Inorganic Nitrate Supplementation Lowers Blood Pressure in Humans

Role for Nitrite-Derived NO

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Abstract—Ingestion of dietary (inorganic) nitrate elevates circulating and tissue levels of nitrite via bioconversion in the entero-salivary circulation. In addition, nitrite is a potent vasodilator in humans, an effect thought to underlie the blood pressure–lowering effects of dietary nitrate (in the form of beetroot juice) ingestion. Whether inorganic nitrate underlies these effects and whether the effects of either naturally occurring dietary nitrate or inorganic nitrate supplementation are dose dependent remain uncertain. Using a randomized crossover study design, we show that nitrate supplementation (KNO_3 capsules: 4 versus 12 mmol [n=6] or 24 mmol of KNO_3 (1488 mg of nitrate) versus 24 mmol of KCl [n=20]) or vegetable intake (250 mL of beetroot juice [5.5 mmol nitrate] versus 250 mL of water [n=9]) causes dose-dependent elevation in plasma nitrite concentration and elevation of cGMP concentration with a consequent decrease in blood pressure in healthy volunteers. In addition, post hoc analysis demonstrates a sex difference in sensitivity to nitrate supplementation dependent on resting baseline blood pressure and plasma nitrite concentration, whereby blood pressure is decreased in male volunteers, with higher baseline blood pressure and lower plasma nitrite concentration but not in female volunteers. Our findings demonstrate dose-dependent decreases in blood pressure and vasoprotection after inorganic nitrate ingestion in the form of either supplementation or by dietary elevation. In addition, our post hoc analyses intimate sex differences in nitrate processing involving the entero-salivary circulation that are likely to be major contributing factors to the lower blood pressures and the vasoprotective phenotype of premenopausal women. **(*Hypertension*. 2010;56:274-281.)**

Key Words: clinical science ■ diet ■ NO ■ endothelium ■ blood pressure

Cardiovascular disease (CVD) is the biggest killer worldwide and is likely to increase in proportion as the non-Western world adopts a Western lifestyle (World Health Organization, fact sheet 317, www.who.int). Hypertension is a major risk factor for CVD and is predicted to reach a global prevalence of 30% by 2025.[1] Because blood pressure (BP) remains elevated in ≈50% of all treated hypertensive patients,[2,3] novel and cost-effective therapeutic strategies are urgently required for the treatment of this condition. In this regard, over the last decade, there has been a major initiative in the Western world to increase the public consumption of vegetables (Department of Health United Kingdom, 5 a day, www.nhs.uk/5aday) in part, as a strategy to prevent CVD.[4] This approach has been taken because epidemiological,[5] cohort,[6,7] and trial-based data[8,9] demonstrate that increased consumption of a vegetable-rich diet confers protection from CVD, including hypertension. However, the exact mechanisms of the BP-lowering and protective effects of such a diet remain uncertain.

Large-scale clinical trials have failed to show a beneficial cardiovascular effect of several different nutrients found in vegetables, including antioxidant vitamins and folate.[10,11] More recently, attention has been directed toward other possible elements in vegetables that may have a role, including inorganic nitrate.[12] In 2006, Larsen et al[13] demonstrated that supplementation of healthy volunteers with sodium nitrate resulted in a decrease in diastolic BP (DBP) but not systolic BP (SBP). More recently, we have shown that consumption of beetroot, which is a high nitrate-containing vegetable, also exerts a number of beneficial effects in healthy volunteers, including lowering of both SBP and DBP and protection of the endothelium from ischemia-reperfusion (IR)–induced endothelial damage.[14]

The activity of orally ingested inorganic nitrate is thought to lie in its conversion to nitrite by facultative bacteria found

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on the dorsal surface of the tongue.[15] The swallowing of this nitrite-rich saliva permits entry of nitrite into the circulation via the stomach, and then, once within the circulation, nitrite is thought to be converted to the potent vasodilator NO.[16–18] Evidence suggests that this circuit of bioactivation results in both vasodilator effects and protection against IR injury.[19] However, whether the beneficial cardiovascular effects of beetroot juice are specifically attributable to the dietary nitrate content of beetroot and whether the effects of either naturally occurring dietary nitrate or inorganic nitrate supplementation are dose-dependent remain uncertain.

Herein, we have investigated whether the effects of dietary provision of inorganic nitrate is recapitulated using potassium nitrate capsules and whether the effect of inorganic nitrate on circulating nitrite/nitrate levels, BP, and endothelial function is dose and NO dependent in healthy volunteers.

Methods

Volunteers

The studies were granted full ethical approval by the local research ethics committee. All of the subjects gave informed consent after satisfying the inclusion criteria (please see the online Data Supplement at http://hyper.ahajournals.org).

