Acute blood pressure-lowering effects of nitrogen dioxide exposure from domestic gas cooking via elevation of plasma nitrite concentration in healthy individuals

Article

Accepted Version

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; NO_2) is inevitably confounded by exposure to others (e.g. particulate matter; PM). Animal studies suggest that inhaled NO_2 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 injury[2].

We conducted an acute, randomized, controlled, crossover study to assess the impact of 90min exposure to NO_2 (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/m^2, 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 [NO_2]. 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 (α0.05,β0.2) 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 [NO_2]: 276.3±38.5ppb versus 27.6±2.8ppb (P<0.001). Plasma [nitrite] was increased through both the 90min NO_2 exposure and 90min washout (P<0.001; **Figure-1A**). NO_2 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 NO_2 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 nitrate[2]. Furthermore, whilst the level of NO_2 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 pathways[3].

However, our data suggests a more rapid increase in plasma [nitrite] which favors chemical conversion from NO_2 (e.g. via a nitrous acid intermediary) and presents a plausible mechanism through which inhaled NO_2 increases plasma [nitrite][1]. This novel "ecophysiological NOx cycle" may directly feed into the established "nitrate-nitrite-NO pathway" and contribute NO-mediated cardiovascular effects[2]. Adverse respiratory effects of inhaled NO_2 were not investigated here[1].

These data must be considered in the context of the strong epidemiological association between NO_2 exposure and cardiovascular mortality[1]. However, PM-free NO_2 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 NO_2 exposure in epidemiological studies[4, 5]. This study expands our understanding of how inhaled NO_2 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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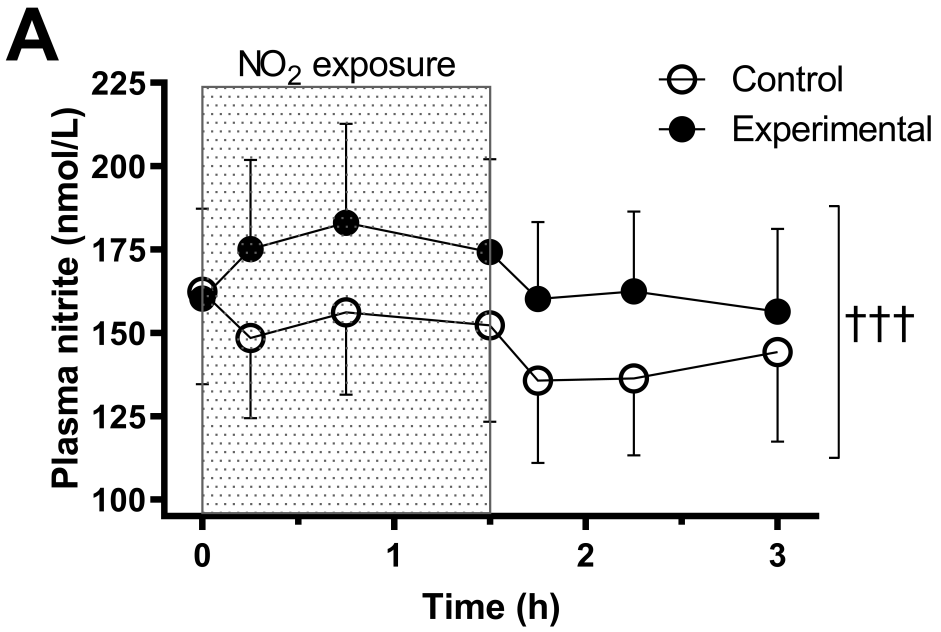
DISCLOSURES
None.

