3 points** | **4 points** |
| **Dopamine (mcg/kg/min)** | 0 < dose ≤ 5 | 5 < dose ≤ 10 | 10 < dose ≤ 15 | >15 |
| **Epinephrine (mcg/kg/min)** | --- | 0 < dose ≤ 0.05 | 0.05 < dose ≤ 0.1 | >0.1 |
| **Norepinephrine (mcg/kg/min)** | --- | 0 < dose ≤ 0.05 | 0.05 < dose ≤ 0.1 | >0.1 |
| **Phenylephrine (mcg/kg/min)** | --- | 0 < dose ≤ 0.4 | 0.4 < dose ≤ 0.8 | >0.8 |
| **Vasopressin (units/min)** | --- | --- | --- | Any dose |

**Supplemental Table 2:** Vasoactive drug use and doses among patients receiving any vasoactive drugs, one vasoactive drug or >1 vasoactive drug. Data presented as N (%) or mean ± standard deviation. Individual peak drug doses include only patients receiving that drug. P value is for chi-squared or Student t test comparing patients receiving one vasoactive drug to patients receiving >1 vasoactive drug. \*All vasoactive drug doses and NEE are reported in mcg/kg/min, except vasopressin (U/min).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variable** | **Any vasoactive drugs**  **(n = 2468, 100%)** | **One vasoactive drug**  **(n = 1286, 52.1%)** | **>1 vasoactive drug**  **(n = 1182, 47.9%)** | **P value** |
| **Number of vasoactive drugs** | 1.8±1.1 | 1.0±0.0 | 2.7±0.9 | <0.0001 |
| **Dobutamine usage** | 406 (16.5%) | 95 (7.4%) | 311 (26.3%) | <0.0001 |
| **Peak dobutamine dose\*** | 5.5±4.5 | 4.9±4.3 | 5.6±4.5 | 0.1393 |
| **Dopamine usage** | 1202 (48.7%) | 495 (38.5%) | 707 (59.8%) | <0.0001 |
| **Low-dose dopamine** | 525 (21.2%) | 262 (20.4%) | 263 (22.2%) | 0.2550 |
| **High-dose dopamine** | 677 (27.4%) | 233 (18.1%) | 444 (37.6%) | <0.0001 |
| **Peak dopamine dose\*** | 8.5±5.9 | 7.0±4.8 | 9.5±6.3 | <0.0001 |
| **Epinephrine usage** | 639 (25.9%) | 97 (7.5%) | 542 (45.8%) | <0.0001 |
| **Peak epinephrine dose\*** | 0.25±0.46 | 0.17±0.44 | 0.26±0.46 | 0.0358 |
| **Milrinone usage** | 602 (24.4%) | 254 (19.8%) | 348 (29.4%) | <0.0001 |
| **Peak milrinone dose\*** | 0.29±0.13 | 0.29±0.12 | 0.29±0.14 | 0.9458 |
| **Norepinephrine usage** | 715 (29.0%) | 161 (12.5%) | 554 (46.9%) | <0.0001 |
| **Peak norepinephrine dose\*** | 0.31±0.45 | 0.17±0.23 | 0.35±0.49 | <0.0001 |
| **Phenylephrine usage** | 363 (14.7%) | 153 (11.9%) | 210 (17.8%) | <0.0001 |
| **Peak phenylephrine dose\*** | 1.07±1.67 | 0.67±1.17 | 1.36±1.91 | <0.0001 |
| **Vasopressin usage** | 557 (22.6%) | 31 (2.4%) | 526 (44.5%) | <0.0001 |
| **Peak vasopressin dose (U/min)** | 0.044±0.028 | 0.041±0.013 | 0.044±0.028 | 0.1525 |
| **Peak cardiovascular SOFA** | 2.7±1.1 | 2.1±1.0 | 3.3±0.7 | <0.0001 |
| **Peak CVI** | 4.0±3.7 | 1.7±1.4 | 6.6±3.8 | <0.0001 |
| **Peak VIS** | 23.9±46.5 | 7.9±16.2 | 41.3±60.5 | <0.0001 |
| **Peak NEE\*** | 0.22±0.46 | 0.06±0.16 | 0.40±0.60 | <0.0001 |

CVI, Cumulative Vasopressor Index; NEE, norepinephrine-equivalent dose; SOFA, Sequential Organ Failure Assessment; VIS, Vasoactive-Inotropic Score.

