A computational model of closed loop respiratory control

Choongseok Park, Yaroslav Molkov, Alona Ben-Tal, Natalia Shevtsova, Jeffrey Smith, Ilya Rybak, Jonathan Rubin

A reduced computational model of core interacting excitatory and inhibitory circuits of the respiratory central pattern generator in the ventral respiratory column (VRC) of the medulla demonstrates realistic multi-phase rhythmic respiratory patterns associated with a variety of experimental manipulations \cite{rubinetal2009,rubinetal2011}. We have coupled an expanded version of this model to a computational model of lung ventilation, gas exchange and blood gas transport \cite{bental2008} to study closed loop respiratory neural control. In an initial formulation, inspiratory neural output in the model activates the diaphragm, while peripheral pulmonary stretch receptors provide feedback to VRC circuits via the nucleus tractus solitarius . Under baseline conditions the model generates a eupneic-like 3-phase rhythmic respiratory pattern and reproduces the experimentally observed lengthening of respiratory period with loss of mechanosensory feedback following vagotomy or with block of pontine input drive to the VRC. The model also exhibits experimentally observed respiratory phase resetting properties associated with transient vagal stimulation. We have augmented the model to include central chemosensory feedback to the retrotrapezoid nucleus (RTN) and to oscillatory units in the parafacial respiratory group as suggested in \cite{molkovetal2011}, which are activated by hypercapnia and drive abdominal musculature to produce forced expiration. This extended model explains the transition to apnea by hyperventilation when the CO2 level in the blood falls below a certain threshold and also shows how elevated CO_2 in the inspired air leads to active expiration via engagement of a second oscillator in the RTN. Model simulations show that depending on conditions, such as CO2 levels, the hypercapnia-induced increase in minute ventilation can be provided by two different mechanisms: by increases in tidal volume involving the expiratory reserve volume or by an increase in breathing frequency.