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Real-time measurement of particulate matter deposition in the lung

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Abstract
Air pollution and cigarette smoke are recognized health risks. A method was developed for the measurement of the deposition fraction (DF) of polydisperse particulate matter (PM) in human airways. Ten normal volunteers [three females, age range 18–67 years, mean age (SD) 43.9 (14)] made single breath exhalations after inhalation to total lung capacity. The exhaled breath was diverted to a multichannel laser diffraction chamber where the particulate profiler measured 0.3–1.0-μm particles. DF was inversely related to expiration flow-rate, 0.69 (0.02) at 4 l min^{-1} and 0.5 (0.01) at 13 l min^{-1}, respectively ($p < 0.05$), and was influenced by the inhalation flow-rate [0.70 (0.02) at 3 l min^{-1} and 0.59 (0.02) at 13 l min^{-1}, respectively ($p < 0.05$)], while no differences were found between nasal and oral inhalation (0.68 (0.05) versus 0.67 (0.06), $p > 0.05$). Higher breath holding times were associated with elevated DF [0.74 (0.02) at 20 s, and 0.62 (0.05) without breath holding ($p < 0.01$)]. When the expiratory flow was controlled and the breath hold time standardized, DF was reproducible (CV = 4.85%). PM can be measured in the exhaled breath and its DF can be quantified using a portable device. These methods may be useful in studies investigating the health effects of air pollution and tobacco smoke.

Keywords: *Particulate matter, exhaled breath, pollution, lung inflammation, particle deposition*

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Introduction

Air pollutants have been recognized as a risk for human health. Airborne particulate matter (PM) is associated with the development of respiratory diseases including lung cancer, chronic obstructive pulmonary disease and asthma exacerbations, as well as with the development of cardiovascular diseases (Lippmann et al. 2003). PM < 10 μm in diameter (PM_{10}) derives mainly from industrial heating, combustion of vehicle fuels and environmental tobacco smoke (ETS) (Lighty et al. 2000) and is responsible for a stepwise increase in mortality for each 10 μg m^{-1} increases of its environmental concentration (Samet et al. 2000). Interestingly, ETS is the major contributor to PM indoor levels, which often exceed outdoor concentrations (Repace & Lowrey 1980). PM < 2.5 μm in diameter ($PM_{2.5}$, fine particles) is considered to be more dangerous

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because it can penetrate peripheral airways reaching pulmonary alveoli, and deposit itself in the respiratory bronchioles (Churg & Brauer 2000, Pinkerton et al. 2000).

To date, most experimental studies of particle deposition in the human respiratory tract have relied on monodisperse synthetic aerosols (Kim 2000, Martonen et al. 2000). However, despite the negative health implications of PM, at present not much is known about the distribution and retention in the respiratory system of polydisperse particles such as environmental PM, with the exception of studies on PM derived from tobacco smoking (Strong et al. 1994, Morawska et al. 1999, Hofmann et al. 2001). Recently, Montoya et al. measured the lung deposition of ultrafine ambient particles in the airways. However, only a small number of subjects ($n=6$) were included and the lung deposition of PM was measured during tidal breathing. Because, like in previous studies, the authors employed a tidal breathing technique (Strong et al. 1994, Hofmann et al. 2001, Kim 2000, Martonen et al. 2000), which is difficult to standardize, the intra- and intersubject variability were significant.

In view of the need to measure the deposition of ambient PM along the respiratory tract, we developed a new method based on a laser particle counter that allows the measurement of environmental fine particles concentration in human exhaled breath in real time, and to determine the particle deposition fraction in the respiratory system. The method is based on a single-breath exhalation, which is easier to control and standardize. We studied the major environmental and physiological variables that may influence the measurements and have standardized the method.

Measuring ambient PM deposition in the lung could contribute to an understanding of many diseases associated with air pollution. Furthermore, the quantification of PM deposition would allow us to investigate how much environmental pollution can damage the lung. This could have interesting implications in the study of the effects of indoor and outdoor pollution or in investigations measuring the effect of ETS on airway disease. Furthermore, this method may also be useful in assessing the deposition of inhaled medications.

