Differentiating between Hemorrhage and Sepsis for Hypotensive Subjects Using Arterial Pressure Data

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Introduction

Hemorrhage and sepsis are two critical medical conditions which share hypotension as the major early symptom. However, induced by different causes, these two conditions require different treatments and if not timely treated, both can lead to shock and, eventually, death. In current practice, the recognition of the specific condition that a hypotensive patient is exposed to highly depends on the vigilance of the clinical personnel. Previous studies[1,2] mainly focus on the prediction and analysis of sepsis using high-resolution physiological data instead of the distinction between sepsis and hemorrhage. In this work, we propose a data-driven machine learning approach to differentiate between these two conditions in hypotensive subjects by utilizing large amounts of routinely collected physiological time series. Our approach, demonstrated in laboratory animal experiments, confidently identifies the majority of septic subjects apart from hemorrhagic subjects at early stages of hypotension episodes. The proposed method has the potential to inform timely treatment decisions and facilitate favorable patient outcomes in critical care settings.

Methods

Data

We used laboratory animal data for our analysis. 22 healthy Yorkshire pigs were anesthetized and stabilized for one hour. Then 15 subjects were subject to induced bleeding at a constant rate of 5 mL/min until their mean arterial pressure (MAP) decreased to 30 mmHg, and the other 7 subjects were given two subsequent lipopolysaccharide (LPS) infusions to induce sepsis. The first LPS infusion was intended to weaken the subjects' immune mechanisms, and the second infusion was performed to induce sepsis-related symptoms. Arterial pressure was collected at 250 Hz.

We utilized data during the first episode of induced bleeding, and the second infusion of LPS, respectively, for the two groups, and extracted data from hypotension onset to the end of the experiments. Hypotension was defined as arterial pressure dropping below 60 mmHg. Statistical features including mean, median, standard deviation, and range, as well as spectral (Discrete Fourier Transform) features of different frequency bands (0.04-0.15Hz, 0.15-0.4Hz, 0.4-10Hz, 10-125Hz) were computed for 4-minute moving time windows updated at 2 Hz, extracted from arterial pressure waveform. These features were standardized using the first minute of induced bleeding or LPS infusion to mitigate possible subject-dependent biases introduced by the induced pathologies, so that the arterial pressures of two groups were at comparable levels.

Model and Evaluation Protocol

We trained a Random Forest machine learning model over the statistical features to differentiate between hemorrhage (negative class) and sepsis (positive class). To accommodate a relatively small cohort size, we evaluated the performance using leave-one-pair-out cross-validation: one negative subject and one positive subject, both randomly chosen, were held-out as the test set and the model was trained using the remaining subjects. This process was repeated 105 times (15 negatives x 7 positives), and the mean and 95% confidence intervals (CI) of performance metrics were reported.

Results

When evaluated on the entire period from the onset of hypotension to the end of induced bleeding or LPS infusion, our approach achieves AUROC 0.878 ± 0.042 (mean and 95% CI), and is able to confidently identify 64.6% septic patients while only giving 1 false alert out of 10,000 such predictions on average, as shown in Figure 1. We also evaluated the models on different truncated time intervals. As shown in Figure 2, during 5-10 minutes after the onset of hypotension, our approach achieves AUROC 0.852 ± 0.058, and identifies 80.4% septic patients at extremely low false positive rate, and during 10-15 minute interval, our approach improves to AUROC 0.910 ± 0.049, and identifies 87.8% septic patients with high confidence, as more discriminative evidence becomes available over time in arterial pressure waveforms.

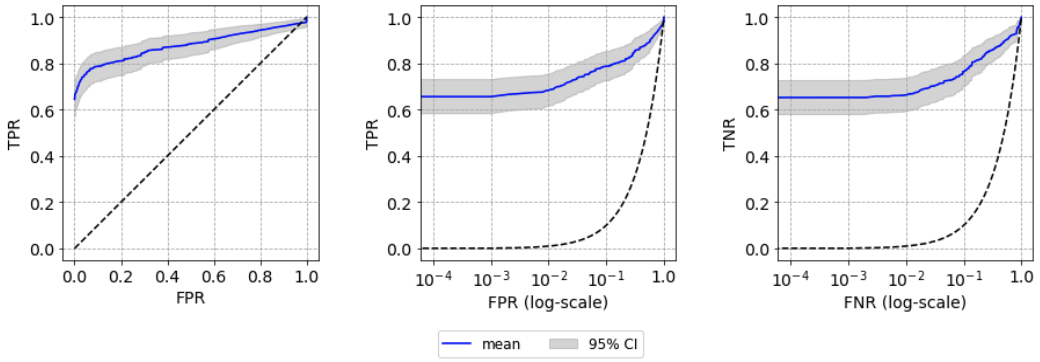

Figure 1: ROC curves when our approach is evaluated on the entire period of disease. False Positive Rate (FPR) and False Negative Rate (FNR) in the middle and right plots are shown in logarithmic scales to emphasize the performance at clinically relevant low FPR and low FNR settings. Dashed lines represent a random predictor for reference.

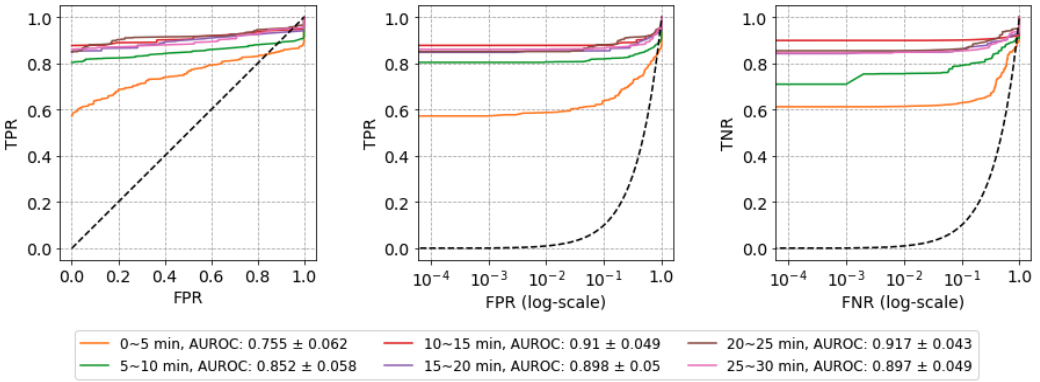

Figure 2: Mean ROC curves when our approach is evaluated at different truncated time intervals into the disease. The mean and 95% CI of AUROC are shown in the legend.

Conclusions and Discussion

Our results show that during a short time period after the onset of hypotension, our approach is capable of identifying the majority of septic subjects from hemorrhagic subjects using features derived from arterial blood pressure waveforms, despite both groups having similar mean arterial pressures. By utilizing the high-frequency physiological data collected from patients continuously monitored at the bedside, it should be possible to differentiate sepsis from hemorrhage within minutes of the onset of hypotension, and inform treatment that substantially differs between these two conditions. Our approach has the potential to be applied in critical care settings to support clinical decision making and resuscitation resource allocation. Future work includes the exploration of the utility of hemodynamic vital signs other than arterial pressure, and further investigation of the generalizability of the proposed approach on larger and more complicated datasets collected in bedside monitoring of human subjects.

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