BP Studies

Volunteers were entered into 1 of 3 different studies. In the first study, 21 subjects were randomized to receive potassium nitrate capsules (KNO_3: 24 mmol giving 1488 mg of nitrate; Martindale Pharmaceuticals) and an equivalent dose of potassium chloride (KCl, Martindale Pharmaceuticals) with 500 mL of low nitrate-containing water (nitrate: 61.2±1.9 μmol/L; nitrite: 0.20±0.03 μmol/L; Zepbrook Ltd) in this double-blind, crossover study. In a separate study, 6 additional individuals were randomized to receive either 4 or 12 mmol (248 or 744 mg of nitrate, respectively) of KNO_3 with 500 mL of water in an open-label, crossover study. A further randomized, open-label, crossover study was performed in 9 healthy subjects to investigate dose dependency of the effects of beetroot juice–derived nitrate relative to our previous findings where 500 mL of juice were administered.[14] Volunteers received either 250 mL of beetroot juice (James White Drinks Ltd) or 250 mL of water. In all of the groups, blood samples were taken and BP determined at baseline and then at specific intervals for ≤24 hours.

Flow-Mediated Dilatation Study

The impact of an IR insult on endothelial function was assessed in 12 healthy subjects by measuring brachial artery diameter in the nondominant arm in response to reactive hyperemia (please see the online Data Supplement). Subjects were randomized in a double-blind (for capsules only) crossover study design to receive either 24 mmol of KNO_3 or KCl with 500 mL of water and, on another occasion, 250 mL of beetroot juice 90 minutes before ischemia.

BP Measurements

All of the BP and heart rate (HR) measurements were taken in triplicate in the seated position using an Omron 715IT before and after capsule, beetroot juice, or water ingestion for ≤24 hours (please see the online Data Supplement).

Blood Sampling

Blood samples were taken at baseline; then after capsule, beetroot juice, or water ingestion, every 30 minutes up to 3 hours; then in some studies hourly from 3 to 6 hours; and then again at 24 hours (please see the online Data Supplement).

Measurement of Plasma Nitrate/Nitrite and cGMP Concentration

Plasma nitrite and nitrate (NOx) concentration were measured using ozone chemiluminescence (please see the online Data Supplement). cGMP was determined using an enzyme immunoassay (cGMP EIA Biotrak System, GE Healthcare UK Ltd) according to the manufacturer's instructions.

Statistical Analysis

The data were analyzed by an individual who was blinded to the different interventions, using Graphpad Prism software version 5. All of the data are expressed as mean±SEM, unless otherwise specified. For BP measurements and plasma nitrate and nitrite concentration, repeated-measures ANOVA was used, with Dunnett posttest for comparison to baseline control and Bonferroni post test for comparison between groups at individual time points. Unpaired *t* tests were used for comparisons of baseline statistics. For flow-mediated dilatation and cGMP responses, repeated-measures ANOVA followed by Bonferroni posttests for individual group comparisons was used. Determinations of correlations between plasma nitrite or nitrate concentration with changes in SBP were completed using the Pearson correlation coefficient analysis.

Results

There were no significant differences in the general characteristics of the individuals recruited for the separate phases of the BP study (Table S1, available in the online Data Supplement). Beetroot juice was generally well tolerated by the subjects. The nitrate concentration in the beetroot juice was 22.4±3.8 mmol/L, whereas nitrite concentration was <50 nmol/L. Capsules were well tolerated in general, although one volunteer, who had not taken toast with the capsules, was treated for gastritis after consumption of capsules. This individual was unblinded and withdrawn from the study. On unblinding, it was discovered that gastritis occurred after taking chloride capsules. All of the subsequent subjects were made to take toast with the capsules, and there were no further adverse effects.

Dose-Dependent Increases in Circulating NO_3^- and NO_2^- After Oral Inorganic Nitrate Capsule Ingestion

After ingestion of KNO_3 capsules (24 mmol), there was a rapid (within 30 minutes) increase in circulating plasma nitrate concentration, peaking at 3 hours and remaining significantly elevated at 24 hours (Figure 1A). In contrast, the rise in plasma nitrite concentration was moderate, followed by a slower time course and significantly raised levels first evident at 1.5 hours, plateauing at ≈2.5 hours, sustained to 6 hours, and remaining elevated at 24 hours (Figure 1B). These effects of KNO_3 were dose dependent with plasma nitrate concentration elevated above baseline by ≈35-, 27-, and 7-fold after administration of 24, 12, and 4 mmol of KNO_3, respectively. The rises in plasma nitrite concentration also showed dose dependency, albeit with a more moderate rise of a 4.0-, 2.0-, and 1.3-fold increase, respectively (Figure 1).