Materials and methods

Exhaled breath manoeuvre and measurement of PM concentration

Experiments were carried out in a laboratory located in Chiavenna, northern Italy. All subjects were exposed to environmental air, which was not filtered or conditioned. After inhaling ambient air from functional residual capacity (FRC), exhaled PM was measured during a single exhalation from total lung capacity to residual volume at a constant exhalation flow rate. A calibrated flow meter provided visual feedback for the subjects to maintain a constant exhalation flow rate. The exhaled air was diverted to a laser chamber by a pump at the constant flow of 2.83 l min^{-1}, and the air in excess was diverted to an expansion pipe (Figure 1), which acted as a reservoir.

The analyser consisted of a laser diffraction particulate profiler (model 9012, Metone Instruments, Inc. Grants Pass, OR, USA), which was used in other studies (Marufu et al. 2005), calibrated for the measurement of PM with a channel counting particles within 0.3 and 1.0 μm of aerodynamic diameter. The system operated at the sampling rate of one measurement s^{-1}. The laser detector measures six channel sizes: 0.3–1.0, 1.1–2.0, 2.1–3.0, 3.1–4.0, 4.1–5.0 and >5.1 μm, but this study reports only data from channel 1: 0.3–1.0. The size and concentrations of each channel were factory calibrated using polystyrene latex National Institute of Standards and

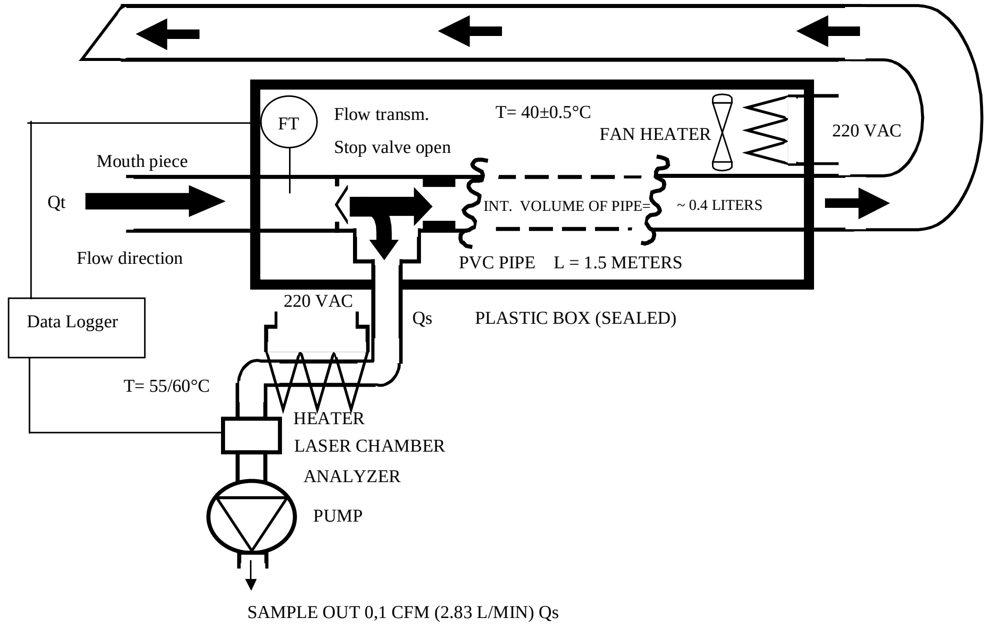

Figure 1. Equipment used to measure particulate matter (PM) concentration in the exhaled air. Exhaled air is diverted from the mouthpiece into the laser analyser, while the air in excess is directed to an expansion pipe. All the equipment is maintained at 40 ± 0.5°C.

Technology (NIST) traceable PM. Each channel detects signals included between two levels of laser pulses, i.e. all pulses from the pre-amplifier comprised two different voltage levels. The number of pulses corresponded to the number of particles passing through the laser and the amplitude reflected their size. The concentrations of PM and the exhalation flow rate were recorded in real-time on a computer. Because the high humidity of exhaled breath could have interfered with the PM measurement, the equipment was kept inside a heated chamber at a constant 40 ± 0.5°C in accordance with US Environmental Protection Agency (EPA) recommendations to avoid evaporation of semi-volatile hydrocarbons and ammonia nitrates.

