Development of a CO_2 triggered alveolar air sampler

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***Abstract*—Despite its enormous potential, breath analysis is far from reaching a widespread use in the clinical practice. Among many reasons, the lack of effective and reproducible sampling procedures plays a primary role. In this paper, the design of an alveolar air sampler is presented.**

I. Introduction

In the last years promising results revealed the potential of a noninvasive biochemical monitoring of the exhaled breath [1,2,3,4,5,6,7,8]. In fact, thanks to an almost instantaneous equilibrium between the pulmonary blood and the air in the alveoli of the lung [3,7], volatile substances in breath exhalation can provide insights of biochemical processes. Sensor-based electronic devices are expected to play the main role when specific patterns of disease markers have been defined, and a new generation of breath test instruments could, in time, become ordinary in medical screening [3,9,10,11,12]. At present, despite the potentiality, breath analysis is still challenging. The main technical obstacles are the development of suitable techniques for the sampling and the analysis of volatile compounds at trace level as well as their correlation to specific changes induced in the metabolism by the pathologies, while the main methodological issue is the standardization. Generally accepted standards do not exist, hence reproducibility and reliability of sampling methods and analytical measurement procedures are of critical importance. The only available guideline concerning sample collection for breath analysis was released in 1999 by the American Thoracic Society/European Respiratory Society in the case of NO monitoring in breath [13]. This document also contains useful indications concerning the cleaning procedures of devices and the safety of patients. Exhaled air can be sampled in two ways: mixed expiratory sampling and alveolar sampling. The former method entails the collection of the total breath, including the air contained in the upper airways which experiences no gas exchange with blood (dead space), while the latter method involves the collection of the only alveolar air, which contains most of the chemical information on blood composition. Mixed expiratory sampling is often used due to its simplicity, but the variable individual dilution of the alveolar air with dead volume introduces a noise in the data.

Concentrations of endogenous volatiles are higher in samples containing just the alveolar air, so alveolar sampling provides a further advantage when the concentration of target compounds is low. Moreover, alveolar air samples have the lowest concentration of environmental volatile organic compounds [14,15], another large source of errors. In the present work, a device for the sampling of the alveolar fraction of breath is presented.

II. How Can Dead Space Air Be Discriminated From Alveolar Air?

The respiratory system may be divided into a section which mainly acts as a conducting airway (dead space) and a section whose chief function is gas exchange (alveoli, alveolar sacs and atria). Unfortunately, a sharp separation cannot be made between the two because of the absence of a distinct anatomical boundary and the diffusion and mixing of gases occurring across this boundary region during expiration, phenomena which depend on the anatomy and rate of respiration. For this reason, Fowler defined a 'physiological dead space' as the volume of the conducting airway down to the location at which a large change in gas composition occurs [16]. He found possible, by simultaneous measurement of nitrogen concentration and volume flow of expired gas, to separate dead space gas from alveolar gas by applying the Bohr's formula:

$$V_e \times C_e = (V_e - V_{ds})\, C_a + V_{ds} \times C_i \qquad (1)$$

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where V_e is the volume of expired air, C_e the concentration of a gas in V_e, V_{ds} the volume of the dead space, C_a is the concentration of the same gas in alveolar air and C_i is the concentration of the same gas in inspired air.

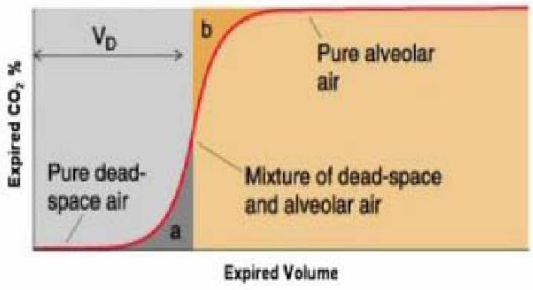

Fig. 1. Fowler's graphical method to determine the point of transition between dead space air (grey) and pure alveolar air (orange), where the *a* and *b* region have the same area. The curve in red represents the concentration of the target gas in the expired air as a function of the volume of expired air.

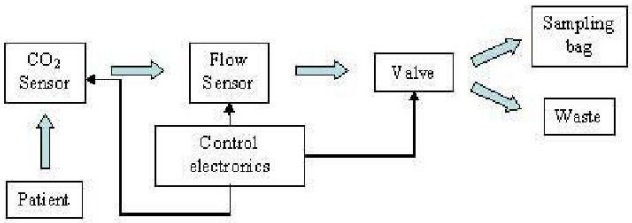

Fig. 2. Block diagram of the alveolar air sampler; hydraulic and electric connections are represented by arrows and connectors respectively.

This formula is expression of a simplified model conceiving the expired breath as the sum of two unmixed fractions, the inspired air contained in the dead space and the alveolar air.

Fowler's is essentially a graphical method (Fig. 1) that allows to assess a transition point between dead space and alveolar air once that the dependence of nitrogen concentration in expired air on the expired volume is known. Firstly developed using nitrogen as tracer compound, its validity was later demonstrated for other gases such as carbon dioxide, oxygen, and helium [17]. Several simplified approaches have been proposed to avoid the long and tedious Fowler's procedure and obtain easier determinations [18-20], but such approximations deliver quantities which are different from Fowler's dead space by as much as 10% or more [18]. More recently, an algorithm was proposed to be used on real time computer-assisted determinations [21].