Inorganic Nitrate Supplementation Elevates Plasma cGMP Concentration

Plasma cGMP concentration was significantly raised compared with baseline at 3 and 24 hours after ingestion of KNO_3 capsules (24 mmol; Figure 1E).

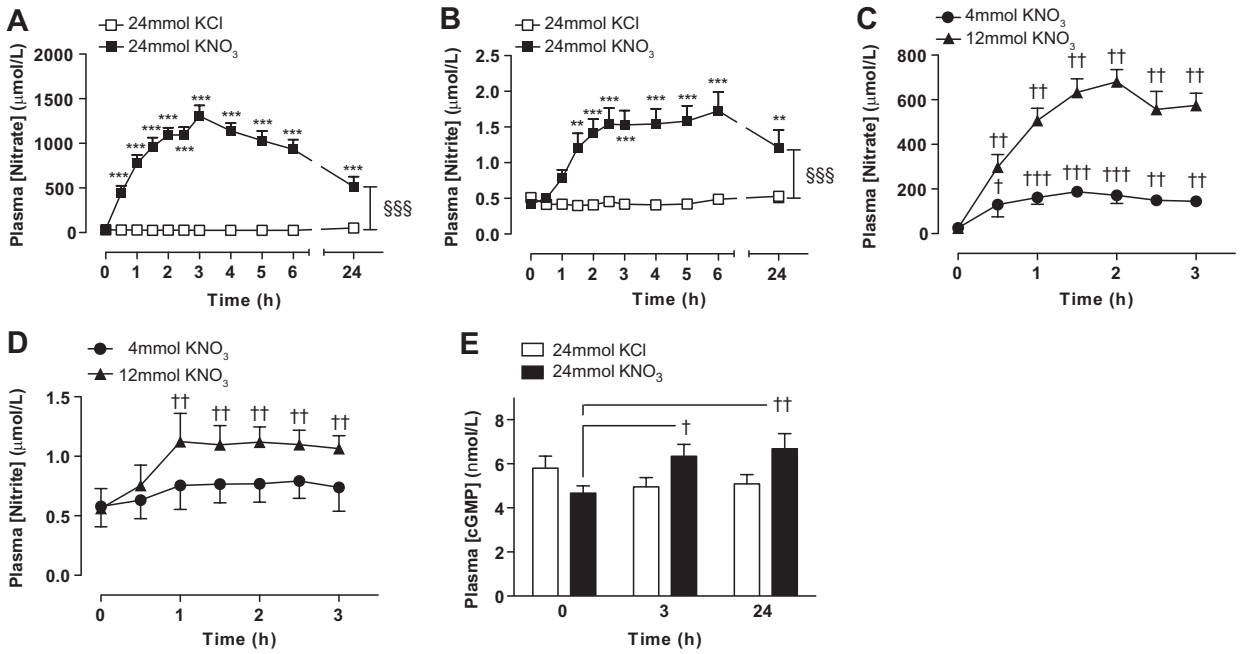

Figure 1. Dose-dependent effects of orally administered inorganic nitrate supplementation on plasma NOx. The effects of KNO_3 (24 mmol) and KCl (24 mmol) control capsules on circulating plasma (A) nitrate, (B) nitrite, and (E) cGMP (n=20); and the effects of 4 and 12 mmol of KNO_3 on circulating plasma (C) nitrate and (D) nitrite (n=6). Data are expressed as mean±SEM. Significance shown for comparisons between groups as §§§$P<0.001$ for 2-way ANOVA; **$P<0.01$ and ***$P<0.001$ for Bonferroni post hoc tests; and †$P<0.05$, ††$P<0.01$, and †††$P<0.001$ for 1-way ANOVA followed by Dunnett posttest comparison with baseline (t=0).

Dose-Dependent Decreases in BP After Oral Inorganic Nitrate Capsule Ingestion

KNO_3 (24 mmol) ingestion caused reductions in both SBP and DBP over 24 hours compared with KCl control. The peak differences between the 2 limbs were 9.4±1.6 mm Hg (at 6 hours) and 6.0±1.1 mm Hg (at 2.75 hours) for SBP and DBP, respectively (Figure 2A and 2B). There was no significant difference in the HR response between the 2 groups (Figure

