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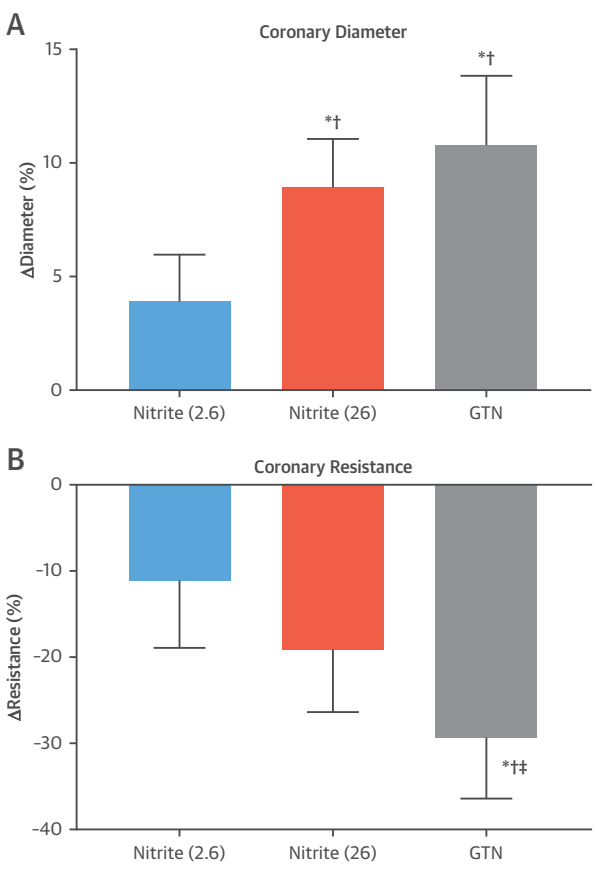
Letters

Inorganic Nitrite Selectively Dilates Epicardial Coronary Arteries

Inorganic nitrite (NO_2^-) as sodium nitrite or derived from dietary nitrate found in green leafy vegetables and beetroot has potential as a tolerance-free therapy in heart failure with preserved ejection fraction (1), including pulmonary hypertension-associated heart failure with preserved ejection fraction (2). Nitrite affects small and large arteries and veins. Previous studies demonstrated hypoxia (vs. normoxia) enhanced nitrite-induced dilation by 30% to 50% in small-resistance arterioles but not veins (because venous blood is already desaturated) (3). We recently demonstrated that nitrite selectively dilates peripheral conduit arteries in a normoxia-dependent/hypoxia-inhibited manner and selectively lowers aortic blood pressure (afterload) (4). We confirmed this latter effect with 6 months' dietary nitrate (beetroot juice) in 126 patients (5). We also found that nitrite has selectivity similar to that of nitroglycerin (a.k.a., glyceryl trinitrate [GTN]) for conduit arteries versus small-resistance arterioles (4). We therefore investigated whether nitrite also selectively vasodilated epicardial coronary (conduit) arteries.

FIGURE 1 Percentage of Changes



(A) Coronary Artery Diameter. **(B)** Coronary resistance. **Nitrite (2.6)** and **Nitrite (26)** denote nitrite (2.6 μmol/min) and nitrite (26 μmol/min), respectively. Data are mean ± SEM. *p < 0.05 vs. baseline; †p < 0.05 vs. nitrite (2.6 μmol/min); ‡p < 0.05 vs. nitrite (26 μmol/min). GTN = glyceryl trinitrate.

Following institutional and ethical approvals and informed consent, we recruited patients undergoing diagnostic coronary angiography, including those with an angiographically normal coronary artery and without previous coronary intervention.

