Is there opportunity for automated decision-support and closed-loop control in ICU patients receiving vasopressor infusion?

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***Abstract*— Vasopressors are administered to critically ill patients suffering from a body-wide reduction in blood circulation. In theory, if the vasopressor infusion is either too high or too low, it could be harmful to the patient. In a retrospective analysis, we investigated the degree to which today's intensive care unit (ICU) patients receive appropriate vasopressor therapy, in terms of how often the mean arterial pressure (MAP) was kept within a normative range. Using the MIMIC II database, we studied patients with minute-by-minute MAP data, sourced from the bedside monitor, who were receiving vasopressor therapy. For each record, we identified MAP samples that were out-of-range, i.e., MAP < 60 mmHg or MAP > 100 mmHg, and grouped these into out-of-range episodes. Each out-of-range episode was categorized as either transient (< 15 min) or sustained (≥ 15 min). Out of the 224 ICU stays, we identified 152 ICU stays (68% of ICU stays) with at least one sustained MAP out-of-range episode. In that subset, MAP was frequently out-of-range (out-of-range 18.4% of the time) due to a combination of sustained episodes of hypotension and hypertension. Compared with all ICU stays, those stays with sustained out-of-range events did not demonstrate an increased MAP variability per hour. It is possible that the out-of-range events resulted from insufficient dose-adjustment. Technologies that might continuously optimize vasopressor dosing throughout the patient's stay and thereby minimize these abnormal cardiovascular states may be worthy of further study.**

I. Introduction

Vasopressors are a class of medications that elevate arterial blood pressure (BP) in critically ill patients suffering from a body-wide reduction in blood circulation [1], [2]. When cardiac output is reduced, or vascular tone is abnormally low, vasopressors result in improved perfusion of critical organs (e.g., brain and heart) though they may reduce perfusion of less essential organs. Effectively administered, vasopressors may reduce morbidity and mortality in critically ill patients [3]–[6].

Because they have a relatively short half-life, vasopressors are administered by continuous infusion. Different patients have varied cardiovascular responses to a given dose [7], [8]. Because of innate variability between patients, as well as temporal variability in their underlying physiological state, it may not be possible to select the optimal dose in advance. Rather, the dose must be iteratively titrated: a given dose is administered, the response observed, and then, if necessary, the dose is adjusted.

In theory, if the vasopressor infusion is not properly dosed, it could be harmful to the patient. When too small a dose is given, hypoperfusion may persist, which can lead to ischemia and organ damage [9]–[11]. However, a vasopressor dosage that is too high may cause other adverse outcomes, such as tachycardia [8]–[11] or excessive afterload, or excessive vasoconstriction of peripheral tissue beds. Based on the theoretical benefit of providing optimal infusion doses, our collaborative team has explored algorithms to predict dose-response relationships during vasopressor infusion, e.g., [12], [13].

We decided it would be valuable to investigate the degree to which today's intensive care unit (ICU) patients receive appropriate vasopressor infusion therapy, in terms of how often the patients' mean arterial pressures (MAP) are kept within a normative range. Typically, MAP < 60 mmHg is consistent with insufficient perfusion pressures, whereas MAP > 100 mmHg is supra-physiological and in theory could be associated with needless myocardial demand or peripheral tissue vasoconstriction/hypoperfusion. With a goal to better evaluate today's practices involving vasopressor titration in the ICU, we examined a publically available database of ICU clinical data, MIMIC II (Multi-Parameter Intelligent Monitoring in Intensive Care) [14]. Our goal was to better characterize opportunities for new technologies, such as automated decision-support and closed-loop control, in the management of ICU patients receiving vasopressor infusions.

II. Methods

A. Data Collection and Pre-Processing

In retrospective analysis, we analyzed the MIMIC II database, which is a publicly available research database containing archives of adult ICU patient data from a set of ICUs within one tertiary care hospital. MIMIC II includes clinical documentation and vital sign trends.