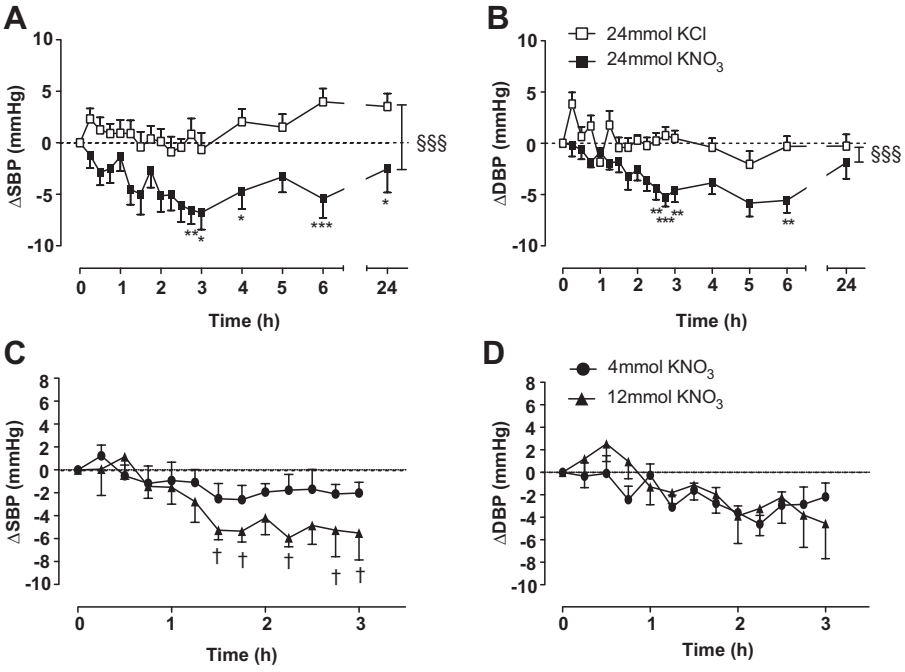

Figure 2. Inorganic nitrate supplementation lowers BP. The effects of KNO_3 (24 mmol) and KCl (24 mmol) on (A) SBP and (B) DBP (n=20) and the effects of 4 and 12 mmol of KNO_3 on (C) SBP and (D) DBP (n=6). Data are expressed as mean±SEM. Significance shown for comparisons between groups as §§§$P<0.001$ for 2-way ANOVA; *$P<0.05$, **$P<0.01$, and ***$P<0.001$ for Bonferroni post hoc tests; and †$P<0.05$ for 1-way ANOVA followed by Dunnett posttest comparison with baseline (t=0).

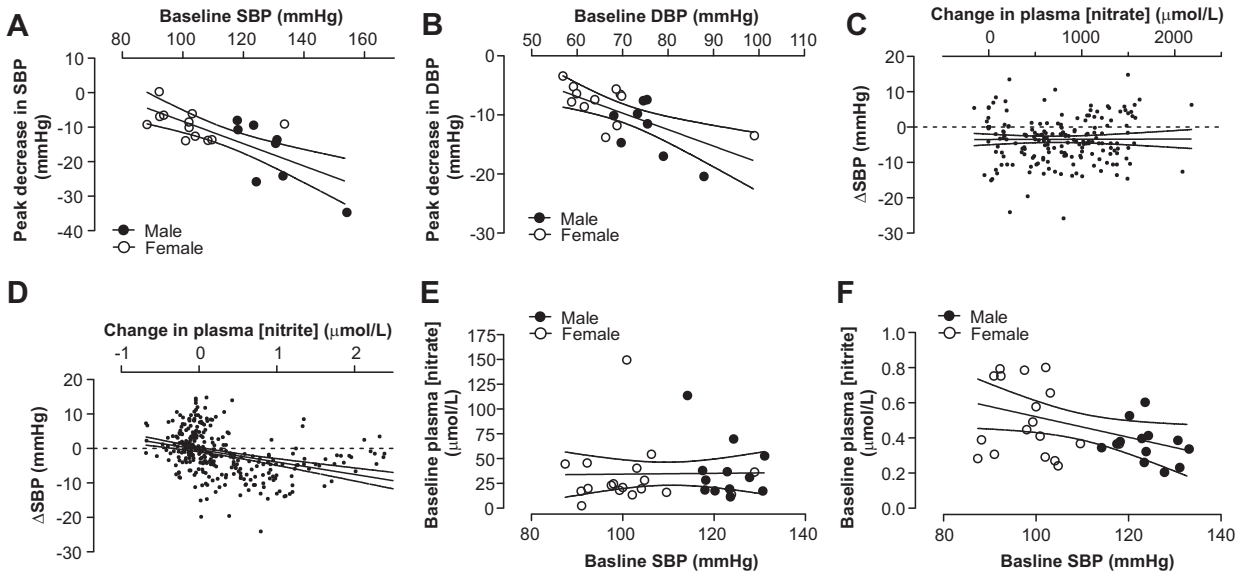

Figure 3. Plasma nitrite determines BP. Correlation of peak changes in (A) SBP and (B) DBP to baseline SBP, correlation of changes in (C) nitrate and (D) nitrite to changes in SBP, and correlation of baseline SBP to baseline (E) nitrate and (F) nitrite after KNO_3 or KCl (24 mmol) ingestion. All of the graphs show Pearson linear regression of best-fit ±95% CIs.

