Diesel exhaust inhalation increases thrombus formation in man†

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Aims

Although the mechanism is unclear, exposure to traffic-derived air pollution is a trigger for acute myocardial infarction (MI). The aim of this study is to investigate the effect of diesel exhaust inhalation on platelet activation and thrombus formation in men.

Methods and results

In a double-blind randomized crossover study, 20 healthy volunteers were exposed to dilute diesel exhaust (350 µg/m³) and filtered air. Thrombus formation, coagulation, platelet activation, and inflammatory markers were measured at 2 and 6 h following exposure. Thrombus formation was measured using the Badimon ex vivo perfusion chamber. Platelet activation was assessed by flow cytometry. Compared with filtered air, diesel exhaust inhalation increased thrombus formation under low- and high-shear conditions by 24% (change in thrombus area 2229 μm², 95% confidence interval (CI) 1143–3315 μm², P = 0.0002) and 19% (change in thrombus area 2451 μm², 95% CI 1190–3712 μm², P = 0.0005), respectively. This increased thrombogenicity was seen at 2 and 6 h, using two different diesel engines and fuels. Diesel exhaust also increased platelet–neutrophil and platelet–monocyte aggregates by 52% (absolute change 6%, 95% CI 2–10%, P = 0.01) and 30% (absolute change 3%, 95% CI 0.2–7%, P = 0.03), respectively, at 2 h following exposure compared with filtered air.

Conclusion

Inhalation of diesel exhaust increases ex vivo thrombus formation and causes in vivo platelet activation in man. These findings provide a potential mechanism linking exposure to combustion-derived air pollution with the triggering of acute MI.

Keywords

Air pollution • Particulate matter • Thrombosis • Platelet activation

Introduction

Chronic exposure to air pollution is a major cause of cardiovascular morbidity and mortality worldwide.1 Recently, exposure to traffic-derived air pollution has been associated with the triggering of acute myocardial infarction (MI).2,3 Although air pollution consists of a heterogeneous mixture of gaseous and particulate matter, adverse cardiovascular events are most strongly associated with exposure to fine particulate matter (diameter <2.5 μm, PM2.5).4,5 An important component of PM2.5 is nanoparticulate matter generated during the combustion of diesel fuel.6 These particles, with an aerodynamic diameter ≤100 nm, readily deposit within human alveoli and possess a considerable surface area that may contribute to their biological toxicity.7

Despite the strength and consistency of observational data, the pathophysiological mechanisms linking air pollution with adverse cardiovascular events remain unclear. They have been proposed to include endothelial dysfunction,8–10 myocardial ischaemia,10
Thrombosis plays a central role in the pathogenesis of atherosclerosis. As well as contributing to atherogenesis, thrombosis at the site of a disrupted coronary arterial plaque may cause acute vessel occlusion, resulting in an acute coronary syndrome (ACS). In pre-clinical studies employing a thrombotic vascular injury model, tracheal instillation of diesel exhaust particles caused platelet activation and increased arterial and venous thrombus formation. Given that exposure to combustion-derived pollutants appears to act as a trigger for MI and that the majority of such events are due to thrombus formation at the site of an atherosclerotic plaque, we hypothesized that exposure to diesel exhaust would increase in vivo platelet activation and enhance thrombus formation in an ex vivo clinical model of arterial injury.

Methods

Subjects

Twenty healthy non-smokers aged between 21 and 44 years were enrolled into the study (Table 1). The study was performed with the approval of local research Ethics Committees, in accordance with the Declaration of Helsinki and the written informed consent of all volunteers. Volunteers were recruited using advertisements and from local healthy volunteer databases. Exclusion criteria were the use of regular medication or clinical evidence of atherosclerosis, arrhythmias, diabetes mellitus, hypertension, renal or hepatic impairment, asthma, occupational exposure to air pollution, intercurrent infective disease, or any other clinically significant illness. Subjects had normal lung function and reported no symptoms of respiratory tract infection within the 6-week period preceding the study.

Study design

Subjects attended on two occasions at least one week apart and received either filtered air or dilute diesel exhaust in a double-blind randomized crossover design. Exposures were performed at separate dedicated exposure facilities by technical staff with no involvement in the clinical studies. The order of the exposures was randomized based on an independently determined exposure protocol. Subjects performed periods of exercise as described earlier. Exposures to diesel exhaust were standardized using continuous measurement of nitrogen oxide (NOx) concentrations to deliver a particulate concentration of 350 μg/m³. The study was performed with the Declaration of Helsinki and the written informed consent of all volunteers.