Background particle counts from expansion pipe and directly from ambient air

Background ambient indoor air PM concentrations were measured by sampling the ambient air through the expansion pipe. To verify whether PM levels were artificially reduced because of their deposition along the expansion pipe, we compared PM concentrations obtained by sampling directly from the environment and through the expansion pipe itself. No statistically significant differences were found (mean (SD), 530 000 (2378) and 530 300 (2454) respectively, $p > 0.05$).

Calculation of total deposition fraction (DF)

DF was calculated by measuring the area under the curve (AUC) of PM concentration over time, according to the following formula (Kim 2000):

$$(\text{Total area} - \text{AUC})/\text{total area},$$

where AUC equals the number of particles retained in the airways and the area above the curve reflects the number of particles that are actually exhaled. The ratio [(Total area – AUC)/total area] is defined as the DF. Because the DF takes into account both the inhaled and exhaled concentrations, any volume change will not affect the ratio.

Setting

Studies were conducted in a laboratory room. To ensure a high stability of the PM concentrations, the air exchange rate was reduced to a minimum and internal ventilation was provided to ensure a good mixing factor. Particle concentrations were representative of ambient pollution in different days (about 100 000 particles l^{-1}). Furthermore, to test the performance of the equipment at high concentrations (about 500 000 particles l^{-1}), in one experiment we artificially increased indoor PM concentrations by means of environmental tobacco smoke generated from smouldering cigarettes. Background values were measured before and after each exhalation recording to take into account the slow deposition of the PM due to the gravity.

Subjects

Ten normal volunteers [three females, age range 18–67 years, mean (SD) age 43.9 (14)] were enrolled from a doctor's practice. All subjects had normal spirometry, and none was on medication. No patient reported chest or systemic infections in the 4 weeks before the study. Eight of the subjects were lifelong non-smokers, one was an ex-smoker, and one was a current smoker. A consent form was filled in and signed by all the participants to the study.

Statistics

The mean $\pm$SD was calculated from triplicates experiments. A Student's t-test was used for data comparison. Reproducibility of AUC was studied by means of the Bland and Altman test (Bland and Altman 1986). The statistical analysis and AUC were calculated using GraphPad Prism 3 Statistical Package.

Study design

A number of experiments were carried out to standardize the performance of the system and to study the physiological variables that could affect the results. System performance tests:

- Background measurements of reliability and repeatability at different particle concentrations.
- Reliability of particle exhalation curves.
- Analysis of particle exhalation curve.
- Reproducibility of AUC.
- Plotting exhaled instantaneous flow and incremental volumes versus exhaled particle concentration.

Physiological parameters that the method enables to study:

- Calculation of individual DF.

- Reproducibility of DF.
- Influence of exhaled flow rate on DF.
- Influence of inhaled flow rate on DF.
- Influence of breath-holding on deposition fraction.
- Influence of inhaling from the mouth or the nose on DF.

Results

System performance tests

Background measurements, reliability and repeatability at different particle concentrations. To prove the stability and repeatability of the background measurements of PM, we examined 300 consecutive measurements recorded for 5 min at different ambient air particle concentrations. We found a mean (SD) background PM concentration of 529 500 (3071), 155 000 (3836) and 71 320 (3301) particles l^{-1}, for high, intermediate and low ambient PM concentrations. These data show the stability of the PM concentrations during the time of measurement (5 min) confirming the good stability and repeatability of the recordings. In addition, the background $PM_{0.3-1.0}$ measured through the facemask, mouthpiece, flow meter and stop valve were not significantly different compared with the same measurement carried out sampling through the expansion pipe only and excluding the breathing apparatus. Although this indicates that there was no $PM_{0.3-1.0}$ deposition in the breathing system, we cannot exclude that particles of larger size were affected.