S1). The effect of KNO_3 on BP was dose dependent (Figure 2C and 2D).

Changes in SBP Correlate With Baseline BP and Plasma Nitrite But Not Nitrate Concentration

Post hoc analysis of the KNO_3/KCl capsule study demonstrated that the decreases in BP after nitrate ingestion are not correlated with changes in plasma nitrate concentration ($P=0.95$, linear regression; Figure 3A) but are correlated with changes in plasma nitrite concentration ($r=-0.350$; $P<0.001$, linear regression; Figure 3B). In addition, the peak decreases in BP are also correlated negatively with baseline BP (SBP: $r=-0.728$, $P<0.001$; DBP: $r=-0.657$, $P<0.01$; Figure 3C and 3D). Finally, baseline BP is correlated negatively with baseline nitrite ($r=-0.373$; $P<0.05$) but not nitrate ($P=0.93$; Figure 3E and 3F).

Sex Differences in Responses to Nitrate

Interestingly, the above post hoc correlations exposed a prominent sex difference in the responses to nitrate. Separation of the KNO_3/KCl capsule comparison study data by sex demonstrates that female volunteers had significantly lower baseline SBP, DBP, and body mass index (Table S2) compared with the male volunteers. In addition, whereas baseline plasma nitrate concentration was similar between the sexes, plasma nitrite concentration was significantly higher in the females (Table S2).

Additionally, the rise in plasma nitrate and nitrite concentration in males after KNO_3 ingestion appeared significantly lower compared with females (Figure 4A and 4B). However, the fold increases in plasma nitrite concentration from baseline were similar (≈3.3- and ≈4.1-fold for males and females, respectively). Conversely, KNO_3-induced reduction in SBP and DBP was substantially greater in males compared with females (Figure 4C and 4D). There were no significant effects on HR (Figure S1). No sex differences in the response to KCl with respect to SBP, DBP, or HR were found (Figure S2). The dose of nitrate per kilogram of body weight administered to females was 0.45±0.02 mmol/kg and for males was 0.32±0.021 mmol/kg (see Figure S3 for normalized plasma NOx relative to dose given).

Inorganic Nitrate Prevents IR-Induced Endothelial Dysfunction

In addition to the reduction in BP, nitrate capsules prevented IR-induced endothelial dysfunction (Figure S4). Moreover, this effect was not evident after chloride capsule ingestion.

Dose-Dependent Effects of Beetroot Juice

After juice ingestion (5.5 mmol nitrate dose), plasma nitrate rose rapidly and remained elevated over the 3-hour time course compared with water control (Figure 5A). Plasma nitrite concentration also increased, peaking at 2.5 hours with a ≈1.6-fold rise above baseline levels and also remaining significantly elevated over the 3-hour time course compared with water control (Figure 5B). In addition, cGMP levels were elevated at 3 hours compared with baseline after beetroot juice ingestion (Figure 5E). Although SBP decreased with a peak reduction of 5.4±1.5 mm Hg (SBP; Figure 5C) and endothelial dysfunction caused by IR injury prevented (Figure S3), there were no significant differences in DBP or HR between the limbs (Figures 5D and S1).

Discussion

Determining how vegetables confer protection against CVD and exploiting this to therapeutic advantage are likely to have considerable health and economic implications. Recently, it has been suggested that dietary nitrate found in high levels in vegetables might underlie some of the beneficial effects of vegetable-rich diets.[12,14] In the present study we have shown that inorganic nitrate capsules or a dietary nitrate load, in the

