

Abstract

Mathematical modelling of “blood-gas kinetics” for validation of breath-based diagnostics.

1. INTRODUCTION

Breath gas analysis as a non-invasive method for clinical diagnostics will soon be developed to the point that it can be put into use. Pilot studies demonstrate the importance of this method for early detection diagnosis as well as for clinical monitoring of certain diseases. Patients accept the process of taking breath gas samples obligingly which makes it easy to obtain even multiple samples. Breath gas samples can be obtained in real-time and therefore enable continuous monitoring of body substances, e.g., on the ergometer or at the sleep laboratory.

Human breath contains more than 200 volatile organic compounds (VOCs) as byproducts at trace level. With the development of modern mass spectrometry we can identify today substances at ppb level (1 ppb = one part in a billion). This high sensitivity makes it necessary to measure very carefully to get reproducible results since contaminations and artifacts can easily compromise results and lead to wrong conclusions.

Since human breath is connected via pulmonary alveoli with blood by a thin membrane every substance occurring in blood will appear in traces in breath. Exhalation kinetics and blood to gas ratios may significantly affect concentrations of potential molecular marker substances in breath. Therefore, mathematical models describing the relationship between blood and breath gas concentrations of certain marker substances have been developed and implemented in this project.

As first candidates we chose isoprene and carbon dioxide for normalization. These two substances are easy to measure with PTR-MS or SIFT-MS and a CO₂-sensor and occur in sufficiently high concentrations, (i.e., typical isoprene levels are 50 – 250 ppb).

2. RESULTS

The mathematical model consists of five compartments (Figure 1)

- lung compartment,
- richly perfused tissue compartment (RPT) (including brain, intestine, kidney and spleen),
- fat compartment,
- muscle compartment and
- liver compartment.

The lung compartment is assumed to be homogenous, where the gas exchange between the alveolar air and the blood in capillaries takes place by diffusion. Isoprene production occurs in the liver compartment with a constant rate and metabolic elimination occurs in the liver compartment and in richly perfused tissue (by resorption in intestine and elimination by urine in kidney) described by Michaelis-Menten kinetics and/or linear kinetics. Fat compartment and muscle compartment are non-active compartments in the sense that neither metabolism nor production takes place. Isoprene has a high solubility in fat, so the concentration of isoprene in fat compartment is 82 times the concentration of isoprene in blood. Thus, if the isoprene concentration decreases in blood, the fat compartment may take the role of an isoprene buffer. Physical activity has a crucial impact on the isoprene concentration in blood, therefore the muscle compartment becomes important when we describe the effects of physical activity.

The model is described by a series of mass balance differential equations which quantify the rate of change of the amount of isoprene in each model compartment.

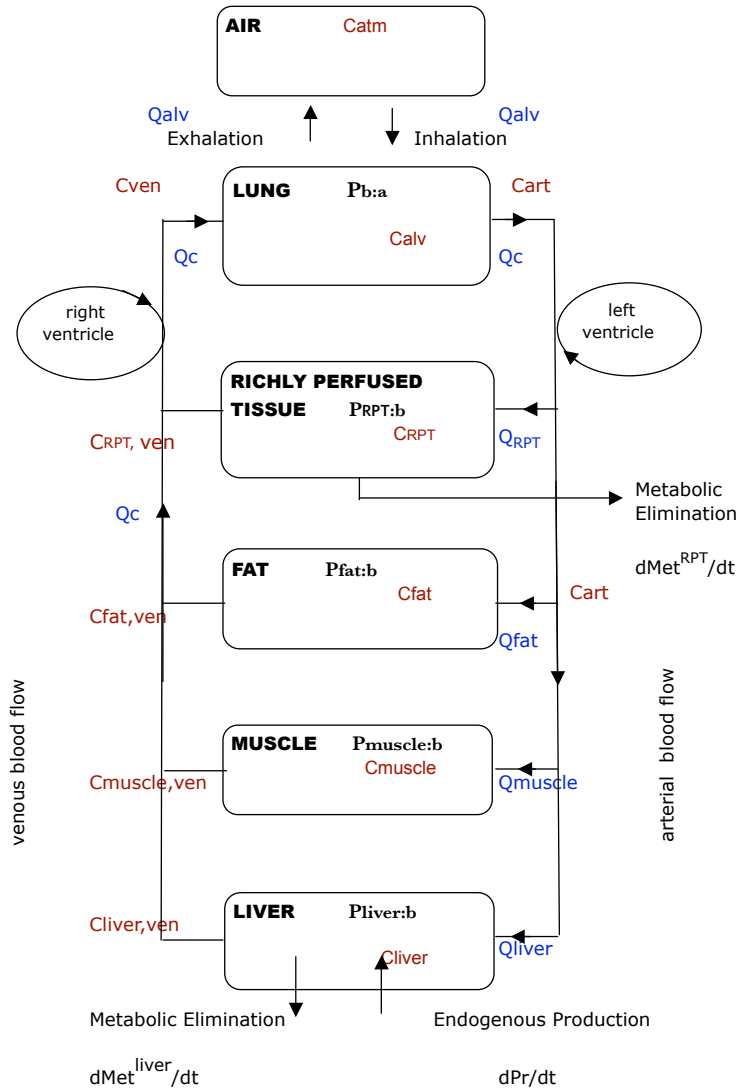


FIGURE 1. Five compartment model

3. DISCUSSION

When the workload w on the ergometer increases the model predicts that the isoprene concentration in breath decreases approx. $1/w$. This coincides with the following fact. While cardiac output during exercise increases by a factor of 3 to 4, alveolar breath minute volume increases by a factor of 12 to 16 at the same time.

In order to validate and refine the model, ergometer tests with stepwise increasing workloads under different conditions (before and after meal; morning and evening) will be performed in a consecutive project.