Reliability of particle exhalation curves. An example of the recording of particle concentrations in the exhaled breath is shown in Figure 2, which shows three consecutive tests performed by the same subject. Immediately after each exhalation, the particle levels consistently decreased with a similar slope in the three different tests. The exhaled PM concentrations approached a value close to zero at the end of the exhalation. Subsequently, PM concentrations returned to the background values. All the exhalation tracings were remarkably similar indicating that the test is reliable as further confirmed by the AUC repeatability data.

Reproducibility of AUC. An example of AUC is represented by the shaded grey area in Figure 2. Each AUC was calculated starting from the beginning until the end of exhalation, and it represents the sum of exhaled particles that are not retained in the respiratory system of a specific subject, whereas the area above the curve reflects the deposition fraction of the inhaled PM. The intra-session reproducibility was assessed in ten volunteers by the Bland and Altman test. The measurements of the average plotted against the difference of the PM concentrations were within 2 SD of the mean confirming the reproducibility of the method (Figure 3), with a coefficient of variability of 5.27%.

Plotting exhalation flow rate and incremental exhaled volumes versus exhaled particle concentration. The equipment allows the subjects to keep a constant exhalation flow rate by means of a visual feedback. In addition, it is also possible to analyse simultaneously instant particle concentration in the exhaled breath, and incremental exhaled air volume (Figure 4).

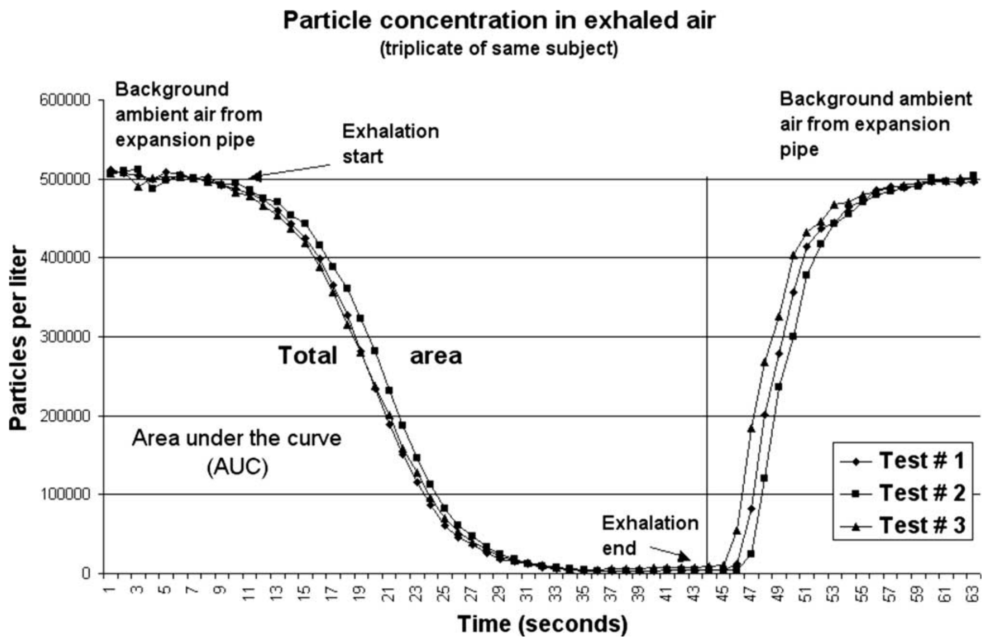

Figure 2. Tracings of real time on line measurement of exhaled particulate matter 0.3–1.0 μm. Three measurements performed in the same subject are shown.

Physiological parameters

Calculation of individual deposition fraction (DF). The DF could be measured in every subject. The means of three measurements are shown in Figure 5. With measurements made at a constant exhalation flow rate of 10 l min^{-1}, the DF ranged from 0.46 to 0.63, with a mean of 0.57 (0.05).