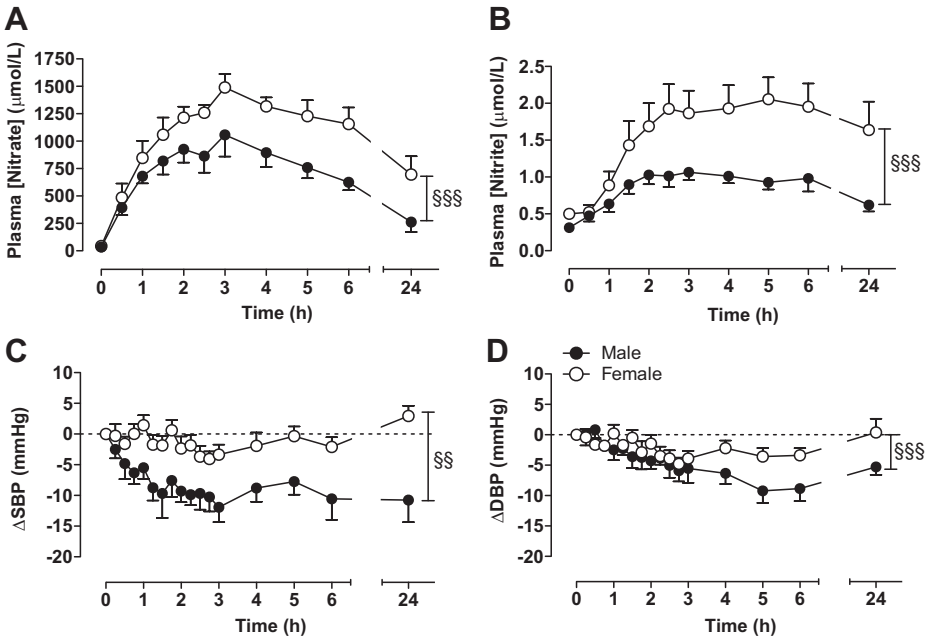

Figure 4. Sex differences in circulating plasma (A) nitrate and (B) nitrite and (C) SBP and (D) DBP after administration of KNO_3 (24 mmol) capsules. Data are expressed as mean±SEM of males (n=8) and females (n=12). Significance shown for comparisons between groups as §§$P<0.01$ and §§§$P<0.001$ for 2-way ANOVA.

form of beetroot juice, results in dose-dependent increases in plasma nitrite concentration via bioconversion in vivo. Stieglitz postulated,[20] >80 years ago, that the beneficial effects of inorganic nitrate (bismuth subnitrate) in hypertensive patients were because of conversion to nitrite in vivo, and our findings confirm that this bioactive nitrite, after reduction to NO, causes dose-dependent decreases in BP and prevents IR-induced endothelial dysfunction in healthy volunteers.

Ingestion of KNO_3 capsules caused rises in circulating plasma nitrate and thence nitrite concentration that were dose and time dependent. Significant rises in plasma nitrate concentration were evident sooner than nitrite (30 minutes versus

