Project Title:

Modeling the Role of Brainstem Inflammation in Systemic Dysfunction during Sepsis

Investigators:

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Project Summary:

Brainstem inflammation occurs quickly after systemic infection and potentially mirrors peripheral inflammation. Our goals are: 1) to model brainstem inflammation, 2) to quantify cardio-respiratory patterning and coupling during the transition from systemic inflammatory response syndrome (SIRS) to sepsis and 3) to define a set of biometrics that prognosticates the tipping point from a beneficial to pathologic inflammatory process.

1 Define Context

Models:

Dr. Vodovotz developed a model for the peripheral inflammatory response to systemic infection. Building on his prior work, we will apply Dynamic Network Analysis (DyNA) and Dynamic Bayesian Network (DyBN) models of cytokine expression in the brainstem and include our biometrics as variables.

Dr. Molkov worked with Ilya Rybak using his model of respiratory pattern generation and has developed a preliminary computational model of cardiorespiratory coupling. Our goal is to model cardiorespiratory coupling in health and its uncoupling in disease states. Respiratory modulation of autonomic activity is mediated by connections between neurons in the medullary ventral respiratory column and ventrolateral medulla that drive automatic tone.

2 Appropriate data

Data for the DyNA and DyBN models (Dr. Vodovotz)

Rats: Physiologic recordings of arterial blood pressure, electrocardiogram and whole-body, flow-through plethysmography. Harvesting tissues of CNS (pons, medulla, cerebrum, cerebellum and cervical spinal cord) and of the periphery (serum, liver, heart, lungs and bronchoalveolar lavage fluid). Measuring cytokines in tissue.

Humans: Physiologic recordings of arterial blood pressure, electrocardiogram and ventilatory pattern extracted from measurements of Pco_2 in inhaled and exhaled gases. We measure serum cytokines in blood sample.

Year 1, we have completed an initial series of experiments to identify the dose of *Escherichia coli* (*E. coli* $25x10^6$ cell in fibrinogen pellet) on which to base the DyNA & DyNB models.

Year 2 (which started Sept. 1st, 2018 for us), we will complete a second series of experiments in rats to generate critical data for the DyNA and DyBN models, in which the dynamics of patterns and cytokines will be associated at time points from 6 to 48 h.

Year 2, we have to date recruited 7 Medical Intensive Care Unit (MICU) patients with sepsis or at risk for septicemia. We analyze their cardio-respiratory patterning and serum cytokines. These data will also be included in DyNA and DyBN models.

Data for the computational model (Dr. Molkov)

Rats: We are using an existing computational model for neural control of respiration and extending it to include cardiorespiratory coupling. We are data mining an existing data set of single-unit, extracellular recordings of ventrolateral medullary activity recorded from perfused *in situ* rat preparations. This experimental model generates coupled phrenic, sympathetic and vagal efferent activity that is coupled. We are analyzing these data to determine: 1) their sensitivity to baro-activation and 2) their connectivity to other simultaneously recorded activity including efferent phrenic and autonomic activities. These data address the mechanism of cardioventilatory coupling (CVC), which is defined as the tendency for last heart beat in expiration to occur at a preferential latency before the onset of inspiration in animals and humans. CVC is weak, independent of the stronger respiratory-modulation of cardiac rhythm and arterial blood pressure and is not present in rats with systemic infection.

Year 1&2, currently we are approximately half-way through the data set and will complete data mining in the first half of this grant year. Initial modelling exposed a poor understanding of the mechanisms of inspiratory onset in existing network models. Thus, we are focusing on the role of augmenting expiratory neurons on the expiratory-to-inspiratory phase transition. We are presenting our work at the Society for Neuroscience in November.

Year 2. We have de-identified the physiologic recordings (respiration, aBP and ECG) of MICU patients to be examined by Dr. Molkov

3 Evaluate within context

Dr. Vodovotz validated the DyNA and DyBN models of peripheral inflammation. These models have biologic credibility in the sense that these models replicate the course of cytokine expression and identified critical-nodes, where targeted interventions affect the course of inflammation.

Year 2, we will begin development of DyNA and DyBN models of central inflammation for which validation and biologic credibility testing will be performed as published previously.

Dr. Molkov and co-workers

Year 2, we have begun and will continue to develop our computational model of cardiorespiratory coupling focusing on respiratory modulated neuronal activity that is excited by arterial pulse pressure and that acts on the Expiration-to-Inspiration phase transition.

4 List Limitations

As these models are developed the qualifications for the use of the models will be defined. For example, we propose to generate, compare and test the DynA and DyBN models in male and female rats.

5 Version Control

Given that version 1 of the computational model is in development and the DyNA and DyBN models require the data being generated now, it is an ideal time to establish how to handle the different version as they are generated. We anticipate that as the versions of the models are generated the naming system will include the Version Number at the end.

6 Documentation

Manuals will be generated as the models are developed.

7 Dissemination

Models and documentation will be made available as a supplement to the manuscript and through sponsored resources as discussed at IMAG and MSM meetings.

8 Independent Review

We have committed to two independent reviews; the first one is scheduled in the summer of 2019 and the evaluators will be a scientist and an engineer at CWRU who are knowledgeable of rhythmic biologic data and modeling but not directly involved in this project.

9 Test Implementations

We will have data from male and female rats and consequently, will model males and females separately and expect differences.

10 Conform to Standards

Models will conform to standard set by the MSM group and/or Model databases.