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Effects of chronic dietary nitrate supplementation on the hemodynamic response to dynamic exercise

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Lee JS, Stebbins CL, Jung E, Nho H, Kim JK, Chang MJ, Choi HM. Effects of chronic dietary nitrate supplementation on the hemodynamic response to dynamic exercise. Am J Physiol Regul Integr Comp Physiol 309: R459–R466, 2015. First published June 17, 2015; doi:10.1152/ajpregu.00099.2015.—While acute treatment with beetroot juice (BRJ) containing nitrate (NO3−) can lower systolic blood pressure (SBP), afterload, and myocardial O2 demand during submaximal exercise, effects of chronic supplementation with BRJ (containing a relatively low dose of NO3−, 400 mg) on cardiac output (CO), SBP, total peripheral resistance (TPR), and the work of the heart in response to dynamic exercise are not known. Thus, in 14 healthy males (22 ± 1 yr), we compared effects of 15 days of both BRJ and nitrate-depleted beetroot juice (NDBRJ) supplementation on plasma concentrations of NOx (NO3−/NO2−), SBP, diastolic blood pressure (DBP), mean arterial pressure (MAP), CO, TPR, and rate pressure product (RPP) at rest and during progressive cycling exercise. Endothelial function was also assessed via flow-mediated dilation (FMD). BRJ supplementation increased plasma NOx from 83.8 ± 13.8 to 167.6 ± 13.2 µM. Compared with NDBRJ, BRJ reduced SBP, DBP, MAP, and TPR at rest and during exercise (P < 0.05). In addition, RPP was decreased during exercise, while CO was increased, but only at rest and the 30% workload (P < 0.05). BRJ enhanced FMD-induced increases in brachial artery diameter (pre: 12.3 ± 1.6%; post: 17.8 ± 1.9%). We conclude that 1) chronic supplementation with BRJ lowers blood pressure and vascular resistance at rest and during exercise and attenuates RPP during exercise and 2) these effects may be due, in part, to enhanced endothelium-induced vasodilation in contracting skeletal muscle. Findings suggest that BRJ can act as a dietary nutraceutical capable of enhancing O2 delivery and reducing work of the heart, such that exercise can be performed at a given workload for a longer period of time before the onset of fatigue. 

nitrate; nitrite; total peripheral resistance; afterload; rate × pressure product; endothelial function

NITRIC OXIDE (NO) IS A SIGNALING molecule that has numerous functions in the human body, including blood flow regulation, neurotransmission, glucose and calcium homeostasis, muscle contractility and mitochondrial respiration (11, 12, 33). It is well documented that NO is produced by oxidation of l-arginine in a reaction catalyzed by the NO synthases (30). NO can also be produced from dietary nitrate (NO3−) via the NO3−-nitrite (NO2−)-NO pathway (28). NO3− is found in many vegetables, such as mustard leaf, lettuce, spinach, arugula, and beetroot (BR) (20). Following dietary consumption, NO3− can be reduced to NO2− by commensal bacteria in the oral cavity and further reduced to NO via numerous pathways that include xanthine oxidoreductase, deoxygenated myoglobin, and deoxygenated hemoglobin (28). As such, NO3− and NO2− have been suggested to represent a storage reservoir for NO (5).