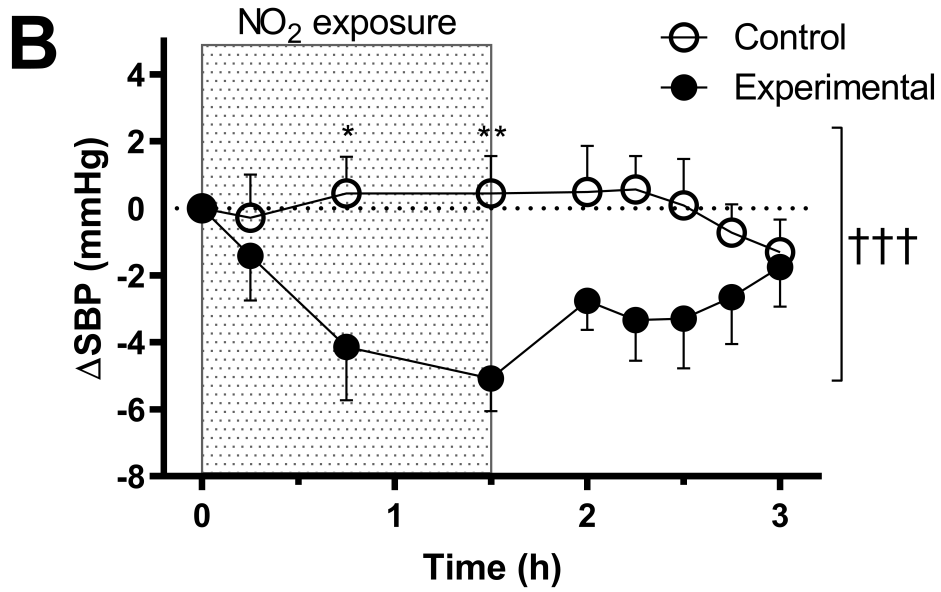
REFERENCES

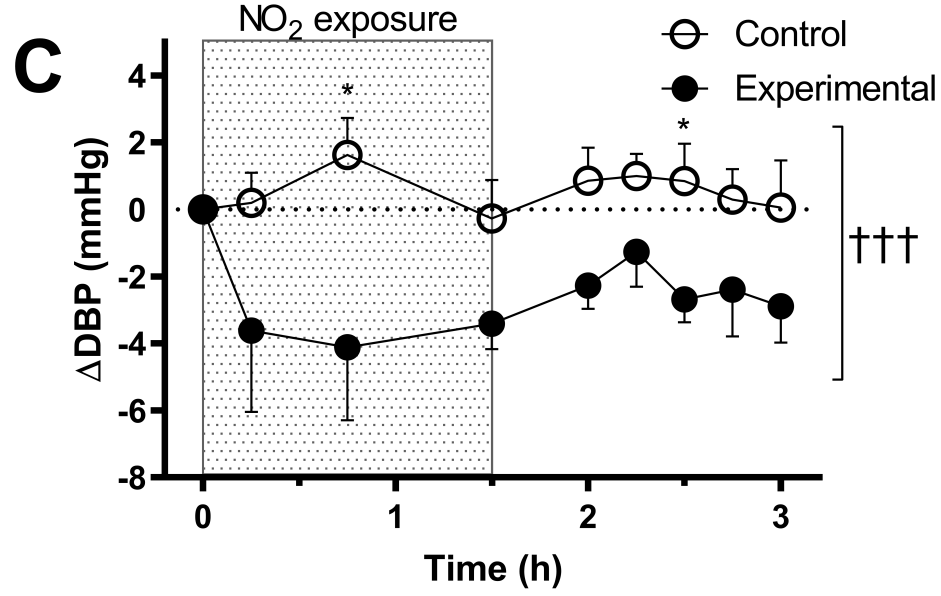
1. World Health Organisation. Review of evidence on health aspects of air pollution – REVIHAAP project: final technical report 2013.
2. Khatri J, Mills CE, Maskell P, et al. It is rocket science - why dietary nitrate is hard to 'beet'! Part I: twists and turns in the realization of the nitrate-nitrite-NO pathway. *Br J Clin Pharmacol*. 2017;83:129-139.
3. Langrish JP, Unosson J, Bosson J, et al. Altered nitric oxide bioavailability contributes to diesel exhaust inhalation-induced cardiovascular dysfunction in man. *J Am Heart Assoc*. 2013;2:e004309.
4. Langrish JP, Lundback M, Barath S, et al. Exposure to nitrogen dioxide is not associated with vascular dysfunction in man. *Inhal Toxicol*. 2010;22:192-8.
5. Scaife A, Barclay J, Hillis GS, et al. Lack of effect of nitrogen dioxide exposure on heart rate variability in patients with stable coronary heart disease and impaired left ventricular systolic function. *Occup Environ Med*. 2012;69:587-91.

FIGURE LEGEND

Figure 1: Effect of NO_2 exposure on (A)plasma [nitrite], (B)systolic blood pressure (ΔSBP), (C)diastolic blood pressure (ΔDBP). Comparison between experimental and control shown as †††P<0.001, and individual timepoints as *P<0.05, **P<0.01. Data expressed as mean±SEM (n=12).


A
NO2 exposure
Control
Experimental
Plasma nitrite (nmol/L)
225
200
175
150
125
100
0
1
2
3
Time (h)
†††


B
NO2 exposure
Control
Experimental
ΔSBP (mmHg)
4
2
0
-2
-4
-6
-8
*
**
0
1
2
3
Time (h)
†††


C
NO2 exposure
Control
Experimental
ΔDBP (mmHg)
4
2
0
-2
-4
-6
-8
*
*
0
1
2
3
Time (h)
†††