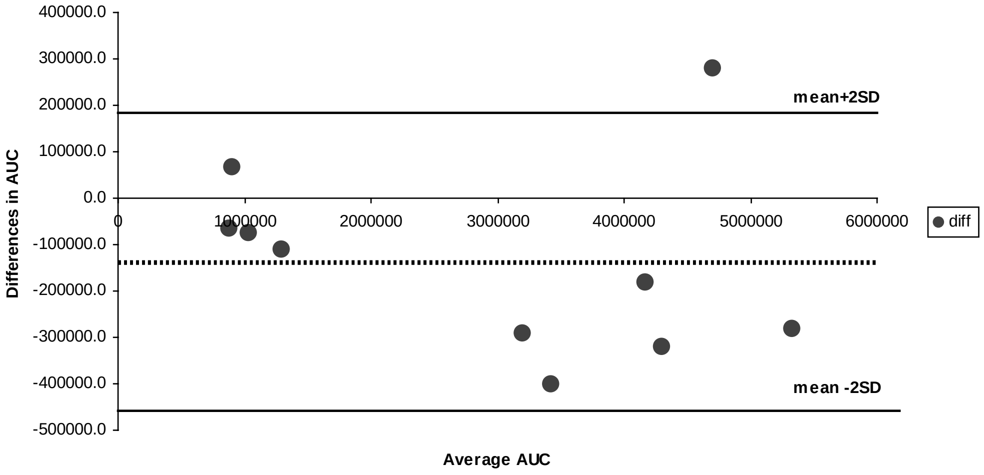

Figure 3. Intra-session variability of exhaled particulate matter (area under the curve, AUC) in ten subjects (Bland and Altman's test). Duplicate measurements in each subject were recorded at 10-min intervals.

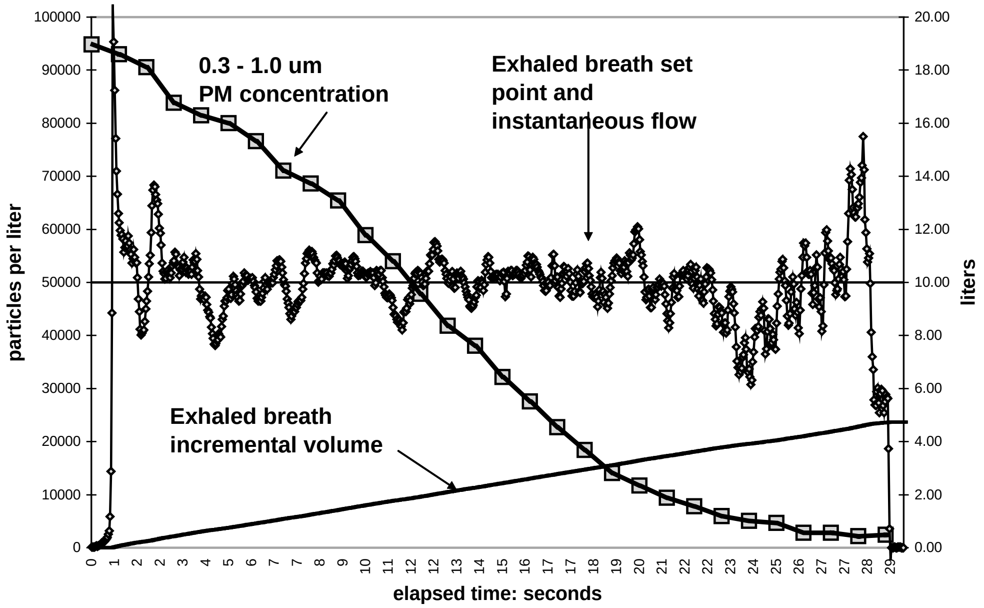

Figure 4. Example of real-time tracings for particulate matter 0.3–1.0 μm particle concentration, flow rate and exhaled air volume following a single breath exhalation.

Reproducibility of DF. The reproducibility of DF was assessed by the Bland and Altman test. The measurements of the average plotted against the difference of particle concentrations were within 2 SD of the mean confirming the reproducibility of the method. In addition, the reproducibility of the method was further confirmed by the intra-session (4.85%) and intersession (5.31%) coefficient of variability.

