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Review

Carbon loading in airway macrophages as a biomarker for individual exposure to particulate matter air pollution — A critical review

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ABSTRACT

Exposure to particulate matter (PM) is associated with adverse health effects, including chronic lung diseases, lung cancer and cardiovascular disease. Personal exposure varies depending on the generation of particles locally, background levels, activity patterns and meteorology. Carbon loading in airway macrophages (AM) is a novel marker to assess personal exposure to combustion-derived particles. This review summarizes the published evidence and describes the validity and reliability of this marker with a focus on the technical aspects. Carbon loading in AM is reported in nine published studies assessing personal exposure to particulate air pollution. The carbon content is quantified by image analysis and is suggested to be suited to assess cumulative exposures. While there is some variation in study technique, these studies each indicate that internal AM carbon reflects either external exposure or important health effects. However, some uncertainty remains regarding potentially confounding materials within particles, the time frame of exposures that this technique reflects, and the optimal strategy to accurately quantify AM carbon. These aspects need to be clarified or optimized before applying this technique in larger populations.

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1. Introduction

An increasing body of evidence has shown correlations between exposure to particulate matter (PM) air pollution, particularly PM_{10} (PM with aerodynamic diameter ≤ 10 μm) and $PM_{2.5}$ (PM with aerodynamic diameter ≤ 2.5 μm), and human health outcomes, including cardiopulmonary conditions, chronic respiratory diseases, and lung cancers (WHO, 2006). However, although these findings are robust, the correlations between health effects and PM_{10} or $PM_{.2.5}$ are not perfect. This is due to the presence of other pollutants, e.g. ozone and nitrogen dioxide, as shown by the attenuation of the associations when two-pollutant models are used (Brunekreef et al., 2009; Eze et al., 2014; Romieu et al., 2012). However, another important reason is that in epidemiological studies the exposures to PM are not measured at the individual level, but they are simply estimated or assumed based on external measurements made by air pollution stations dispersed over large areas. However, PM_{10} is dominated by the large regional and weather-related distribution of PM, rather than that it reflects local PM in smaller geographic areas (HEI., 2010). In addition, the deposition of inhaled particles is size dependent. Fine ($PM_{2.5}$) and ultrafine ($PM_{0.1}$, PM with aerodynamic diameter ≤ 0.1 μm) particles deposit throughout the respiratory tract, particularly in distal airways and alveoli, whereas coarse particles ($PM_{2.5–10}$) are preferentially deposited in the proximal airways (Brand et al., 1999; Kim et al., 1996; Möller et al., 2008). Although external proxy measurements such as proximity to major roads, stationary monitoring from roadside and background sites, and traffic intensity are valuable alternatives, they also cannot reflect accurately an individual's exposure to inhaled PM, since this is also determined by personal factors and activity patterns. In this sense, an accurate personal exposure method is needed to establish accurately the relation between health outcomes and exposure to environmental pollutant particulates.

Inhaled particles are phagocytosed by airway macrophages (AM) residing on the epithelial surfaces in the alveoli and lumen of the bronchi (Alexis et al., 2006). The carbon core of the major particles that constitute urban PM, i.e. diesel exhaust particles, can be visualized using light microscopy. Black carbon (BC) inside AM could, therefore, serve as a marker to reflect an individual's exposure to particulate air pollution. Particle-loading in macrophages isolated from alveoli and central airways has been reported in animal models (Calderón-Garcidueñas et al., 2001; Finch et al., 2002). In human studies, it has been used to measure prior exposure to pollutant particles in occupational settings by analyzing the aggregates of particles engulfed in macrophages (Fireman et al., 1999, 2004; Giovagnoli et al., 1999).

Different components of PM have different impacts on health (WHO, 2007). BC generated from fossil-fuel combustion is thought to be a valuable marker to evaluate the health risk of primary combustion-derived air pollution (Janssen et al., 2011). Mammalian cells do not contain aggregates of elemental carbon per se (Harrison and Yin, 2008; Kupiainen and Klimont, 2007; Schaap and Denier van der Gon, 2007). However, a number of technical and other issues remain to be addressed before AM BC becomes a valid tool for use in large-scale epidemiological studies, especially since other biomarkers (such as urinary molecules or DNA oxidation) also exist for the purpose of assessing personal (ongoing or recent) exposure to air pollution (Rylance et al., 2013). This review aims to provide an evaluation of studies that have used carbon loading in AM as a biomarker of exposure to PM air pollution with respect to its technique, validity and application, and future perspectives.

2. Materials and methods

2.1. Study identification and selection

In this study, we identified and characterized carbon loading in AM as a metric to study air pollution exposures in original studies. We focused on studies that met the following criteria:

i. Published in English.
ii. Carbon loading in AM used to quantify individual exposure.
iii. Modeled PM air pollution exposures derived from traffic emission or biomass combustion.
iv. Presented original data.

Based on these criteria, we excluded animal and in vitro studies, and studies of occupational exposures. Nevertheless, we did take into account relevant information derived from experimental and other studies.

2.2. Systematic review process

A systematic literature review was undertaken to identify eligible studies within online databases including PubMed, Medline, Web of Science and Google searching engines in April 2013 followed by an updated search in July 2014. We used the following key terms “carbon” AND “airway macrophages” OR “alveolar macrophages” plus combinations of the following terms: “sputum induction”, “bronchoalveolar lavage”, “air pollution”, “particulate matter”, “diesel exhaust”, “motor vehicle”, “traffic related” and “biomass”. The reference lists of the identified studies by this method were reviewed for links to additional literature.

A total of 10 studies were identified in the literature search. One report (Grigg et al., 2008), extending on the data described by Kulkarni et al. (2006), was removed. Nine articles met the pre-specified eligibility criteria for this review. Studies using AM obtained via sputum induction were compared with the European Respiratory Society (ERS) consensus methodology to assess their technical aspects. Only one (Jacobs et al., 2010) of the two studies by Jacobs et al. (2010, 2011) was included in the latter comparison due to repeated use of the same data.

3. Results and discussion

Following the systematic review, 9 studies were selected as eligible. Table 1 summarizes these 9 identified studies, with the following data being shown: first author, year of publication, study location, characteristics of subjects, sampling technique and exposure assessment.

3.1. Bronchoalveolar lavage (BAL) versus induced sputum (IS)

Quantifying AM BC includes three procedures: sampling macrophages from the airways, specimen processing, and image analysis. AM may be obtained by either bronchoalveolar lavage (BAL) from the distal bronchioles and alveoli (Meyer et al., 2012) or by induced sputum (IS) from the central airways (Paggiaro et al., 2002). Each technique has advantages and limitations (Table 2). First, BAL sampling provides a more morphologically homogenous sample containing large numbers of macrophages compared to complex cellular profiles and fewer macrophages in IS (Alexis et al., 2000; Geiser, 2002; Lehnert, 1992). AM for imaging are identified by morphological features and this is not too difficult for an experienced individual. However, in IS the presence of many different cell types (AM, neutrophils, eosinophils, squamous