NO3− appears to be an ergogenic nutraceutical that can improve exercise performance. In this regard, dietary supplementation with BR or sodium nitrate has been shown to reduce submaximal O2 cost during cycling at a fixed power output (26) and improve exercise time trial performance (7). Since NO3− can reduce resting blood pressure (25, 38), chronic dietary supplementation with BR juice (BRJ) may also have beneficial effects on the cardiovascular system during exercise. Acute administration of 500 ml of BRJ containing ~750 mg of NO3− has been reported to have effects on the cardiovascular response to graded submaximal cycling exercise in young, overweight women (2). In this regard, BRJ reduced systolic blood pressure (SBP) and rate × pressure product (RPP) (i.e., heart rate [HR] × SBP), an index of myocardial oxygen demand) at rest and during all workloads. Total peripheral resistance (TPR) was also reduced at rest and during all but the highest work intensity. However, no effects on diastolic blood pressure (DBP), mean arterial pressure (MAP), cardiac output (CO), or HR were observed. These findings suggest that a single dose of NO3− can reduce the afterload on the heart and lower myocardial oxygen demand at a given exercise intensity. However, it is not known whether chronic dietary supplementation can maintain these effects on exercise hemodynamics over time and/or modulate other important cardiovascular responses during exercise. For example, these cardiovascular effects of BRJ, particularly reductions in TPR, may be due, at least in part, to enhanced vascular function, as a positive correlation between plasma levels of nitrite/nitrate and endothelium-induced vasodilation has been established (6). Therefore, we hypothesized that 1) chronic dietary supplementation with BRJ attenuates SBP, DBP, MAP, and RPP and enhances stroke volume (SV), CO, and endothelial function responses to progressive elevations in exercise intensity and 2) these effects are partly due to endothelium-induced reductions in peripheral vasoconstriction.

MATERIALS AND METHODS

Fourteen healthy male subjects (aged 22 ± 1) participated in this study. Prior to testing, all subjects gave written informed consent. All procedures were reviewed and approved by the Kyung Hee University...
Physioflow is an impedance technique that emits a high-frequency process. Impedance cardiography measures changes in thorax recording the ECG, and two electrodes placed at the xiphoid side of the neck, two electrocardiography electrodes used for measuring cardiac parameters in healthy subjects (21, 31, 36). The awareness of the type of beverage being consumed by the subjects. NDBRJ. The investigators administering the exercise tests were not aware of the type of beverage being consumed by the subjects. A 2-wk washout each morning. Neither NDBRJ nor BRJ supplements were taken for 0.5 g), and sodium (0.1 g), fiber (0.1 g). Beetroot contained protein (2.6 g), sugar (9.3 g), carbohydrates (15 g), fat (0.2 g), and potassium (480 mmol/day) or 70 ml of organic nitrate-depleted beetroot juice/day (NDBRJ) (Beet It, James White Drink, Ipswich, UK). The BRJ was chosen because it is condensed compared with other vegetables and because it can be consumed as a juice.

Subjects were instructed to drink the juice around the same time each morning. Neither NDBRJ nor BRJ supplements were taken for 24 h prior to exercise testing. NDBRJ was similar to the experimental beverage in appearance, odor, taste, and texture. A 2-wk washout period separated the supplementation periods. The experimental order between the BRJ and NDBRJ supplementation was balanced such that seven subjects took BRJ first, while the other seven initially received NDBRJ. The investigators administering the exercise tests were not aware of the type of beverage being consumed by the subjects.

Measurement of hemodynamic variables. SV and HR were measured continuously via impedance cardiography (Physioflow, Manatec Biomedical, Paris, France). This device provides real-time CO data and measures cardiac parameters in healthy subjects (21, 31, 36). The bioimpedance device consists of two impedance cardiography electrodes, placed above the supraclavicular fossa at the base of the left side of the neck, two electrocardiography electrodes used for recording the ECG, and two electrodes placed at the xiphoid process. Impedance cardiography measures changes in thorax impedance during the cardiac cycle to calculate SV (3). The Physioflow is an impedance technique that emits a high-frequency (75 kHz) and low-magnitude (1.8 mA) alternating electrical current via skin electrodes during the cardiac cycle. This results in a waveform from which SV is calculated (9). Initially, the stroke volume index (SVi) is calculated at rest over 24 heartbeats during an autocalibration procedure, and then resting SBP and DBP are entered. The autocalibration measures the largest impedance variation during systole, the largest rate of variation of the impedance signal (i.e., the contractility index), the thoracic flow inversion time, and HR.