**Supplemental Table 3:** Baseline characteristics of the study population and vasoactive drug use divided by year of admission. Data displayed as N (%) or mean ± standard deviation, with P value for between-groups comparison using chi squared or analysis of variance.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variable** | **Admitted from 2007 to 2009 (n = 3693)** | **Admitted from 2010 to 2012 (n = 3282)** | **Admitted from 2013 to 2015 (n = 3029)** | **P value** |
| **Age** | 67.5±15.2 | 67.3±15.2 | 67.5±15.3 | 0.7358 |
| **Female** | 1424 (28.6%) | 1207 (36.8%) | 1115 (36.8%) | 0.2118 |
| **Caucasian** | 3366 (91.2%) | 3037 (92.5%) | 2833 (93.5%) | 0.0011 |
| **BMI (kg/m2)** | 29.3±6.8 | 29.5±7.3 | 29.8±7.2 | 0.0419 |
| **Charlson Comorbidity Index** | 2.3±2.6 | 2.4±2.6 | 2.5±2.7 | 0.0124 |
| **Day 1 SOFA score** | 3.5±3.1 | 3.6±3.2 | 3.7±3.4 | 0.0375 |
| **Day 1 cardiovascular SOFA** | 1.2±0.8 | 1.2±0.8 | 1.3±1.0 | 0.2282 |
| **Maximum week 1 SOFA** | 3.9±3.3 | 4.0±3.4 | 4.1±3.5 | 0.0976 |
| **Peak cardiovascular SOFA** | 1.34±0.94 | 1.34±0.96 | 1.37±1.05 | 0.4513 |
| **APACHE-III score** | 61.4±25.2 | 61.1±25.5 | 60.5±25.2 | 0.3308 |
| **Vasoactive drug use** | 854 (23.1%) | 796 (24.2%) | 818 (27.0%) | 0.0009 |
| **Vasopressor use** | 737 (20.0%) | 684 (20.8%) | 669 (22.1%) | 0.1015 |
| **Inotrope use** | 318 (8.6%) | 289 (8.8%) | 321 (10.6%) | 0.0106 |
| **Inotropes only** | 117 (3.2%) | 112 (3.4%) | 149 (4.9%) | 0.0004 |
| **>1 vasoactive drug** | 408 (11.0%) | 381 (11.6%) | 393 (13.0%) | 0.0467 |
| **# vasoactive drugs** | 0.43±0.95 | 0.43±0.90 | 0.49±0.98 | 0.0048 |
| **# vasopressors** | 0.33±0.79 | 0.33±0.75 | 0.38±0.83 | 0.0243 |
| **Peak CVI** | 0.98±2.63 | 0.90±2.35 | 1.10±2.63 | 0.0074 |
| **Peak VIS** | 5.91±24.46 | 5.82±27.45 | 6.02±23.93 | 0.9492 |
| **Peak NEE** | 0.053±0.238 | 0.054±0.270 | 0.058±0.240 | 0.6982 |
| **Dobutamine use** | 166 (4.5%) | 118 (3.6%) | 122 (4.0%) | 0.1635 |
| **Dopamine use** | 516 (14.0%) | 434 (13.2%) | 252 (8.3%) | <0.0001 |
| **Epinephrine use** | 231 (6.3%) | 194 (5.9%) | 214 (7.1%) | 0.1588 |
| **Milrinone use** | 181 (4.9%) | 195 (5.9%) | 226 (7.5%) | <0.0001 |
| **Norepinephrine use** | 156 (4.2%) | 191 (5.8%) | 368 (12.2%) | <0.0001 |
| **Phenylephrine use** | 131 (3.6%) | 110 (3.4%) | 122 (4.0%) | 0.3379 |
| **Vasopressin use** | 203 (5.5%) | 159 (4.8%) | 195 (6.4%) | 0.0217 |

**Abbreviations:** APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; CICU, cardiac intensive care unit; CVI, Cumulative Vasopressor Index; NEE, norepinephrine equivalents; SOFA, Sequential Organ Failure Assessment; VIS, Vasoactive-Inotropic Score.

**Supplemental Table 4:** Univariate analysis of vasoactive drug requirements and severity of illness scores as predictors of hospital mortality. Odds ratios are for single unit changes in score. Patients not receiving vasoactive drugs were assigned scores of zero for the vasoactive drug scores.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Predictors of hospital mortality** | **All patients** | | | **Patients receiving vasoactive drugs** | | |
| **Variable** | **Unit OR** | **95% CI** | **AUROC** | **Unit OR** | **95% CI** | **AUROC** |
| **Day 1 cardiovascular SOFA sub-score** | 2.49 | 2.35-2.64 | 0.720 | 1.82 | 1.67-1.99 | 0.685 |
| **Max number of vasoactive drugs** | 2.26 | 2.14-2.38 | 0.750 | 1.68 | 1.55-1.83 | 0.666 |
| **Peak cardiovascular SOFA sub-score** | 2.75 | 2.59-2.91 | 0.771 | 2.72 | 2.41-3.07 | 0.738 |
| **Peak CVI** | 1.36 | 1.33-1.39 | 0.756 | 1.24 | 1.21-1.27 | 0.733 |
| **Peak VIS** | 1.049 | 1.045-1.053 | 0.767 | 1.032 | 1.028-1.036 | 0.772 |
| **Peak NEE (per 0.01 mcg/kg/min)** | 1.047 | 1.044-1.052 | 0.761 | 1.031 | 1.027-1.034 | 0.769 |
| **APACHE-III score** | 1.047 | 1.044-1.050 | 0.823 | 1.030 | 1.026-1.033 | 0.737 |
| **Day 1 SOFA score** | 1.42 | 1.39-1.45 | 0.828 | 1.25 | 1.22-1.28 | 0.732 |
| **Max week 1 SOFA score** | 1.45 | 1.42-1.48 | 0.849 | 1.33 | 1.29-1.37 | 0.780 |

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; AUROC, area under the receiver-operator characteristic curve; CI, confidence interval; CVI, Cumulative Vasopressor Index; NEE, norepinephrine equivalents; OR, odds ratio; SOFA, Sequential Organ Failure Assessment; VIS, Vasoactive-Inotrope Score.