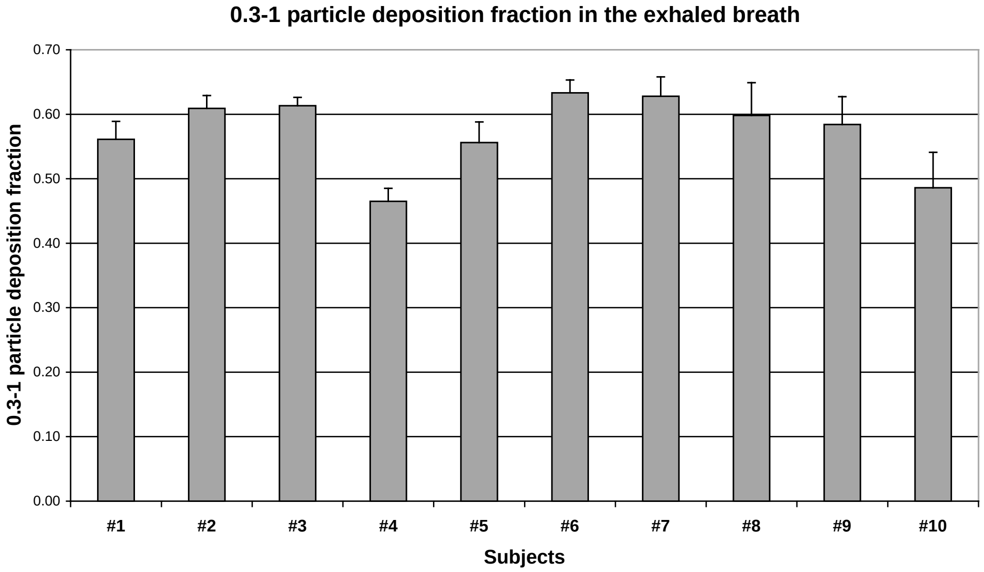

Figure 5. Deposition fraction of particulate matter 0.3–1.0 μm in 10 normal subjects.

Influence of exhalation flow rate on DF. In five subjects, DF proved to be exhalation flow rate-dependent. At low flow rates (4 l min^{-1}), the mean DF was elevated [0.69 (0.02)] compared with higher flow rates [0.63 (0.03), 0.58 (0.02), and 0.53 (0.01) at 6, 10, and 13 l min^{-1}, respectively, $p < 0.05$] (Figure 6, A).

Influence of inhalation flow rate on DF. When the exhalation flow rate was kept constant at 10 l m^{-1}, the DF was influenced by the inhalation flow rate. At low flow rates (3 l min^{-1}) the mean DF proved to be elevated [0.70 (0.02)] compared with higher flow rates [0.65 (0.01), 0.58 (0.03) and 0.59 (0.02) for an inhaled flow of 6, 10, and 13 l min^{-1}, respectively, $p < 0.05$] (Figure 6, B).

Influence of breath holding on DF. Increasing breath holding times were associated with higher DF. As shown in Figure 7, DF was 0.62 (0.05) and 0.74 (0.02) without and with 20 s breath holding, respectively ($p < 0.05$). A separate experiment showed that the volume at which the inhalation is started does not affect DF.

Effect of nasal versus oral inhalation on DF. In five subjects, DF was not different when performing nasal breathing through as facemask with an adapter for a mouthpiece [nasal inhalation and exhalation DF = 0.66 (0.05)] compared with oral breathing [oral inhalation and exhalation, DF = 0.65 (0.08), $p > 0.05$] (Figure 8).

Discussion

A new method for the real-time measurement of exhaled PM and its lung deposition was developed. The method was standardized and the variables that could potentially modify the final exhaled PM concentration, such as the exhalation flow rate and the breath hold time, were controlled. The method proved to be reliable and reproducible.