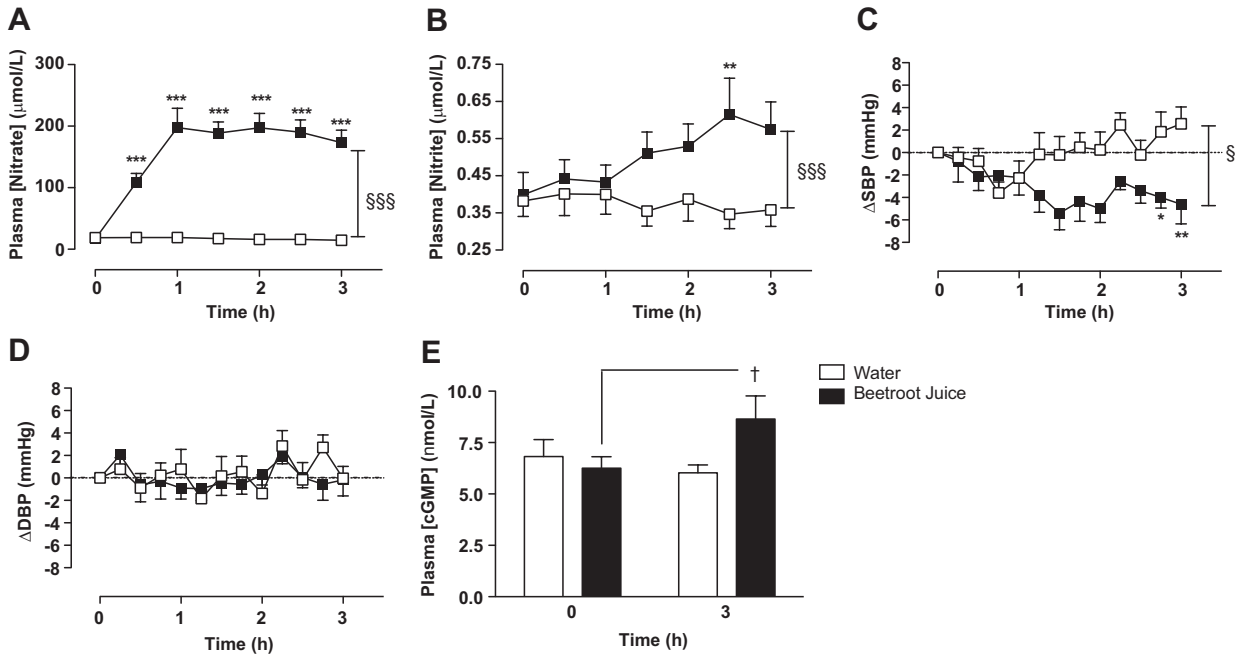

Figure 5. Dietary nitrate supplementation with beetroot juice raises plasma nitrite and lowers BP. The effects of beetroot juice (250 mL; 5.5 mmol of nitrate) or water control on circulating plasma (A) nitrate, (B) nitrite, (E) cGMP, (C) SBP, and (D) DBP. Data are expressed as mean±SEM of n=9. Significance shown for comparisons between groups as §$P<0.05$ and §§§$P<0.001$ for 2-way ANOVA; *$P<0.05$, **$P<0.01$, and ***$P<0.001$ for Bonferroni post hoc tests; and †$P<0.05$ for paired Student *t* test.

1.5 hours for 24 mmol of KNO_3) reflecting the use of the entero-salivary pathway and lingual bacterial reduction of nitrate to nitrite.[14,21] Approximately similar time courses for changes in both plasma nitrate and nitrite concentration were evident with lower doses of nitrate provided by either KNO_3 capsule or beetroot juice ingestion. Indeed, the dose of nitrate administered via beetroot juice of 5.5 mmol caused fold rises in plasma nitrate and nitrite concentration that fell between the effects of either 12 or 4 mmol provided via nitrate capsule. These findings indicate that, irrespective of source, that is, nitrate salt or in dietary form, the pharmacokinetics of nitrate and nitrite after an oral nitrate load remain largely unchanged and are dose dependent.

KNO_3 capsule ingestion substantially lowered SBP and DBP over 24 hours, whereas a similar dose of KCl did not alter BP over the same time period. These findings suggest that the BP changes were not attributed to the K^+ content and, more likely, dependent on the endogenous conversion to nitrite and, thence, to NO, because the changes in plasma nitrite correlated closely with reductions in BP. Nitrite, within the realm of physiological concentrations, vasodilates both the arterial and venous sides of the forearm circulation of humans,[17,22] and systemic nitrite application decreases BP in both primates[18] and humans.[17] In the main, it is thought that these effects of nitrite are because of its reduction to NO within the blood vessel wall[23,24] and within the red blood cell,[17,25] although there is some evidence that nitrite may exert direct effects independent of NO formation.[26,27] The effects of inorganic nitrate were found to be dose dependent as reflected by the decreasing magnitude of response in SBP to a 24-, 12-, 5.5-, and 4-mmol dose. Importantly, as with plasma NOx, this dose dependency appeared to hold irrespective of whether the inorganic nitrate load was administered by KNO_3 capsules or beetroot juice. The similarities between the activity of these 2 distinct approaches to inorganic nitrate administration are further reflected by the demonstration that KNO_3 capsules protect against the endothelial dysfunction induced by an IR insult much in the same manner as shown previously for a matched nitrate dose in beetroot juice.[14] This latter finding provides further support for our contention that inorganic nitrate underlies the beneficial effects of beetroot juice on the cardiovascular system.

Although it is largely accepted that NO underlies the bioactivity of nitrite, this has not been demonstrated clearly in humans in vivo. In the present study we demonstrate a temporal relationship between the rise in circulating nitrite concentration with a rise in cGMP levels. cGMP is the most sensitive indicator of NO bioactivity,[28] and evidence of its elevation provides unequivocal evidence of the generation of bioactive NO.

Post hoc analyses of the KNO_3 capsule data demonstrate that the magnitude of the BP response is directly related to baseline BP (ie, the higher the baseline BP the greater the peak BP reduction achieved). This relationship is consistent with the observation that the effect of BP-lowering drugs in patients is also proportional to resting BP.[29] Interestingly, in our cohort, baseline BP was closely correlated with baseline plasma nitrite but not nitrate concentration. Baseline plasma nitrite levels has been proposed to be an accurate reflection of endogenous NO generation via endothelial NO synthase–dependent conversion of L-arginine to NO,[30] and our findings may simply be highlighting the known relationship between classic NO synthase–derived NO and BP. However, with the appreciation that nitrite is a bioactive molecule, our findings also support the possibility that the correlation of baseline plasma nitrite with BP is actually a reflection of the functional activity of physiological nitrite reduction as first proposed in 2000 by Gladwin et al.[31] This, in turn, raises the possibility that intrinsic plasma nitrite concentration may be involved in "setting" the BP of healthy volunteers. Interpretation of plasma NOx is challenging because of the fact that multiple pathways for the generation and destruction of NOx and NO exist.[19] Indeed, changes in plasma nitrite concentration may reflect endothelial NO synthase activity,[30] NO oxidation,[32] nitrate reduction,[14,21] or all 3 at once. Nevertheless, plasma nitrite concentration correlated with BP at baseline and with changes in BP after nitrate supplementation, with corresponding increases in plasma cGMP concentration, suggesting that the measure of plasma nitrite does reflect, at least in part, nitrite bioactivity. Our data also appeared to suggest some clustering of responsiveness to nitrate into 2 groups, that is, although small changes in nitrite ($\approx<1$ μmol/L) effected apparently substantial changes in BP, where the changes in nitrite were >1 μmol/L, little effect on BP was evident. Further post hoc analyses of our data suggest that, indeed, 2 distinct groups of responsiveness to inorganic nitrate dosing exist within our cohort according to sex.