Using MIMIC's query engine, its Virtual Machine, we identified subjects who received vasopressor infusion. We queried for subject records with documented administration of dopamine, epinephrine, Levophed or Neosynephrine. We then obtained the timing, vasopressor dose, crystalloid volume bolus details, and nursing documentation from the Virtual Machine. Next, for this set of potential subjects, we also obtained their MAP data using the "PhysioBank ATM"

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978-1-4244-7929-0/14/$26.00 ©2014 IEEE

which provided the minute-by-minute trends in MAP originally sourced from the patients' bedside physiological monitors.

We conducted further analysis using our own routines implemented in MatLab (Mathworks, Natick MA). We identified all subjects with MAP trend data available during documented infusion of vasopressors. We excluded subjects who did not have MAP data available during the episodes of vasopressor infusion, and subjects who died within 48 hours of the end of the data (we excluded those who died because of the possibility of abnormal pathophysiology that made it impossible to maintain 60 mmHg ≤ MAP ≤ 100 mmHg, regardless of vasopressor dose).

Ultimately, we analyzed records from 224 distinct ICU stays, from a total of 182 different patients (within MIMIC-II, when patients returned to the ICU after any extended absence, it is treated as a new ICU stay). The MAP data were filtered using a fifth order median filter (i.e., 5-min window) to remove transient outlying data.

B. Data Analysis

We commenced with a record of each subject's vasopressor dosage as a function of time, along with each patient's minute-by-minute MAP trends (after median filtering, as above).

For each record, we identified MAP samples that were out-of-range, i.e., MAP < 60 mmHg or MAP > 100 mmHg, and grouped these into out-of-range *episodes*. Each out-of-range episode started upon the first out-of-range MAP and terminated with any subsequent in-range MAP sample. Each out-of-range episode was categorized as either *transient* (< 15 min) or *sustained* (≥ 15 min).

For each record, we computed a series of descriptive statistics about the proportions of MAP that were *i*) in-range, *ii*) out-of-range during transient events, and *iii*) out-of-range during sustained events (Fig. 1). We computed descriptive statistics about these events. Finally, we computed descriptive statistics for the entire study population.

III. Results

Out of the 224 ICU stays (182 distinct patients), we identified 27 ICU stays (27 distinct patients), representing 12% of ICU stays, where MAP was wholly in-range for every MAP sample (recall that isolated samples of abnormal MAP had been removed by median filtering during pre-processing). We identified another 45 ICU stays (44 distinct patients), representing 20% of ICU stays, who had episodes of MAP out-of-range, but never sustained for 15 min or longer. Finally, we identified 152 ICU stays (127 distinct patients), representing 68% of ICU stays, who experienced at least one sustained MAP out-of-range episode.

General statistics summarizing the 224 ICU stays are available in Table 1. Additional statistics about the ICU stays with the episodes of sustained out-of-range MAP are shown in Table 2. Finally, statistics about individual episodes of out-of-range MAP are shown in Table 3.

TABLE I. General statistics summarizing 224 ICU stays

General Statistics	
Expression	**Number**
Total number of distinct subjects, n	182
Total number of ICU stays, n	224
Length on pressors per ICU stay, [min]	Median = 962 IQR = 300 - 2362
% of in-range MAP, [%]	Median = 89.6 IQR = 76.0 - 97.7
% of MAP out-of-range during transient episodes, [%]	Median = 3.0 IQR = 0.8 - 5.9
% of MAP sustained < 60 mmHg, [%]	Median = 1.7 IQR = 0 - 13.5
% of MAP sustained > 100 mmHg, [%]	Median = 0.0 IQR = 0.0 - 3.9
Variation of MAP per hour, [%]	Median = 3.8 IQR = 2.7 - 5.7
Number of vasopressor dose changes per hour, (average for ICU stays ± std. dev., n)	0.5 ± 0.5

TABLE II. Statistics for patients with sustained out-of-range episodes

Statistics for Patients with Sustained Out-of-Range Episodes	
Expression	**Number**
Total number of distinct subjects, n	127
Total number of ICU stays, n	152
Length on pressors per ICU stay, [min]	Median = 1276 IQR = 569 - 2980
% of in-range MAP, [%]	Median = 81.6 IQR = 66.9 - 91.7
% of MAP out-of-range during transient episodes, [%]	Median = 3.7 IQR = 1.9 - 6.2
% of MAP sustained < 60 mmHg, [%]	Median = 8.5 IQR = 1.6 - 20.1
% of MAP sustained > 100 mmHg, [%]	Median = 0.0 IQR = 0.0 - 3.9
Variation of MAP per hour, [%]	Median = 4.1 IQR = 2.9 - 6.2
Number of vasopressor dose changes per hour, (average for ICU stays ± std. dev., n)	0.5 ± 0.4