Table 1 Baseline volunteer characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>26 ± 5</td>
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<tr>
<td>Height (m)</td>
<td>1.8 ± 0.1</td>
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<tr>
<td>Weight (kg)</td>
<td>73 ± 3</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>22 ± 1</td>
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<tr>
<td>Pulse (bpm)</td>
<td>58 ± 2</td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>120 ± 3</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>71 ± 2</td>
</tr>
<tr>
<td>Forced expiratory volume in 1 s (FEV1, L)</td>
<td>4.9 ± 0.1</td>
</tr>
<tr>
<td>% Predicted FEV1</td>
<td>108 ± 3</td>
</tr>
<tr>
<td>Forced vital capacity (FVC, L)</td>
<td>5.8 ± 0.2</td>
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<tr>
<td>% Predicted FVC</td>
<td>103 ± 3</td>
</tr>
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</table>

Data are presented as mean ± standard deviation. Pooled data from protocols 1 and 2 (n = 20).

Ex vivo thrombosis studies

Thrombus formation was measured using the Badimon chamber. This technique has principally been used previously to assess the efficacy of novel antithrombotic agents. In brief, a pump was used to draw blood from an antecubital vein through a series of three cylindrical perfusion chambers maintained at 37°C in a water bath. Carefully prepared strips of porcine aorta, from which the intima and a thin layer of media had been removed, acted as the thrombogenic substrate. The rheological conditions in the first chamber simulate those of patent coronary arteries (low-shear rate, ~212 s⁻¹), whereas those in the second and third chambers simulate the conditions of the second and third coronary arteries (high-shear rate).
Diesel exhaust inhalation increases thrombus formation

second and third chambers simulate those of mildly stenosed coronary arteries (high-shear rate, \( \sim 1690 \text{ s}^{-1} \)). The model thus acts as one of the deep coronary arterial injury. Each study lasted for 5 min during which flow was maintained at a constant rate of 10 mL/min. All studies were performed using the same perfusion chamber and by the same operator.

Immediately after each study, porcine strips with thrombus attached were removed and fixed in 4% paraformaldehyde. Strips were wax-embedded, sectioned, and stained with Masson’s Trichrome. Images were acquired at \( \times 20 \) magnification, and the thrombus area was measured using an Arios image acquisition system (Applied Imaging, USA) and Image-Pro Plus software (Media Cybernetics, USA) by a blinded operator. Results from at least six sections were averaged to determine thrombus area for each chamber, as described previously.\(^{14-16} \)

Flow cytometry

Samples were obtained at 2 and 6 h, immediately prior to each thrombosis study, and processed according to previously described protocols.\(^{17} \) In brief, blood was taken from an antecubital vein using a 21-gauge cannula and anticoagulated with \( \alpha \)-phenylalanyl-l-prolyl-l-arginine chloromethylketone (75 µm; Cambridge Biosciences, UK). Samples were not analysed unless venesection achieved rapid and uninterrupted blood flow. Five minutes after sample collection, samples were stained with the following conjugated monoclonal antibodies: phycoerythrin (PE)-conjugated CD14 (Dako, Denmark), PE-conjugated CD62P, and PE-conjugated CD154 (Becton-Dickinson, UK); PE-conjugated CD11b, PE-conjugated CD40, fluorescein isothiocyanate (FITC)-conjugated CD42a, and FITC-conjugated CD14 (Serotec, USA); and appropriate control isotypes. All antibodies were diluted 1:20. Once stained, samples were incubated for 20 min at room temperature to identify P-selectin and CD40L on the platelet surface and CD40 on the monocyte surface. Monocyte and platelet-leucocyte samples were fixed with FACS-Lyse (Becton-Dickinson). Platelet samples were fixed with 1% paraformaldehyde. Samples were analysed within 24 h using a FACScan flow cytometer (Becton-Dickinson). Platelet–monocyte and platelet–neutrophil aggregates were defined as monocytes or neutrophils positive for CD42a. Data analysis was performed using Flowjo (Treestar, USA).