The authors believe that measuring exhaled PM and its lung deposition will improve the understanding of the effect of environmental pollution and cigarette smoke on the airways. Because the method is completely non-invasive and easy to perform, and the equipment is affordable, the measurements can be repeated and

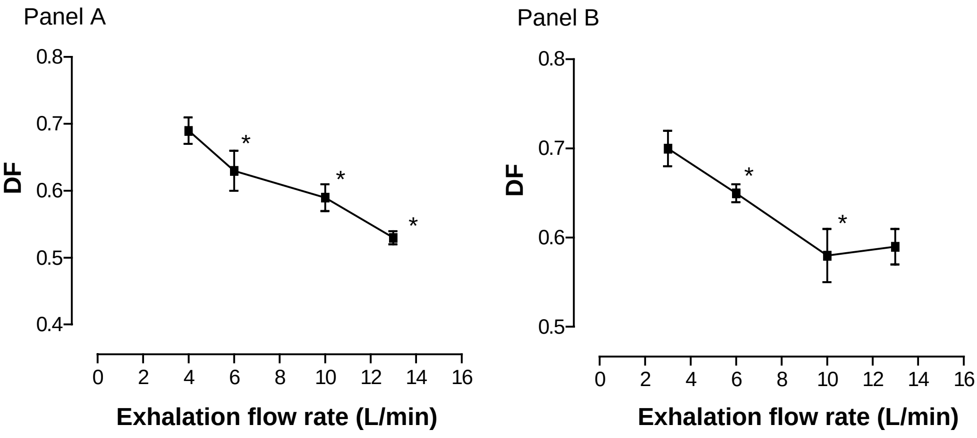

Figure 6. Effect of different exhalation (A) and inhalation (B) flow rates on particulate matter 0.3–1.0 μm deposition fraction (DF). *$p < 0.05$.

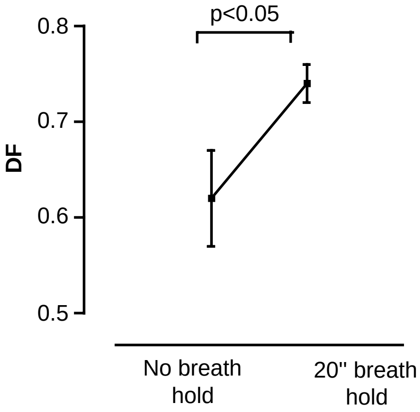

Figure 7. Effect of a 20-s breath hold on particulate matter 0.3–1.0 μm deposition fraction (DF).

used in longitudinal studies or to investigate the effect of challenges with pollutants or cigarette smoke. It is suggested that measuring the lung deposition of ambient PM may provide a tool to quantify how much of the background environmental pollution may be retained by the lung in epidemiological studies, and may provide a further quantitative tool to assess the relation between pollution and hyperresponsiviness or inflammation in future studies.

Particle deposition in the airways may be associated with a relevant health risk. Therefore, it is important to understand the dynamics of PM deposition and to quantify the particle retained by the lung and study their topographical distribution. The importance of these issues is underscored by several studies based on mathematical models and artificial monodispersed particles (Kim 2000, Martonen et al. 2000).

The current study, for the first time, was able to measure environmental particle concentration in the exhaled breath in real time, allowing us to calculate on site the total particle deposition fraction. Different steps were taken to standardize the method. These included the use a single breath manoeuvre instead of a tidal breathing technique such as in previous studies, and this allowed us to standardize the exhaled

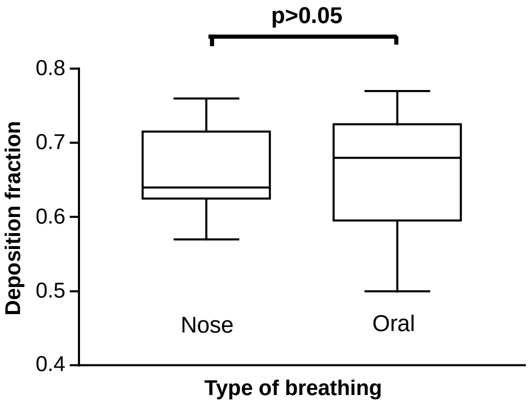

Figure 8. Influence of nasal versus oral breathing on particulate matter 0.3–1.0 μm deposition fraction (DF).

breath controlling the inhalation and the exhalation flow rates and breath hold times. In addition the reliability of the method was optimized keeping the whole equipment in a heating chamber avoiding condensation that would have interfered with the particles and impaired the readings. Furthermore, the measurements were made more reproducible and reliable by providing a constant sample flow to the analyser through an expansion pipe. When the exhalation manoeuvre was standardized for inhalation and exhalation flows and the condensation was excluded, the method proved to have a good reproducibility both for background ambient air and for exhaled breath measurements.

