Mechanisms and Consequences of Sleep Apnea: Insights from Modeling of Chemoreflex Control of Ventilation

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With regard to the genesis of periodic breathing and apneas, the use of physiologically-based computational models of chemoreflex control of breathing has provided general insights into the roles of specific mechanisms involved in the feedback control of ventilation. Our early studies utilized formal mathematical approaches to simplify complex models of this type so that their behaviors could more easily be predicted from various combinations of physiological and environmental parameters. Because it is difficult to apply such models to individual patients, we subsequently pursued a "black-box" approach in which the objective was to characterize the dynamic properties of the system for individual subjects, then relate these properties to physiological and environmental parameters. By stimulating ventilation through pseudorandom variations in inspired CO_2 (or O_2) level, we estimated input-output models, both open-loop (i. e., from end-tidal P_{CO_2} to ventilation) and closed-loop (i. e., from inspired CO_2 to ventilation). We have shown that the dynamic properties of the resulting models differ between normal subjects and both sleep apnea patients and heart failure patients. We also demonstrated in normal subjects that the closed-loop model does not change between wakefulness and quiet sleep, even though the gain of the open-loop (or controller) model decreases. To explore the mechanistic basis for these findings using a detailed, physiologically-based, chemoreflex model, we felt it necessary to enhance the typical model of this type by improving the representation of O_2 transport and distribution beyond the usual, single lumped-compartment, approach. In our new model, brain and muscle tissue each comprise two subcompartments with intercompartmental diffusion and arterio-venous shunting, as well as O_2 binding to myoglobin in muscle. We are using this model to predict changes in brain tissue P_{O_2} during sleep apnea.