A significant difference in baseline plasma nitrite concentration (but not plasma nitrate) associated with lower baseline BP was evident in our female volunteers compared with the male volunteers. This finding is supportive of the view that a close relationship between nitrite levels and BP exists in humans. This correlation has been demonstrated previously but attributed to differences in vascular endothelial NO synthase expression and activity,[33] an effect that, in addition to endothelium-derived hyperpolarizing factor,[34] has been proposed to mediate the prevalence of lower BP in premenopausal women compared with age-matched men.[35] Our data herein also raise the further possibility that the association of circulating nitrite levels with lower BP evident in premenopausal women may relate, in part, to the bioactivity of the elevated levels of nitrite. This difference in basal nitrite levels may underlie the apparent decreased sensitivity to further elevations in plasma nitrite concentration. Dejam et al[18] have demonstrated that, whereas low micromolar concentrations of nitrite produced substantial increases in blood flow in the forearm, a saturation of the vasodilatory effect was observed with higher micromolar levels. It is possible that the apparent lack of effect of nitrite in females relates to a similar "saturation" of its vasodilating effect.

In addition, our analyses intimate sex differences in the endogenous handling of nitrate. Indeed, a similar dietary nitrate load, whilst resulting in only subtle differences in nitrate levels between the sexes, caused a $\approx$2-fold higher plasma nitrite concentration in females compared with males. These data hint at intriguing sex differences in the processing of NOx. Although differences in absorption and excretion of NOx may underlie some of these differences, it is possible

that the differences in nitrite levels reflect different lingual bacterial loads or species responsible for nitrate reduction to nitrite. Currently, it is thought that the predominant lingual bacteria responsible for nitrate reduction is Gram-negative *Veillonella spp* and Gram-positive *Actinomyces spp*.[36] Whether sex differences exist in the colonization of the tongue or nitrate reductase activities of these bacteria is currently unknown. It is also possible that the differences in plasma NOx levels simply reflect the differences in body weight between the 2 sexes, which were greater in the females compared with the males. However, normalization of plasma NOx concentrations to body weight did not alter the shape of the profiles seen, and significant differences in plasma nitrite concentration still persisted.

Taking all of the post hoc analyses together, we suggest that these apparent differences in processing of nitrate are likely to contribute to the prevalence of lower baseline BP in women compared with men.[35] An important limitation of our findings is that the sex differences were exposed with post hoc analyses. Further investigation in a prospective fashion to corroborate these analyses is clearly warranted. In addition, we did not control for the stage of the menstrual cycle in our female volunteers, and this may have some relevance, because resting BP is different throughout the menstrual cycle.[37]

Finally, in all of the measures of bioactivity, no significant changes were observed in the control limb using KCl capsules to match the 24-mmol KNO_3 dose. The significance of this finding is 2-fold. First, this suggests that the effects on BP were attributable specifically to the activity of nitrate. Secondly, the lack of any BP effect of KCl also supports the view that, whilst potassium (dietary or supplementation[38]), known to exert a number of beneficial effects on the cardiovascular system, particularly decreases in BP, it is not responsible for the effects of KNO_3 supplementation and is unlikely to underlie the effects of beetroot juice.

Perspectives

Although we acknowledge that our studies represent the responses of a healthy volunteer population, our evidence suggests that a dietary nitrate approach to CVD may have therapeutic use. This view is supported by the fact that the dose of 24 mmol administered in this study roughly approximates to the estimated nitrate content (≈20 mmol)[39] in the Dietary Approaches to Stop Hypertension diet,[9] a diet associated with significant decreases in BP. Extrapolation of the beneficial effects of dietary (inorganic) nitrate to the wider population, including patients with CVD, will require large-scale outcome trials to prove the thesis that dietary (inorganic) nitrate is a potential preventative measure or treatment for CVD. Furthermore, we suggest that important sex differences in baseline levels and handling of NOx species may underpin differences in BP and CVD in the general population. Finally, there may be a role for nitrate in delaying and preventing hypertension, and supplementation either in water or by diet may provide a cheap and effective global health strategy to combat the prevalence of CVD.

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Disclosures

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