A 0.014-inch coronary Doppler wire (Flow Wire, Phillips Volcano, Amsterdam, the Netherlands) was positioned within the proximal artery, and average peak velocity (APV) was measured following 5-min infusions of 0.9% saline (baseline), low-dose sodium nitrite (2.6 μmol/min), high-dose sodium nitrite (26 μmol/min), and GTN (1 μg/min). Angiographic images were obtained simultaneously. Quantitative coronary analysis was performed offline with measurements of vessel diameter (d) in the 5-mm segment distal to the tip of the Doppler wire. Coronary blood flow (CBF) (cm^3/s) was calculated according to the equation: CBF = (APV/2) × cross-sectional area. Coronary resistance (mm $Hg/cm^3/s$) was calculated as mean arterial pressure divided by CBF.

Nine patients (mean 56 years of age; 5 males; 78% hypertensive) received doses of both nitrite and GTN and had angiographic and Doppler flow traces of sufficient quality to be included in the analysis. The higher dose of nitrite (26 μmol/min) and GTN significantly dilated the coronary artery compared to baseline, where mean diameter change was: +8.9% (95% confidence interval [CI]: +2.0 to +15.8) (p = 0.01)

and +10.8% (95% CI: +1.0 to +20.5) (p = 0.03); respectively (Figure 1A), with no significant differences between nitrite and GTN (p = 0.45). The lower dose of nitrite (2.6 μmol/min) had no significant effect (+3.9%; 95% CI: −2.8 to +10.6; p = 0.30).

GTN increased coronary flow relative to that of baseline (median [interquartile range (IQR)]): +23.9% (IQR: +6.3 to +72.7); p = 0.02. Nitrite (2.6 μmol/min and 26 μmol/min) lacked significant effect on coronary flow: +12.0% (IQR: −10.2 to +24.1); p > 0.99; and +16.9% (IQR: +3.2 to +64.4); p > 0.99, respectively. This occurred despite relatively high estimated intracoronary nitrite concentrations of 73.7 μM (IQR: 57.8 to 154.9 μM) for nitrite (2.6 μmol/min) and 705 μM (IQR: 555 to 1,179 μM) for nitrite (26 μmol/min).

GTN also lowered coronary resistance relative to that of baseline, mean: −29.3% (95% CI: −52.8 to −5.9) (p = 0.02), and compared to nitrite (26 μmol/min) mean: −10.4% (95% CI: −18.3 to −2.4) (p = 0.01). By contrast, nitrite (2.6 μmol/min and 26 μmol/min) had no significant effect on coronary resistance, mean: −11.1% (95% CI: −36.7 to +14.5) (p = 0.52); and mean: −19.0% (95% CI: −43.4 to +5.4) (p = 0.13), respectively (Figure 1B).

There were no significant overall differences in central systolic, diastolic, or mean blood pressure levels with any of the interventions compared to baseline. Heart rate changed −3.1 beats/min (95% CI: −0.2 to −6.1) (p = 0.02) with nitrite (2.6 μmol/min) but not with nitrite (26 μmol/min) or GTN.

In summary, these are the first data to show that inorganic nitrite dilates epicardial coronary arteries; moreover, this dilation was selective (and dose-dependent). Although the results should be interpreted with caution, given the small sample size, the indirect measurements of coronary flow, and the trend toward a change in coronary flow/resistance, they support our findings in the peripheral circulation (4) of nitrite's physiological action as a normoxia-dependent selective conduit artery dilator over resistance arteries, even in the metabolically active myocardium. These findings also have important implications for our understanding of the potential beneficial cardiovascular properties of nitrite derived from dietary nitrate sources such as beetroot and green leafy vegetables: nitrite acts principally on large, rather than small vessels in the heart.

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Cardiovascular Mortality Reduction With Empagliflozin in Patients With Type 2 Diabetes and Cardiovascular Disease

Diabetes is associated with a significant decrease in life expectancy (1). In the EMPA-REG OUTCOME trial (NCT01131676), empagliflozin given in addition to standard of care reduced the risk of cardiovascular death by 38% (hazard ratio [HR]: 0.62; 95% confidence interval [CI]: 0.49 to 0.77; p < 0.0001) and all-cause mortality by 32% (HR: 0.68; 95% CI: 0.57 to 0.82; p <0.0001) versus placebo in patients with type