ORIGINAL ARTICLE

Components of ambient air pollution affect thrombin generation in healthy humans: the RAPTES project

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ABSTRACT

Objectives Increases in ambient particulate matter (PM) have been associated with an elevated risk of stroke, myocardial ischaemia and coronary heart disease, with activation of blood coagulation likely playing an important role. PM-mediated activation of two major activation pathways of coagulation provides a potential mechanism for the observed association between PM and cardiovascular disease. However, it remains unclear which specific characteristics and components of air pollution are responsible.

Methods In order to investigate those characteristics and components, we semiexperimentally exposed healthy adult volunteers at five different locations with increased contrasts and reduced correlations among PM characteristics. Volunteers were exposed for 5 h, exercising intermittently, 3–7 times at different sites from March to October 2009. On site, we measured PM mass and number concentration, its oxidative potential (OP), content of elemental/organic carbon, trace metals, sulphate, nitrate and gaseous pollutants (ozone, nitrogen oxides). Before and 2 and 18 h after exposure we sampled blood from the participants and measured thrombin generation using the calibrated automated thrombogram.

Results We found that thrombin generation increases in the intrinsic (FXII-mediated) blood coagulation pathway in relation to ambient air pollution exposure. The associations with NO_2, nitrate and sulphate were consistent and robust, insensitive to adjustment for other pollutants. The associations with tissue factor-mediated thrombogenicity were not very consistent.

Conclusions Ex vivo thrombin generation was associated with exposure to NO_2, nitrate and sulphate, but not PM mass, PM OP or other measured air pollutants.

What this paper adds

- Ambient PM has been associated with an elevated risk of stroke, myocardial ischaemia or coronary heart disease.
- · Air pollution is a complex mixture and its specific characteristics and components responsible for health effects remain unclear.
- Air pollution can activate FXII-dependent blood coagulation pathway ex vivo.
- Using a semiexperimental volunteer exposure design we identified independent contributions of particularly NO_2, nitrate and sulphate.

INTRODUCTION

Epidemiological studies have shown associations of exposure to ambient air pollution with adverse cardiovascular effects[1 2] and prothrombotic changes are considered to play an important role.[1 3 4] Next to well-established links of particulate matter (PM) air pollution with arrhythmia, stroke and myocardial infarction, recent studies also demonstrated the association between PM exposure and increased risk of deep vein thrombosis.[5 6] One of the possible mechanisms is PM-driven activation of the blood coagulation cascade leading to a hypercoagulable state:[3 7] Baccarelli *et al*[8] showed associations between exposure to air pollution (PM_{10}, CO, NO_2) and shorter prothrombin time. Rudez *et al*[9] found that increased thrombin generation was associated with increased levels of CO, NO and NO_2, which can represent the associations with those gases itself, but since those can be considered markers for traffic-related air pollution—also with other air pollutants with which these gases are highly correlated. Bonzini *et al*[10] reported that exposure to PM was associated with decreased prothrombin time and increased thrombin generation. The latter was also associated with PM_{10} exposure at residence address in a study by Emmerechts *et al*.[11]

Currently, two scenarios involving the blood coagulation are considered; in the first one, PM causes an inflammatory response in the lungs, resulting in IL-6 release, which in turn increases cellular expression of tissue factor (TF) that further activates factor (F) VII (extrinsic pathway), eventually leading to conversion of prothrombin into thrombin.[2 3 12 13] Both epidemiological[11] and toxicological studies[14 15] showed that increase in TF was associated with elevated PM concentrations. In the second scenario, particles translocate across the lung–blood barrier and initiate the intrinsic pathway of blood coagulation through activation of factor (F) XII (and possibly FXI), leading to thrombin formation.[3 12 16] A recent toxicological study demonstrated plausibility of this pathway through ultrafine particles-mediated

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