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Review

Selected physiological effects of ultrafine particles in acute cardiovascular morbidity

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ABSTRACT

Ultrafine particles (UFPs) have emerged as a potentially important environmental health concern as they are produced in large numbers by vehicle emissions and may contribute to previously reported associations between traffic pollution and acute cardiovascular morbidity. This review examines recent epidemiological evidence of UFP exposures and selected physiological outcomes that may be modified as part of the underlying causal pathway(s) linking particulate air pollution and acute cardiovascular morbidity. Outcomes examined included changes in heart rate variability (HRV) (autonomic function), ST-segment depression (myocardial ischemia), QT-interval (ventricular repolarization), and endothelial vasomotor function. Twenty-two studies were reviewed in total: 10 prospective panel studies and 12 randomized cross-over studies. Sixteen studies identified a significant relationship between UFPs and at least one of the above outcomes and current evidence generally supports the biological plausibility of a relationship between UFPs and acute cardiovascular morbidity. However, discrepancies were apparent in the direction of observed associations, particularly for HRV and ventricular repolarization. Reasons for these discrepancies may include differences in particle composition, time-point of clinical evaluation, and population susceptibilities. Nevertheless, evidence to date suggests that UFPs have a measureable impact on physiological measures known to be altered in cases of acute cardiovascular morbidity. Moving forward, expanded use of personal exposure measures is recommended for prospective panel studies to minimize exposure misclassification. In addition, effort should be made to include more women in studies of the acute cardiovascular effects of UFPs as findings to date generally reflect responses in men.

Contents

Abbreviations: CAD, Coronary artery disease; HF, High frequency power; LF, Low frequency power; LF/HF, The ratio of low frequency and high frequency power; $PM_{0.25}$, Particulate matter less than 0.25 μm in diameter; $PM_{2.5}$, Particulate matter less than 2.5 μm in diameter; pNN50, Percentage of adjacent NN intervals differing by more than 50 ms; HRV, Heart rate variability; RMSSD, Root mean square of successive differences in adjacent NN intervals; SDNN, Standard deviation of all normal-to-normal (NN) intervals; SDANN, Standard deviation of the average normal-to-normal intervals calculated over 5-min intervals; UFPs, Ultrafine particles

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1. Introduction

Numerous epidemiological studies have observed increased cardiovascular morbidity and mortality in association with exposure to ambient air pollution, particularly fine particulate matter ($PM_{2.5}$) (Brook et al., 2004, 2010; Brook, 2008; Bhaskaran et al., 2009; Simkhovich et al., 2008; 2009). More recently, ultrafine particles (UFPs) (particle diameter < 0.1 μm) have emerged as air contaminants that may contribute to cardiovascular morbidity (Delfino et al., 2005; Stolzel et al., 2007; Atkinson et al., 2010). In particular, UFPs may play an important role in previously reported associations between traffic exposure and acute cardiovascular effects (Peters et al., 2004; Tonne et al., 2007) as vehicle emissions are a major source of these pollutants. In addition, some evidence suggests that UFPs can reach the systemic circulation within minutes of exposure (Nemmar et al., 2002; Brook, 2008; Brook et al., 2010); however, the precise mechanisms underlying a potential relationship between UFPs and acute cardiovascular morbidity have yet to be thoroughly described.

Here we review studies examining the relationship between UFP exposures and selected physiological outcomes potentially involved in underlying causal pathway(s) linking particulate air pollution and acute cardiovascular morbidity. These measures include components of the so called "cardiac death triangle": the autonomic nervous system (HRV), myocardial substrate (QT-interval), and myocardial vulnerability (QT-variance, *T*-wave alternans) (Zareba et al., 2001) as well as endothelial vasomotor function. In general, the aim of this review was to evaluate consistency between studies examining these outcomes as well as factors that may explain discrepancies between studies such as the type of exposure measurements (i.e. personal vs. ambient fixed-site monitors), the primary source of UFP exposure (e.g. traffic vs. non-traffic), study population, and the time-point of clinical evaluation. Finally, it is important to note that a number of studies have examined physiological outcomes such as blood pressure (e.g. Chuang et al., 2005), coagulation (e.g. Stewart et al., 2010), and inflammation (e.g. Hertel et al., 2010) that may also play an important role in acute cardiovascular morbidity in response to UFP exposures; however, these studies were excluded in an effort to limit the scope of this review.