CO was calculated according to the following formula: CO = HR × SVi × BSA, where HR is obtained from the R-R interval determined from the first derivative of the ECG. SVi is the SV index (i.e., SV/BSA). BSA (body surface area, in m²) was determined according to the Haycock formula: BSA = 0.024265 × BM0.5378 × H1.3064, where BM is the body mass in kilograms and H is the height in centimeters. The Physioflow technique has been validated against the direct Fick method at rest and during exercise (9). CO assessed by the direct Fick method is not significantly different from that obtained by the Physioflow at rest and during submaximal and maximal workloads (9, 31).

Brachial artery blood pressure was measured by a sphygmomanometer during the 30%, 60%, and 80% workloads under steady-state conditions. Blood pressure was measured by the same investigator in each subject throughout the experiment. MAP was calculated using the formula: MAP = [SBP – DBP] × 1/3 + DBP. TPR was calculated as MAP/CO and RPP as HR × SBP.

Flow-mediated dilation. The flow-mediated dilation (FMD) technique was used to determine endothelial function in the brachial artery before and after BRJ supplementation. This noninvasive technique is a well-known bioassay of peripheral endothelial function that involves the release of a temporary occlusion of the arm vasculature to induce an acute increase in shear stress (8). The subsequent FMD is dependent, in part, on endothelial release of NO (13). Brachial artery diameter and velocity were measured by an ultrasonic 12-MHz linear-array vascular probe (ClearVue 550). The probe was placed 3–5 cm proximal to the bifurcation of the antecubital fossa. When images were obtained, the width of the artery was insonated at an angle of 60°. Blood velocity was acquired simultaneously using pulsed-wave Doppler. Measurements were made by the same examiner in a blinded manner. Ten cardiac cycles were evaluated to calculate baseline arterial diameter. To elicit reactive hyperemia and increase shear stress, a pressure cuff was placed on the upper arm and inflated to 200 mmHg for 5 min, followed by a rapid deflation. Brachial artery images were recorded for 2 min. Peak diameter was determined as the average of five cardiac cycles. Brachial artery images were selected when they occurred near the end of diastole. The absolute change in diameter was determined, and FMD was expressed as a percent change in diameter from baseline (%ΔFMD).

Measurement of plasma NO3 and NO2 (NOx). To obtain blood samples during the NDBRJ and BRJ conditions for measurement of plasma NOx, which was used as an index of NO3 levels, a catheter with a 12-gauge needle was inserted into a brachial vein. Five milliliters of venous blood were obtained at rest before and after both NDBRJ and BRJ supplementation. Samples were then centrifuged at 3,000 rpm for 10 min. Subsequently, the supernatant was collected and immediately frozen at −80°C until analysis for NOx.

Plasma concentrations of NOx were assessed by a colorimetric assay using the Griess reagent in a microtiter format (Cayman, Ann Arbor, MI) (37). Spectrophotometric quantitation of nitrite, based on the Griess reagent, was straightforward, and the NADH-dependent enzyme nitrate reductase was used to convert nitrate to nitrite prior to Table 1. Physical characteristics of the subjects

<table>
<thead>
<tr>
<th>Variables</th>
<th>Subjects (n = 14)</th>
</tr>
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<tbody>
<tr>
<td>Age, yr</td>
<td>22 ± 1</td>
</tr>
<tr>
<td>Height, cm</td>
<td>177.5 ± 2.5</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>73.7 ± 3.0</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.4 ± 0.8</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>116 ± 1</td>
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<tr>
<td>DBP, mmHg</td>
<td>77 ± 1</td>
</tr>
<tr>
<td>MAP mmHg</td>
<td>90 ± 1</td>
</tr>
<tr>
<td>Resting HR, beats/min</td>
<td>70 ± 2</td>
</tr>
<tr>
<td>VO2peak, ml·kg⁻¹·min⁻¹</td>
<td>44.6 ± 2.3</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SE. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; VO2peak, peak oxygen uptake.