Blood sampling

Samples were obtained before exposure and at 2 and 6 h. Samples were analysed for total white cell count, differential cell count, and platelet by an autoanayser. Plasma interleukin-6 (IL-6), tumour necrosis factor-\( \alpha \) (TNF-\( \alpha \)), soluble CD40 ligand (sCD40L), soluble P-selectin, intercellular adhesion molecule-1 (ICAM-1), and \( C \)-reactive protein were measured with commercially available ELISAs (R&D Systems, UK). Prothrombin time (PT, reagents from Medixor, Sweden) and activated partial thromboplastin time (aPTT, reagents from Dade Behring, USA) were measured using a CA-7000 analyser (Sysmex, Japan).

Statistical analysis

Data presented are pooled from protocols 1 and 2 unless otherwise stated. Continuous variables are reported as mean \( \pm \) standard deviation. Statistical analysis was performed in Excel (Microsoft Corporation, USA), using a modified \( t \)-test (two-sided) to account for potential period effects.\(^{18} \) Statistical significance was taken at \( P \)-value less than 0.05.

Results

Exposures and clinical studies were well tolerated with no adverse symptoms reported. All volunteers completed both study visits. Total leucocyte, monocyte and platelet counts, PT, and aPTT were unaltered following dilute diesel exhaust and filtered air (Table 2). Although neutrophil count appeared to increase and lymphocyte count appeared to decrease following both exposures, there were no differences in the magnitude of these changes following dilute diesel exhaust compared with filtered air (Table 2).

Markers of inflammation and platelet activation

There was a heterogeneous cytokine response following both dilute diesel exhaust and filtered air exposures (Table 3, data from protocol 2). Changes in plasma TNF-\( \alpha \), IL-6, C-reactive protein, and soluble ICAM-1 concentrations were similar following both exposures. Following dilute diesel exhaust exposure, plasma sCD40L concentrations were increased at 2 h (\( P = 0.003 \) vs. filtered air), and the fall at 6 h following filtered air exposure was attenuated (\( P = 0.011 \) vs. filtered air). Similarly, the fall in plasma soluble P-selectin concentration at 6 h following filtered air exposure was attenuated following diesel exhaust exposure (\( P = 0.003 \)).

Flow cytometry

Monocyte surface expression of CD40 and platelet surface expression of CD40L and P-selectin were similar following dilute diesel exhaust and filtered air exposure (data on file). Compared with filtered air, diesel exhaust exposure increased platelet–neutrophil and platelet–monocyte aggregates at 2 h by 52% [absolute change 6%, 95% confidence interval (CI) 2–10%, \( P = 0.011 \)] and 30% [absolute change 3%, 95% CI 0.2–7%, \( P = 0.033 \)], respectively (Figure 1, data from protocol 2). There was a trend towards similar increases at 6 h, although these were not statistically significant.

Thrombus formation

Thrombus formation increased following dilute diesel exhaust by 23% in the low-shear chamber (change in thrombus area \( 1941 \text{ µm}^2, 95\% \text{ CI } 873–3008 \text{ µm}^2, P = 0.002 \)) and by 21% in the high-shear chamber (change in thrombus area \( 2916 \text{ µm}^2, 95\% \text{ CI } 1365–4466 \text{ µm}^2, P = 0.001 \)), compared with filtered air at 6 h (Figure 2).

In protocol 2, thrombus formation at 2 h increased by 27% in the low-shear chamber and 21% in the high-shear chamber following dilute diesel compared with filtered air (change in thrombus area \( 2772 \text{ µm}^2, 95\% \text{ CI } 879–4721 \text{ µm}^2, P = 0.04 \) and change in thrombus area \( 2312 \text{ µm}^2, 95\% \text{ CI } 597–4026 \text{ µm}^2, P = 0.014 \), respectively, Figure 3). Likewise, thrombus formation at 6 h was increased by 22% (change in thrombus area \( 2254 \text{ µm}^2, 95\% \text{ CI } 244–3924 \text{ µm}^2, P = 0.033 \)) in the low-shear chamber and appeared to increase (13%; change in thrombus area \( 1467 \text{ µm}^2, 95\% \text{ CI } -230–3163 \text{ µm}^2, P = 0.083 \)) in the high-shear chamber (Figure 3, data from protocol 2).
Discussion

Short-term exposure to traffic-derived air pollution is associated with acute cardiovascular events. This is the first study to demonstrate that inhalation of diesel exhaust, a common urban air pollutant, causes platelet activation and enhances thrombus formation in men. This provides a plausible mechanism linking exposure to particulate air pollution with acute cardiovascular events including MI.