2. Search strategy

Studies were identified by searching the Medline/PubMed database (http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed) using the key word ultrafine particles in combination with heart rate variability, ST-segment depression, QT-interval, and endothelial dysfunction. Citation lists were also examined. Studies were included in this review if they examined the relationship between UFPs and any of the above outcomes in humans, were published in English before July, 2011, and provided a quantitative measure of UFP exposure (generally particle number concentration). Several studies reported $PM_{0.25}$ (particulate matter less than 0.25 μm) as a measure of UFP exposure; these studies were also included but it is important to note that this measure includes particles slightly larger than the generally accepted cut-off diameter for UFPs (0.1 μm). In addition, studies that specifically evaluated the physiological effects of diesel exhaust exposure were included if they provided a quantitative measure of UFP exposures (e.g. UFP number concentration as opposed to total mass concentration of diesel exhaust particles). Studies of manufactured nanomaterials were not included.

3. Study characteristics

In total, 22 studies were identified that examined the relationship between UFPs and acute changes in heart rate variability (9 studies), ST-segment (4 studies), QT-interval (4 studies), or endothelial vasomotor function (9 studies) (Tables 1–3). Three studies examined more than one outcome (Mills et al., 2007; Samet et al., 2009; Zareba et al., 2009). All studies employed either a prospective panel design that examined the impact of daily or hourly changes in air pollution levels on cardiovascular outcomes or a cross-over design in which participants experienced two or more exposure conditions in random order and served as their own control in the analyses. When necessary, all of the studies reviewed adjusted for relevant confounding factors in the analyses; study-specific factors are listed below the appropriate tables.

4. Results

4.1. Heart rate variability

Heart rate variability (HRV) is regulated by the autonomic nervous system and variations in the intervals between normal heart beats provide information on autonomic control of the heart (Stein and Kleiger, 1999; Task Force, 1996). Specifically, decreased HRV is associated with increased risks of cardiovascular morbidity and mortality (Bigger et al., 1992; Dekker et al., 1997; Kleiger et al., 1987; Liao et al., 1997; Tsuji et al., 1996) and may precede ischemic events among subjects with stable coronary artery disease (Kop et al., 2001). Common HRV parameters include time–domain measures derived directly from intervals between consecutive heart beats (e.g. SDNN, standard deviation of all normal-to-normal (NN) intervals; RMSSD, root mean square of successive differences in adjacent NN intervals; pNN50, percentage of adjacent NN intervals differing by more than 50 ms) and frequency–domain measures which are computationally more complex (e.g. LF, low-frequency power; HF, high-frequency power). Of these, HF, RMSSD, and pNN50 reflect parasympathetic modulation of the heart whereas SDNN reflects total power and LF reflects a mixture of both parasympathetic and sympathetic modulation (Stein and Kleiger, 1999; Task Force, 1996). The ratio of LF to HF (LF/HF) is thought to reflect the balance of sympathetic and parasympathetic control of the heart.

A number of studies have examined the relationship between UFP exposures and acute changes in HRV (Table 1). Chan et al. (2004) reported significant inverse relationships between 1 and 4-h moving averages of personal UFP exposures and SDNN, RMSSD, HF, and LF in a panel of healthy adults and elderly patients in Taiwan. In this study, personal UFP exposures were more strongly related to HRV in elderly subjects than in healthy adults with the strongest association observed at 2-h moving averages; however, the directions of the observed associations were consistent between the two groups. Likewise, a recent cross-over study of healthy adult cyclists reported inverse associations between personal UFP exposures experienced while cycling in traffic and HF and pNN50 in the hours immediately following