Mathematical modeling for breath gas analysis[1]

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ABSTRACT:
We developed two different compartment models relating breath trace gas concentrations to their concentrations in blood. These trace gases are isoprene and acetone, two prototypical substances with very different physico-chemical properties. The mathematical models for the first time correctly describe the exhalation kinetics of these substances under different exercise workloads and breath maneuvers. The models have been validated by various experiments on the ergometer and in a sleep laboratory setting.

1 INTRODUCTON

''Physicians have diagnosed what is ailing the patient from the breath since the days of Hippocrates. The modern era of breath testing commenced in 1971, when Nobel Prize winner Linus Pauling demonstrated that human breath is a complex gas, containing well over 200 different volatile organic compounds (VOCs) in picomolar concentrations.''
(Anil S. Modak in *J. Breath Res.* 4 (2010), 017002)
These compounds are produced in the human body by metabolic processes. Some of them are characteristic markers of physiological events or metabolic disorders, rendering breath gas analysis a promising new tool for medical diagnosis.
Exhaled breath analysis has the advantage of being non-invasive. Breath samples can be extracted as often as desired and can be measured in real-time, even in breath-to-breath resolution. Breath gas analysis hence is an optimal choice for gaining continuous information on the current metabolic and physiological state of an individual.
Mostly, however, there is little evidence of the exact origin of VOCs or their response to changing physical conditions such as ventilation and cardiac output. The last two factors are important to get a better understanding of the exchange processes that determine distribution, disposition and absorption processes of VOCs in the body. Understanding their influence and control is mandatory for achieving an accurate standardization of breath sample collection and for the correct deduction of the corresponding blood concentration levels.

2 THE MODELS

Physiological models describe the behavior of substances by means of compartmental mass conservation. The compartments are defined as functional units of the organism, corresponding either to specific, localized anatomic structures (like liver, lung, kidney, etc.) or types of tissues (such as fat, muscle, viscera, bone, etc.) that are distributed throughout the body, respectively. The concentration time course of a compound in each compartment is subsequently described by a mass-balance differential equation.
Isoprene is extremely sensitive with respect to changes in ventilation or pulmonary perfusion due to its small blood to air partition coefficient. It is exchanged exclusively in the alveoli. During exercise on the ergometer at constant workload the breath concentration profile exhibits a peak-shaped behavior reaching a new steady state after about 15 minutes. After a break a typical wash-out effect is recognizable, with smaller peak heights in repeated exercise segments. We developed a three compartment model consisting of an alveolar compartment, a richly perfused tissue compartment, and a peripheral tissue (containing skeletal muscles) compartment (cf. Fig. 3 and Equations (3)-(5) in reference [1]).
The classical Farhi model predicts a decrease of breath acetone concentrations under workload on the ergometer but in reality an increase is measured. Contrary to isoprene, acetone has a high blood to air partition coefficient and highly hydrophilic characteristics. Hence the airways have a considerable influence on gas exchange, so that inhalation conditions must be taken into account. The exchange is dominated by the mucus layer in the bronchioles. We developed a four compartment model consisting of a bronchial compartment, an alveolar compartment, a liver compartment, and a tissue compartment (cf. Fig. 3 and Equations (14)-(17) in reference [2]).

3 DISCUSSION

The existing theory states that isoprene is mainly produced in the liver by the mevalonate pathway of cholesterol biosynthesis. In contrast, our model for isoprene predicts that isoprene is mainly produced in the skeletal musculature compartment and that the concentration of isoprene differs in various parts of the body. A preliminary measurement of breath isoprene in patients with muscular dystrophy showed that these patients have a breath isoprene concentration of about 3 ppb (normal is 100 ppb), yielding a strong support for this new model. Also former investigations on the age dependency of breath isoprene concentrations and its reduction under statin therapy (statins are myopathic) nicely fit into this rationale (see [1] and the references therein).

REFERENCES

[1] Julian King, et al., Physiological modeling of isoprene dynamics in exhaled breath, *J. Theoret. Biol.* **267** (2010) 626-637, http://dx.doi.org/10.1016/j.jtbi.2010.09.028.
[2] Julian King, et al., A mathematical model for breath gas analysis of volatile organic compounds with special emphasis on acetone, *J. Math. Biol.,* in print (2011), http://dx.doi.org/10.1007/s00285-010-0398-9.