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Acute Blood Pressure-Lowering Effects of Nitrogen Dioxide Exposure from Domestic Gas Cooking via Elevation of Plasma Nitrite Concentration in Healthy Individuals

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Air pollution is a major cause of cardiovascular and all-cause mortality. Disentangling the relative contributions of pollutants is challenging, as epidemiological data measuring exposure to one (e.g. nitrogen dioxide; NO₂) is inevitably confounded by exposure to others (e.g. particulate matter; PM). Animal studies suggest that inhaled NO₂ has the potential to increase plasma [nitrite]¹; a chemical originally considered to be physiologically inert before we found that its reduction to nitric oxide (NO) protects the myocardium against ischaemia-reperfusion injury².

We conducted an acute, randomized, controlled, crossover study to assess the impact of 90min exposure to NO₂ (from sitting next to a domestic gas cooker) versus control (room air) on plasma [nitrite] (primary endpoint) and BP (secondary endpoints) in twelve healthy participants. All underwent both interventions/visits (interval 7-108d) in a computer-generated randomized order. Baseline characteristics (mean±SD): 26±4years, 10/12 female, BMI 21.9±3.0kg/m², systolic BP (SBP) 113.8±7.9mmHg, diastolic BP (DBP) 72.8±5.7mmHg. The exposure phase was followed by a 90min washout phase at background [NO₂]. Participants fasted for 12h before each visit and received 250mL low-nitrate water at Time 0h/1.5h. The study was powered for a difference in plasma [nitrite] of 27±40nmol/L on repeated-measures, two-way ANOVA (α 0.05, β 0.2) following D'Agostino-Pearson normality-confirmation, with Sidak's post-test (GraphPad Prism v8.2.1)³.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Relative to control, exposure increased ambient [NO₂]: 276.3±38.5ppb versus 27.6±2.8ppb (P <0.001). Plasma [nitrite] was increased through both the 90min NO₂ exposure and 90min washout (P <0.001; **Figure-1A**). NO₂ exposure decreased both SBP and DBP (both P <0.001; **Figure-1B/C**). The largest decrease in SBP relative to control occurred at 45min (4.6mmHg, 95%CI 0.2-8.9; P =0.032) and 90min (5.5mmHg, 95%CI 1.2-9.9; P =0.005). The effect of NO₂ on DBP was maximal at 45min (5.7mmHg, 95%CI 0.9-10.5; P =0.009).

The temporal relationship between the increase in plasma [nitrite] and SBP/DBP reduction (~5mmHg) is consistent with studies investigating dietary nitrate². Furthermore, whilst the level of NO₂ exposure (276.3±38.5ppb) was ~2.5-fold greater than recommended limits for exposure (e.g. WHO guideline 105ppb 1h mean), it is less than that recorded adjacent to busy roads or in some domestic kitchens (~2000ppb). Our model is therefore conservative relative to real-world exposure.

Previously, an increase in plasma [nitrite] at 2h following diesel exhaust inhalation was thought to be due to PM-mediated induction of inflammatory pathways³.

However, our data suggests a more rapid increase in plasma [nitrite] which favors chemical conversion from NO₂ (e.g. via a nitrous acid intermediary) and presents a plausible mechanism through which inhaled NO₂ increases plasma [nitrite]¹. This novel “ecophysiological NO_x cycle” may directly feed into the established “nitrate-nitrite-NO pathway” and contribute NO-mediated cardiovascular effects². Adverse respiratory effects of inhaled NO₂ were not investigated here¹.

These data must be considered in the context of the strong epidemiological association between NO₂ exposure and cardiovascular mortality¹. However, PM-free NO₂ does not appear to impair either vascular function, fibrinolysis or affect heart rate variability in patients with coronary heart disease: parameters adversely affected by increased ambient NO₂ exposure in epidemiological studies^{4,5}. This study expands our understanding of how inhaled NO₂ might impact the cardiovascular system, and the role of diet in disease: it's not just what you eat, but how you cook it that matters.

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King's College London

DISCLOSURES

None.

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FIGURE LEGEND

Figure 1: Effect of NO₂ exposure on (A) plasma [nitrite], (B) systolic blood pressure (Δ SBP), (C) diastolic blood pressure (Δ DBP). Comparison between experimental and control shown as ††† P <0.001, and individual timepoints as * P <0.05, ** P <0.01. Data expressed as mean $\pm$ SEM (n =12).