We chose to study PM in the range 0.3–1.0 μm because this particle size includes the large majority of particles derived from tobacco smoke (Morawska et al. 1999) and can be absorbed by the lung causing systemic inflammation (Lippmann et al. 2003). Furthermore, this PM size can easily penetrate indoor (Long et al. 2001) and there is evidence showing that this PM size is better represented in the airways (Martonen et al. 2000). Although we chose to study one specific size class, the equipment allows the measurement of to six different particle size intervals, ranging from fine to coarse PM.

It is known that particle DF varies in relation to the sizes and property of the particles, and to the inhalation and exhalation manoeuvre (Bennett et al. 1996, Kim 2000, Martonen et al. 2000). Utilizing monodisperse di-2-ethylhexyl sebacate particles sized 1.0 μm, Kim et al. found a DF during tidal breathing in the range of 0.12–0.22 with the serial bolus delivery method (Kim et al. 1996, Kim and Kang 1997), while Kohlhaufl et al. (1999) reported an average DF of 0.38 in healthy women with the technique of aerosol bolus dispersion. In studies with particles generated from tobacco smoke, Strong et al. (1994) showed a DF of 0.43 for mouth breathing and 0.54 for nasal breathing with radiolabelled ETS; while Morawska et al. (1999) examined the deposition of ETS particles in the range of 0.1–0.6 μm, reporting an average DF of 0.48 with mouth breathing and of 0.56 with nasal breathing. Evaluating 0.3–1.0 μm ambient particles, the present study found a DF range between 0.46 to 0.63 in ten healthy subjects of different age, sex, height, weight and smoking history who performed a quick and deep inhalation to total lung capacity and exhaled at a constant flow to residual volume, as opposed to the tidal volume technique employed in the previous studies. Despite the different exhalation manoeuvres, the results are consistent with the findings reported in the above-mentioned studies. The present method has several advantages. First, the measurements are carried out in real time and the result is immediately available. Second, the technique is standardized and all the variables related to the exhalation and inhalation manoeuvre are controlled improving the reliability. Third, the method is user friendly and the equipment is portable.

In our experiments, DF was inversely related to the exhalation and inhalation flow rates. This is in keeping with previous reports (Svartengren et al. 1987), and may be explained by the longer transit time in the airways at low flow rates allowing more time to the particles to be retained. For this reason, the exhalation and exhalation flow rates need to be standardized in order to obtain reproducible results. The normal exhalation and inhalation flow rates vary between 1 and 2 l min^{-1} for a normal subject at rest with a respiratory rate of 15 respirations min^{-1}. We suggest that similar flow rates should be used in future studies because they also are comfortable and easy-to-perform for patients with lung disease and a restricted airflow.

DF increased steadily with increasing breath holding times, in agreement with published data (Liu et al. 2002). When breath holding time was extended up to 20 s, a progressive increase in DF was observed, possibly due to gravity and Brownian diffusion. Like low exhalation flow rates, we suggest that longer transit time may allow the deposition of a larger number of particles increasing the DF.

Contrary to previous studies using tidal breathing (Strong et al. 1994, Morawska et al. 1999, Hofmann et al. 2001), we showed that DF is not significantly affected by nasal compared with oral breathing. This may be due to the use of single-breath exhalation manoeuvres in our study and the use of a different respiratory mask in previous studies. The use of different inhalation and exhalation flow rates may also have contributed to the different results.

The authors acknowledge that this study may be limited by the fact that laser PM counting may be affected by the physical/chemical characteristics of the particles. In addition, the present study investigated a single PM interval size. However, the equipment allows selectable multichannel PM size that will be the subject of further studies.

In conclusion, exhaled PM and DF can be measured reliably in real-time. The exhalation manoeuvre was standardized, the variables affecting the performance of the analyser were controlled. We suggest the measurement of the DF may allow one to investigate and quantify the effects of pollution and tobacco smoke on the airways.

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