Table 2: Effects of dilute diesel exhaust on haematological and coagulation variables

<table>
<thead>
<tr>
<th></th>
<th>Before exposure</th>
<th>2 h</th>
<th>6 h</th>
<th>Δ 2 h</th>
<th>Δ 6 h</th>
<th>P-values</th>
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<td></td>
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<tr>
<td>Filtered air</td>
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<tr>
<td>Leucocytes (x 10^9 cells/L)</td>
<td>5.44 ± 1.42</td>
<td>5.27 ± 1.16</td>
<td>5.75 ± 1.07</td>
<td>-0.18 ± 1.08</td>
<td>0.26 ± 1.19</td>
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<tr>
<td>Lymphocytes (x 10^9 cells/L)</td>
<td>2.17 ± 0.67</td>
<td>1.92 ± 0.52</td>
<td>1.68 ± 0.43</td>
<td>-0.48 ± 0.46</td>
<td>-0.51 ± 0.53</td>
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<tr>
<td>Neutrophils (x 10^9 cells/L)</td>
<td>2.62 ± 0.69</td>
<td>3.00 ± 0.75</td>
<td>3.51 ± 0.91</td>
<td>0.42 ± 0.68</td>
<td>0.89 ± 0.86</td>
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<td>Monocytes (x 10^9 cells/L)</td>
<td>0.47 ± 0.16</td>
<td>0.42 ± 0.14</td>
<td>0.41 ± 0.16</td>
<td>-0.06 ± 0.11</td>
<td>-0.06 ± 0.10</td>
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<tr>
<td>Platelets (x 10^9 cells/L)</td>
<td>223 ± 38</td>
<td>221 ± 35</td>
<td>223 ± 30</td>
<td>-1.80 ± 18</td>
<td>1.79 ± 22</td>
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<tr>
<td>INR a</td>
<td>1.00 ± 0.06</td>
<td>1.03 ± 0.07</td>
<td>1.04 ± 0.07</td>
<td>0.02 ± 0.04</td>
<td>0.03 ± 0.05</td>
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<tr>
<td>aPTT (sec)</td>
<td>28.9 ± 0.91</td>
<td>29.1 ± 0.89</td>
<td>28.7 ± 0.90</td>
<td>0.28 ± 0.47</td>
<td>-0.20 ± 0.58</td>
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</table>

Data are presented as mean ± standard deviation.
P-values are for comparison of diesel exhaust vs. filtered air.
aPTT, activated partial thromboplastin time; INR, international normalized ratio of prothrombin time.
Pooled data from protocols 1 and 2 (n = 20, except unavailable for protocol 1).

Table 3: Effects of dilute diesel exposure on markers of inflammation and platelet activation

<table>
<thead>
<tr>
<th></th>
<th>Before exposure</th>
<th>2 h</th>
<th>6 h</th>
<th>Δ 2 h</th>
<th>Δ 6 h</th>
<th>P-values</th>
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<tr>
<td>Filtered air</td>
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<tr>
<td>TNF-α (pg/mL)</td>
<td>0.62 ± 0.73</td>
<td>—</td>
<td>0.36 ± 0.32</td>
<td>—</td>
<td>-0.26 ± 0.30</td>
<td>— —</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>0.60 ± 0.76</td>
<td>—</td>
<td>0.88 ± 0.80</td>
<td>—</td>
<td>0.28 ± 1.1</td>
<td>— —</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>1.02 ± 0.66</td>
<td>1.09 ± 1.42</td>
<td>1.13 ± 1.64</td>
<td>0.07 ± 0.17</td>
<td>0.12 ± 0.16</td>
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<tr>
<td>Soluble CD40L (pg/mL)</td>
<td>66 ± 29</td>
<td>75 ± 8</td>
<td>41 ± 14</td>
<td>9.00 ± 29</td>
<td>-20 ± 26</td>
<td>— —</td>
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<tr>
<td>Soluble P-selectin (mg/mL)</td>
<td>61 ± 27</td>
<td>37 ± 8</td>
<td>44 ± 18</td>
<td>-25 ± 22</td>
<td>-18 ± 26</td>
<td>— —</td>
</tr>
<tr>
<td>Soluble ICAM-1 (mg/mL)</td>
<td>278 ± 65</td>
<td>170 ± 25</td>
<td>271 ± 69</td>
<td>-109 ± 56</td>
<td>-640 ± 66</td>
<td>— —</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation.
P-values are for comparison of diesel exhaust vs. filtered air.
TNF-α, tumour necrosis factor-α; IL-6, interleukin-6; CD40L, CD40 ligand; ICAM-1, intercellular adhesion molecule-1.
Effect of diesel exhaust on thrombosis