TABLE III. Statistics for sustained out-of-range episodes

Statistics for Sustained Out-of-Range Episodes	
Expression	**Number**
Number of episodes per ICU stay, n (amongst ICU stays with at least one episode)	Median = 3 IQR = 1 - 9
Time between episodes, [min]	Median = 86.5 IQR = 60.8 - 487
Duration of episodes, [min]	Median = 27.0 IQR = 22.0 - 37.5
Longest episode per stay, [min] (amongst ICU stays with at least one episode)	Median = 51.5 IQR = 30.0 - 98.0

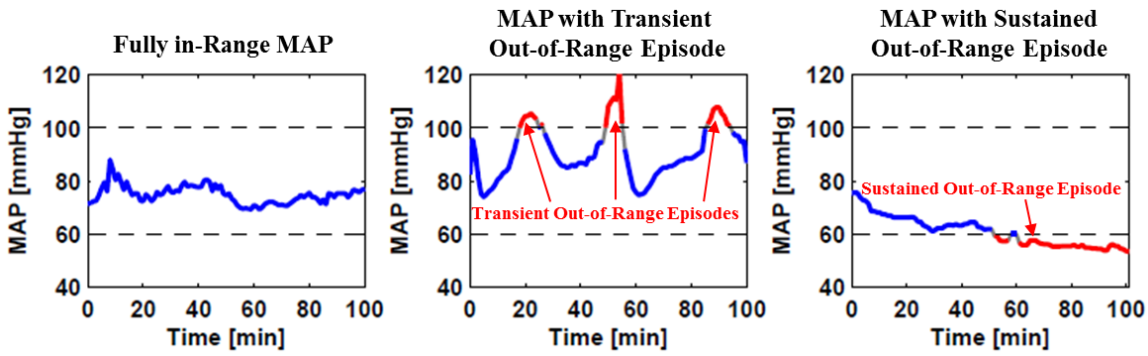

Figure 1: In-range MAP vs. transient/sustained out-of-range MAP episodes

IV. Discussion

In theory, vasopressor infusion is a natural application for automated decision-support and closed loop control technologies. However, to the best of our knowledge, there are no existing data evaluating the potential value of such technologies.

We decided to analyze an ICU database to investigate how often the patients receiving vasopressor infusion therapy remained outside of a physiological range. We only studied subjects who survived at least 48 hours after vasopressor therapy.

We found that more than half (68%) of the ICU stays evidenced a sustained episode of MAP out-of-range. In that subset of ICU stays, MAP was frequently out-of-range (out-of-range 18.4% of the time). There was a combination of sustained episodes of hypotension as well as hypertension.

There was no evidence that these episodes tended to cluster in time. Indeed, there was significant time between each episode, typically. The median episode lasted over 27 min, and episodes longer than that were commonplace.

Compared with all ICU stays, those stays with sustained out-of-range events did not demonstrate a significant increase in MAP volatility, i.e., variation in MAP per hour was similar. Of note, stays with sustained out-of-range events did not evidence any elevated rate of dose changes per hour. We speculate that the out-of-range events may have been mitigated from additional dose-adjustment.

In future work, it will be worthwhile to further study these sustained out-of-range events, to better investigate the clinical circumstances of their occurrence, and how clinicians typically responded to their development, to understand whether superior vasopressor dosing strategies could have minimized such events, maintaining MAP between 60 to 100 mmHg. As well, whether such out-of-range events were truly deleterious to patients is speculative, but there is reasonable physiological justification to believe that if they can be avoided, it would be beneficial for patients.

V. Conclusion

About 68% of the patients in an ICU database who were receiving vasopressor infusion demonstrated frequent sustained episodes where MAP was either below 60 mmHg or above 100 mmHg. Technologies that might continuously optimize vasopressor dosing throughout the patient's stay and thereby minimize these abnormal cardiovascular states may be worthy of further study.

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