

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

Floyd, C. N., Shahed, F., Ukah, F., McNeil, K., O'Gallagher, K., Mills, C. E. ORCID: <https://orcid.org/0000-0002-8313-3700>, Evangelopoulos, D., Lim, S., Mudway, I., Barrett, B., Walton, H. and Webb, A. J. (2020) Acute blood pressure-lowering effects of nitrogen dioxide exposure from domestic gas cooking via elevation of plasma nitrite concentration in healthy individuals. *Circulation Research*, 127 (6). pp. 847-848. ISSN 0009-7330 doi: <https://doi.org/10.1161/CIRCRESAHA.120.316748> Available at <https://centaur.reading.ac.uk/91307/>

It is advisable to refer to the publisher's version if you intend to cite from the work. See [Guidance on citing](#).

To link to this article DOI: <http://dx.doi.org/10.1161/CIRCRESAHA.120.316748>

Publisher: American Heart Association

All outputs in CentAUR are protected by Intellectual Property Rights law, including copyright law. Copyright and IPR is retained by the creators or other

copyright holders. Terms and conditions for use of this material are defined in the [End User Agreement](#).

www.reading.ac.uk/centaur

CentAUR

Central Archive at the University of Reading

Reading's research outputs online

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

Christopher N Floyd¹, Fawzia Shahed¹, Frances Ukah¹, Karen McNeill¹, Kevin O’Gallagher¹, Charlotte E Mills¹, Dimitris Evangelopoulos¹, Shanon Lim¹, Ian Mudway¹, Benjamin Barratt¹, Heather Walton¹, Andrew J Webb¹

¹King’s College London

Running title: Nitrogen Dioxide Lowers Blood Pressure



Circulation Research

Subject Terms:
Cardiovascular Disease
Risk Factors

Keywords: Nitrogen dioxide, blood pressure, nitrite, air pollution.

Address correspondence to:

Dr. Andrew Webb
St. Thomas' Hospital
London, SE1 7EH
andrew.1.webb@kcl.ac.uk

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.

SOURCES OF FUNDING

King's College London

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 'beat'! 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 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).