Despite the suggestion from observational studies that exposure to combustion-derived air pollution is associated with MI, few studies have examined whether controlled exposure alters thrombotic potential. Developing a reproducible in vivo model of thrombosis for use in human studies is challenging. We therefore used the Badimon chamber as a validated ex vivo model of arterial injury and thrombosis. It has previously been used to evaluate the effects of novel antithrombotic regimens and has a number of advantages over other techniques. It allows the measurement of thrombus formation in native (non-anticoagulated) whole blood triggered by exposure to a physiologically relevant substrate and under flow conditions mimicking those in diseased coronary arteries. Thus, this is a particularly relevant model as it broadly simulates the intra-arterial conditions following spontaneous or iatrogenic plaque disruption within the coronary vasculature.

Taken together with our previous finding that dilute diesel exhaust exposure impairs endothelial t-PA release, we suggest that enhanced thrombus formation is an important mechanism that may explain the association of MI shortly after traffic pollution exposure.

Effect of diesel exhaust on platelet activation

Platelets are key components of arterial thrombosis. Shortening of closure times in a platelet function analyser have been observed following tracheal instillation of diesel exhaust particles in hamsters and their addition to human blood enhances platelet

![Figure 1](https://academic.oup.com/eurheartj/article-abstract/29/24/3043/587783/3047)

**Figure 1** Platelet–leucocyte aggregates 2 and 6 h following dilute diesel exhaust (●) and filtered air (○) exposures (protocol 2, n = 12).
Here, we used flow cytometry to measure the surface expression of platelet and leucocyte activation markers as well as platelet–leucocyte aggregates, a technique increasingly recognized as the gold standard measure of in vivo platelet activation, including in patients with ACS.

We observed an increase in platelet–neutrophil and platelet–monocyte aggregates after dilute diesel exhaust exposure, suggesting that enhanced thrombus formation was mediated through platelet activation. These findings are consistent with an increase in circulating platelet–leucocyte aggregates observed in women exposed to biomass smoke. In addition, tracheal instillation of carbon nanotubes increased platelet–leucocyte aggregates and thrombus formation in a murine model of vascular injury. Interestingly, blockade of P-selectin abrogated platelet–leucocyte aggregation and thrombus formation, suggesting that P-selectin serves as a link between pulmonary inflammation, systemic inflammation, and enhanced thrombogenicity. Although platelet–monocyte binding is principally dependent on P-selectin, we did not observe an increase in the platelet surface expression of P-selectin. However, in patients with MI, platelet–monocyte aggregates have been shown to be a more sensitive marker of platelet activation than P-selectin, as P-selectin is rapidly shed from the platelet surface. Exposure to dilute diesel exhaust also increased plasma sCD40L levels. This is in keeping with studies that demonstrated upregulation of the CD40/CD40L pathway in cigarette smokers and following exposure to ultrafine particles. As platelets contain large amounts of CD40L that is released following activation, the increase in sCD40L we observed further strengthens the argument that the enhanced thrombus formation observed was driven principally by platelet activation.

It is not possible from our study to determine the mechanism of platelet activation. Debate remains as to whether inhaled components of diesel exhaust can translocate into the systemic circulation to mediate direct effects on blood and vascular components. A substantial body of evidence supports a role for oxidative stress and inflammation in mediating the adverse effects of air pollution. Although we did not observe an increase in cellular or soluble inflammatory markers, this does not preclude a role for factors not assessed here. The ability of diesel exhaust exposure to cause pulmonary inflammation is not in doubt, and we have demonstrated previously that diesel particles are capable of generating free radicals, which may activate platelets by reducing endothelial and platelet-derived nitric oxide and antioxidants.

