Chapter 6

MECHANISMS OF SLEEP APNEA AT ALTITUDE

William Whitelaw

Department of Medicine, University of Calgary, Calgary, Alberta, Canada.

Abstract: At altitude normal people often develop periodic breathing in sleep - regularly recurring periods of hyperpnea and apnea. This phenomenon is probably explained by instability of the negative feedback system for controlling ventilation. Such systems can be modeled by sets of differential equations that describe behavior of key components of the system and how they interact. Mathematical models of the breathing control system have increased in complexity and the accuracy with which they simulate human physiology. Recent papers by Zbigniew Topor et al. (5,6) describe a model with two separate feedback loops, one simulating peripheral and the other central chemoreceptor reflexes, as well as accurate representations of blood components, circulatory loops and brain blood flow. This model shows unstable breathing when one chemoreceptor loop has high gain while the other has low gain, but not when both have high gain. It also behaves in counter-intuitive way by becoming more stable when brain blood flow is reduced and unresponsive to blood gas changes. Insights from such models may bring us closer to understanding high altitude periodic breathing.

Key Words: mathematical modeling, central apnea, unstable control systems, chemoreceptor feedback

INTRODUCTION

Apnea is one feature of “unstable breathing”, an engineering term used to describe a pattern of breathing in which tidal volume gradually increases to maximum, then decreases to zero, where it remains during the apnea, then increases again in a recurring periodic pattern. At sea level, such recurrent apneas are typically ‘obstructive’. The pharynx falls closed because of relaxation of pharyngeal dilator muscles in sleep. During the apnea, the diaphragm continues to contract but no air flows through the obstructed pharynx. CO₂ gradually rises and PO₂ falls until the chemical stimuli cause sufficient activation of pharyngeal dilator muscles to reopen the pharynx and permit breathing to resume. At altitude,
or on exposure to low inspired oxygen, on the other hand, apneas are typically ‘central’ meaning that when tidal volume falls to zero there is no obstruction and no efforts are made by respiratory muscles during the apnea. (1)

The periodic breathing of altitude can be explained by engineering theories of negative feedback control systems. Such systems are considered unstable if they display a persistent pattern of periodic behavior in response to a disturbance in the controlled output.

A familiar example is the system that controls temperature in a shower. In the showerhead, water from a hot water source and water from a cold water source mix to produce water of a certain temperature. When the water falls on the skin of the person in the shower, temperature receptors signal the temperature to the central nervous system, which compares this temperature with the desired temperature and when necessary emits a command to correct the temperature. If the water temperature is too high, the command is sent through nerves to muscles of the hand and arm which cause the hand to reach out and turn the tap controlling the flow of hot water until the mixture of water coming from the showerhead is at the desired temperature. This is called a negative feedback system because an increase in temperature perceived at the temperature receptors leads to a decrease in the flow of hot water into the showerhead and thus to a corrective decrease in temperature.

The shower control system can be unstable if there is a long pipe between the tap that adjusts the flow of hot water and the showerhead. This causes a delay between the time the tap is adjusted and the time the resulting temperature is perceived at the temperature receptor. If somebody flushes a toilet nearby so that the flow of the cold water into the showerhead goes down and the temperature of the water striking the skin goes up, the subject reaches out and begins turning the tap down to reduce the hot water flowing into the shower. At a certain point the perfect adjustment is reached but the subject does not realize that until the water with the correct temperature has had time to go up the pipe and out the showerhead to the temperature receptors. During this delay, the subject continues to turn the flow of hot water down until the temperature of the water coming out of the showerhead is much too cold. When that cold water reaches the skin the subject reaches out again and winds the tap the other way, but once again overshoots because of the delay in the pipe and allows the temperature to get too hot. It is clear that a system like this could continue to oscillate indefinitely. It is also intuitively clear that oscillations will be more likely to happen and will be bigger when they do occur if the subject has very sensitive skin, because in that case he or she will react much more briskly to small changes in temperature and wind the tap much more quickly round, causing a much bigger overshoot.

The main factors that will make this system unstable are therefore are the delay in the pipe and the sensitivity or the gain in the feedback loop, that is the amount of change in the level.

The feedback control system for arterial P CO2 is analogous. Arterial P CO2 depends on the balance between flow of CO2 into the lung from venous blood and out of the lung, by means of ventilation. Arterial CO2 is sensed by chemoreceptors. There is a delay between the change in ventilation and the change in CO2 at the chemoreceptor. This feedback system can therefore become unstable if the gain in the CO2 feedback loop is high or if the delay is increased.

This kind of system lends itself to mathematical modeling. Numerous researchers with background in engineering have developed mathematical simulations of the respiratory