III. Sampler Design

A. *Block diagram and specifications*

A block diagram of the alveolar air sampler is reported in Fig. 2, where hydraulic and electric connections are represented by arrows and connectors respectively. Several constraints have to be fulfilled for the system to be effective: 1) low head losses (few ml of water) to limit the effort needed to blow the bag;

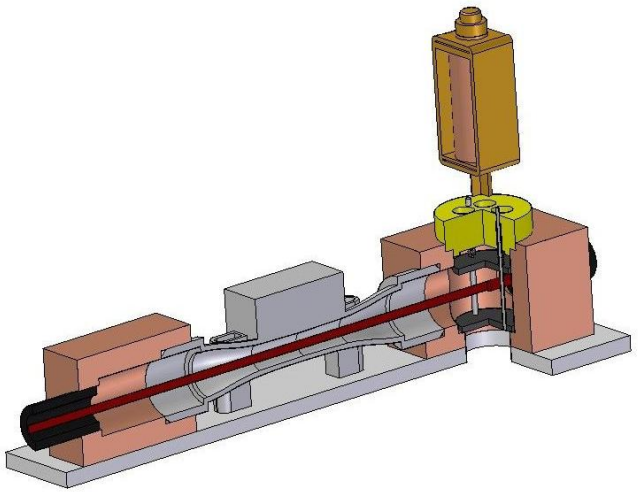

Fig. 3. Schematic drawing of the alveolar air sampler: a) laser system for CO_2 measurements, b) flow sensor, c) solenoid valve.

2) clean materials, i.e. low emission and low absorption rate, to avoid the contamination of the breath sample and memory effects; 3) last but not least, high speed. The average exhalation during quiet breathing lasts about 1.5 -2 sec, so less than a second is available for the data acquisition, calculations and valve actuation.

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2. *System description*

The flow measurement is performed by a microbridge mass airflow sensor (Honeywell AWM5104VN) featuring a Venturi type flow housing. It measures flows as high as 20 standard liters per minute with a maximum repeatability and hysteresis error of 0.5 %. The maximum pressure drop is 2.25" H_2O, which allows to comply with the specifications. The microbridge chip is in direct contact with the flow stream, greatly reducing error possibilities due to orifice or bypass channel clogging. The sensor is provided of circuitry which performs amplification, linearization, temperature compensation and gas calibration and supplies a 1 to 5 Vdc linear output.

The carbon dioxide concentration is measured by wavelength modulation spectroscopy (WMS), an optical absorption technique very effective for the detection of gases. The emission wavelength of a temperature stabilized laser diode is modulated, by varying the injected current, to scan with high resolution a single absorption line of the target gas. In the case of carbon dioxide, a wavelength of 1580 nm has been selected, with an amplitude of the scan range of 1 nm. As light propagates through the sample, the wavelength modulation is converted into an amplitude modulation by the different absorption of the target species in different points of the absorption peak. For this reason, the output signal of the photodiode used as a detector contains AC components at the modulation frequency and its harmonics. The second harmonic was selected by doubling the frequency of the portion of the modulation waveform used to synchronize a lock-in amplifier (demodulation). Theory predicts that if the amplitude of the modulation range is small compared to the line width, the spectrum of the nth harmonic is proportional to the nth derivative of the absorption line spectrum, that can so be calculated. The concentration value is then derived thanks to the well known Lambert-Beer law.

A data acquisition board (USB 6210, National Instruments) is used to acquire data from both the flow sensor and lock-in amplifier, and to command the valve diverting the sample into the sampling bag. A dedicated software has been developed in Labview™ to provide the user of a graphical interface, perform calculation of dead volume and control the valve.

3. *Discussion*

A profile of carbon dioxide concentration in breath during a long single breath is reported in figure 4. The choice of developing a CO_2 sensor based on a tunable laser diode offers both short and long term advantages. A short response time is achievable that is needed to provide data, perform calculations,

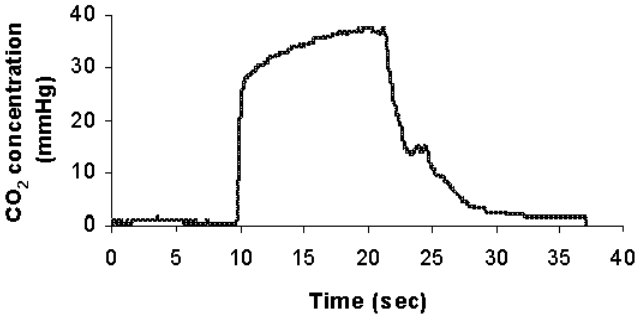

Fig. 4. CO2 profile measured during a long single breath.

estimate dead volume and control the valve quickly enough to sample alveolar air in multiple breaths. Furthermore, the shift in frequency from values near DC to high frequencies of the absorption measurements makes WMS a thousand to one hundred thousands more sensitive compared to ordinary optical absorption techniques. If this feature is relatively not important for carbon dioxide, which is present in breath a partial pressures up to 40 mmHg, it is of fundamental importance to monitor marker compounds, which are present in breath at ppb or even ppt level. In this perspective, the architecture used for the sampling system could be integrated with an array of laser diodes to develop a portable diagnostic instrument.

The choice of sampling multiple breaths should allow to collect large volumes of alveolar air and to detect, after a pre-concentration step, compounds which are present in breath only at trace level. The achievement of this result is not straightforward, a long clinical validation is needed to make sure that artefacts due for example to psychological aspects of human-machine interactions are not neutralising the efforts done to develop the device.

IV. Conclusions

Sampling of the only alveolar fraction of breath is not an easy task. The dead space volume varies significantly among individuals and this is even more true for the physiological dead space defined by Fowler. Moreover, this parameter is affected by the rate of respiration, and it has been proved that individuals begin to hyperventilate when they are asked to breath into a device. For these reasons an on-line estimate of dead volume has is needed, but time available for data acquisition and treatment on a single breath is not much. In the present work, the design of a CO_2 triggered alveolar air sampler was presented and discussed.

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