Infection in the Intensive Care Unit Alters Physiological Networks

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Abstract

Physicians use clinical data to treat patients every day, and it is essential for treating a patient appropriately. However, medical sources of clinical physiological data are only now starting to find use in bioinformatics research. We collected 29 types of physiological data on a minute-by-minute basis from trauma patients in the intensive care unit. We then determined that the correlational network amongst pairs of physiological variables changed based on whether the patient contracted an infection. Examining the variable pairs with the largest change in correlation reveals changes in the way our treatments affect physiology and in how our bodies react to physiological insults. These findings highlight the usefulness of obtaining physiological data from the clinic and suggest new relationships to study while validating previously reported relationships.

Introduction

Physicians have been making use of physiologic data for decades, but these measurements have not always been readily available for research use. Largely due to the advent of electronic medical records and improved methods of extracting data from patient monitoring equipment, we now obtain significant amounts of clinical data both during and after treatment.[1,2,3] This points to a new source of data that has been made available to both clinicians and informatics researchers in ways that were not possible previously.

One of the main thrusts of informatics research using clinical data has been to provide greater context for defining disease using physiological and treatment data.[4,5] Use of clinical data for basic biological research has been successful in linking physiological measurements to already known genetic markers of disease,[6] and has yielded biomarkers of human aging.[7]

One area where there seems to be less research is in the physiological modeling of humans undergoing intensive care in a hospital setting. It is this gap that we seek to fill by providing data showing that even basic physiological models of patients in intensive care are changed under conditions of infection. We also show how treatments administered during intensive care can affect physiology in different ways depending on the state of the patient.

Data Collection and Analysis

- 19 ICU patients at San Francisco General Hospital
- Continuous data from heart monitors, ventilators and muscle microdialysis unit (minute-by-minute)
- Intermittent data from blood gas and other labs
- 92,000 measurements of 29 variables (Table 1)
- 2.7 million total measurements
- Primary outcome: infection
- Secondary outcomes: death, organ failure
- Impute microdialysis between readings
- Calculate pairwise Pearson correlation coefficients for patients with and without infection
- 11/19 patients contracted an infection
- Holm-Bonferroni corrected p-values for correlations considered significant if $p < 0.05$ from Student's t-test
- Consider only cases with significant results in both infection and non-infection cases
- Take differences in correlation > 0.4 between cases

Symbol	Definition
PaO2/PCO2	Arterial O_2 and CO_2 partial pressure
map	Mean arterial blood pressure
hr	Heart rate
pmo2(temp)	Muscle oxygen level (temperature)
spo2	Oxygen saturation percentage
fio2	Fraction of inspired oxygen
GLUC.SER	Serum glucose
Ph	Blood PH
PF	PaO2/fio2 ratio
BD	Base deficit (excess blood acidity)
mLactate	Muscle lactate concentration
mGlucose	Muscle glucose concentration
mGlutamate	Muscle glutamate concentration
mPyruvate	Muscle pyruvate concentration
mLP	Muscle lactate/pyruvate ratio
Lactate	Serum lactate
glucose.value	Bedside glucose reading
compliance	Mechanical lung compliance ($\Delta V / \Delta P$)
peep	Positive end expiratory pressure
minvol	Volume of air delivered to lungs per minute
coretemp	Core temperature
CVP	Central venous pressure
Hb/HCT	Hemoglobin/hematocrit
Chloride	Serum chloride
BUN	Blood urea nitrogen
Cr	Serum creatinine

Table 1. Abbreviations and corresponding definitions of the physiological data/biomarkers collected.

Results

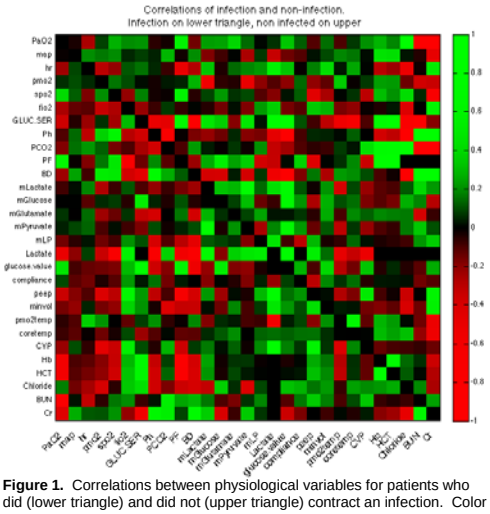

Figure 1. Correlations between physiological variables for patients who did (lower triangle) and did not (upper triangle) contract an infection. Color indicates the magnitude and direction of the correlation as shown in the color bar at the right. Variable names are given on the axes.

Variable Pair	ρ - infection	ρ - no infection
FiO2/PmO2	-0.332	0.0987
mPyruvate/PmO2	-0.0978	-0.506
minvol/mGlucose	-0.148	0.275
compliance/mPyruvate	-0.177	0.224
peep/compliance	0.214	-0.299

Table 2. Correlation coefficients of the variables with the largest change in correlation between conditions.

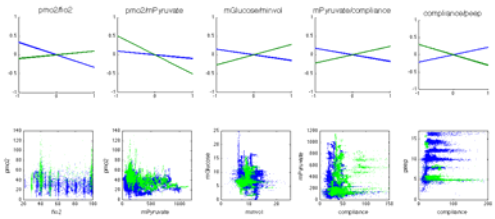

Figure 2. Top row: graphical representation of the correlation coefficients of the five variables with the largest change between conditions. Lines are drawn with a slope equal to the correlation coefficient. Bottom row: scatter plots of the raw data in the two conditions. In all plots blue represents patients who contracted an infection. Green represents patients who did not contract an infection.

Discussion

Fraction of inspired O_2 vs. muscle O_2 content

In rats with infection increasing FiO_2 does not increase PmO_2 effeciently.[9] Lower PmO_2 correlates with worse outcomes in the ICU, including infection.[10] This is despite attempts to increase PmO_2 by increasing FiO_2. We suggest that the infection reduces the coupling of FiO_2 to PmO_2, and then clinical intervention results in increasing FiO_2 while PmO_2 decreases.

Muscle pyruvate vs. muscle O_2 content

In the non-infection group, there is a tighter correlation between oxygen delivered to and pyruvate removed from the tissue via aerobic respiration. Patients with infections deliver less oxygen to tissue, so the rate of metabolism is less tightly coupled to the delivery of oxygen than in patients without infection. This points to the mitochondria as a culprit in this relationship.

Minute volume vs. muscle glucose

In critically ill patients, reduced glucose can be seen largely as a marker for disease severity;[11] infections may cause reduced levels of tissue glucose. They may also need increased ventilation. This leads to minute volume being anticorrelated with tissue glucose.

Conclusions

We have shown that physiological networks can be constructed from clinical measurements from an intensive care unit, and the topology of these networks can change as a patient contracts an infection. Between these two conditions many variables changed the strength or direction of their correlation. We presented potential physiological interpretations for the five largest of these changes. All but one of these variable pairs directly involve parameters for treatment/ventilation chosen by physicians in the ICU. Therefore, we can also conclude that the effects of treatment on physiology changes when infections are contracted in the intensive care unit. Some of these differences have already been reported in the literature while others are novel. This shows that our technique can be used to discover previously unknown relationships between physiologic variables. This work points to opportunities to study the changes that have not yet been reported, potentially opening new doors to discover how our best efforts to heal patients can both alter and be informed by their physiology.

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Acknowledgement

Supported by the Lucile Packard Foundation for Children's Health and the Stanford Bio-X Graduate Fellowship.