**Effect of diesel exhaust on coagulation**

A number of previous ambient and controlled exposure studies have evaluated the association between plasma concentrations of coagulation factors and particulate air pollution with mixed results. Although some have demonstrated increased levels of fibrinogen and von Willebrand factor, other studies measuring the same factors have failed to show any association with particulate exposure. This apparent disparity may well be explained by variations in study design and perhaps, more importantly, the type of exposure investigated. Two previous studies have investigated the effect of controlled diesel exhaust exposure on coagulation factors in men, with neither demonstrating a significant effect. Although a recent observational study reported a small reduction in PT associated with ambient exposure to PM10, we found no effect on PT or aPTT following exposure to diesel exhaust. Despite higher effective particulate matter concentrations, our findings are in keeping with previous controlled diesel exposure studies that failed to demonstrate changes in fibrinogen, von Willebrand factor, D-dimer, pro-thrombin fragments 1 and 2, tissue-plasminogen activator, and plasminogen activator inhibitor-1.

**Population risk and diesel exposure**

Diesel exhaust is an important source of combustion-derived air pollution. We have now performed a large number of inhalation...
exposures in healthy subjects and patients with cardiovascular disease using well-characterized systems. Particulate levels during these exposures are comparable with those in heavy traffic and occupational settings in large cities. Here, we used two types of diesel engines and two different commercially available fuels. The particulate component was similar in both protocols. Despite differences in the method of diesel exhaust generation and the gaseous component, prothrombotic effects were consistent.

Although the overall implications of exposure to traffic-derived pollution are significant from a population perspective, individual risk is modest. Observational data support the notion that risk is greatest in those with pre-existing cardiovascular disease. Indeed, we have recently demonstrated that dilute diesel exhaust inhalation has pro-ischaemic effects in patients with prior MI. In the present study, we have extended these findings using a clinical model of severe arterial injury that is reflective of the intravascular conditions in a patient with a ruptured or denuded atheromatous plaque. Our findings of enhanced platelet activation and thrombus formation further highlight the potential-increased propensity of ‘at-risk’ populations to suffer adverse cardiovascular consequences following exposure to air pollution, although it is not possible from this study to determine
whether diesel exhaust exposure enhances thrombogenicity in patients on antiplatelet therapies.

Conclusions

Inhalation of dilute diesel exhaust causes platelet activation and increased thrombus formation in men. This study provides a plausible pathophysiological link that may explain the association between combustion-derived air pollution and acute cardiovascular events. Further work is required to clarify more precisely the mechanism of enhanced thrombogenicity and to investigate how this potentially harmful effect may be abrogated.

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References

none declared.

Conflict of interest: none declared.

References


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A left atrial mobile cystic thrombus

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A 58-year-old woman was admitted to our clinic for worsening dyspnoea. She had a history of uncontrolled hypertension. Physical examination was unremarkable. Electrocardiogram revealed normal sinus rhythm. Transthoracic echocardiography showed a large, mobile cystic mass with smooth contours (20 × 27 mm) in the body of enlarged left atrium (LA) (Panel A). Left ventricular chamber size was in normal limits but there was moderate hypertrophy accompanied with mild impairment of systolic function (ejection fraction was 45%). Transthoracic echocardiography revealed mobile cystic thrombus in the LA originating from left atrial appendage (LAA) (Panels B and C). We started to treat the patient with intravenous unfractionated heparin with a target activated partial thromboplastin time of 50–70 s. The following day, cystic thrombus decreased in size; however, the very mobile behaviour of the thrombus persisted (Panel D). Transthoracic echocardiographic examinations revealed complete disappearance of thrombus in both LA and LAA 3 days after starting intravenous heparin treatment (Panels E and F). During follow-up, the patient was free of any neurological complication.

LA thrombus formation in the setting of sinus rhythm is rare. Blood screening work-up for conditions predisposing thrombosis formation was negative. The probable predisposing factors for thrombus formation in the present case were mild left ventricular systolic dysfunction, moderate left ventricular hypertrophy, and LA enlargement. The cystic character of thrombus is unusual and differential diagnosis for blood cyst, hydatid cyst, and myxoma should be kept in mind.

Panels A–F. Transthoracic and transesophageal echocardiographic images revealing a large, mobile cystic thrombus with smooth contours (20 × 27 mm) in the body of enlarged LA originating from LAA (A–C). Transthoracic echocardiographic view of the thrombus 1 day after starting heparin demonstrating that the thrombus decreased in size (D). Transesophageal echocardiographic examinations revealed complete disappearance of thrombus in both of LA and LAA 3 days after starting intravenous heparin treatment (Panels E and F). LA, left atrium; CT, cystic thrombus; LA, left atrium; LAA, left atrial appendage; LV, left ventricle; Ao, aorta; RA, right atrium.