AJP-Regul Integr Comp Physiol • doi:10.1152/ajpregu.00099.2015 • www.ajpregu.org
quantitation by the Griess reagent. The intra-assay and interassay coefficients of variation for NOx measurement with this method were 6.6% and 9.2%, respectively.

Data analysis. SV assessed by impedance cardiography was averaged over 30-s periods during steady-state conditions (21, 31, 36). This technique accurately measures absolute values of SV at rest and during submaximal exercise. Effects of dietary NO3/H11002 on cardiovascular responses during exercise were used for comparison purposes. Blood pressure was measured between the 4th and 5th min of each workload, just before blood collection. To compare the effects of BRJ over workloads and between groups, two-way repeated-measures ANOVA and Tukey’s post hoc test were used. Mean values of all variables were compared between groups via an independent Student’s t-test. The Student’s paired t-test was used to compare mean differences between NDBRJ and BRJ supplementation. Statistical significance was accepted at $P < 0.05$.

RESULTS

Physical characteristics of the subjects are shown in Table 1. Table 2 presents effects of BRJ supplementation on plasma NOx and brachial artery FMD. BRJ supplementation caused significant increases in resting plasma NOx concentrations and in FMD. NDBRJ supplementation had no effect on NOx concentrations or FMD. FMD was positively correlated to NOx concentrations ($r = 0.4; P < 0.05$).

Absolute values of all hemodynamic variables at rest and during the 30%, 60%, and 80% of V02peak workloads were not altered by NDBRJ supplementation. Compared with pretreat-

Table 2. Effects of beetroot juice with or without dietary nitrates on plasma NOx and brachial artery FMD at rest

<table>
<thead>
<tr>
<th></th>
<th>NDBRJ</th>
<th>BRJ</th>
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<tbody>
<tr>
<td>NOx, $\mu$M</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>79.3 ± 12.1</td>
<td>98.2 ± 12.5</td>
<td>83.8 ± 13.8</td>
</tr>
<tr>
<td>Baseline diameter, mm</td>
<td>3.78 ± 0.10</td>
<td>3.78 ± 0.09</td>
</tr>
<tr>
<td>Maximal diameter, mm</td>
<td>4.30 ± 0.07</td>
<td>4.32 ± 0.11</td>
</tr>
<tr>
<td>Δ Absolute diameter, mm</td>
<td>0.52 ± 0.05</td>
<td>0.54 ± 0.09</td>
</tr>
<tr>
<td>FMD, %</td>
<td>14.5 ± 1.9</td>
<td>14.4 ± 2.5</td>
</tr>
</tbody>
</table>

NDBRJ, nitrate-depleted beetroot juice, BRJ, beetroot juice; NOx, nitrate/nitrite, FMD, flow-mediated dilation. Values are expressed as means ± SE. *$P < 0.05$ vs. presupplementation.

Fig. 1. Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR) at rest and during exercise before (Pre) and after (Post) supplementation with beetroot juice (BRJ). *$P < 0.05$, vs. presupplementation.
ment conditions, BRJ supplementation reduced SAP, DBP, MAP, and TPR at rest and during all workloads, while RPP was attenuated at every workload \((P < 0.05)\) (Figs. 1 and 2). No effects of BRJ on HR were seen (Fig. 1). SV was higher at rest and at the 30% and 60% of \(\dot{V}O_2\) peak workloads after BRJ supplementation, while CO was elevated at rest and during exercise at the 30% of \(\dot{V}O_2\) peak workload \((P < 0.05)\) (Fig. 2).

Absolute values of all hemodynamic variables at rest and during all workloads were similar when compared between pre-NDBRJ and pre-BRJ supplementation conditions.

When compared with NDBRJ supplementation, BRJ attenuated SBP, DBP, MAP, and RPP responses at rest and during exercise \((P < 0.05)\) (Figs. 3 and 4). In addition, BRJ augmented SV and attenuated TPR at rest and during the 30% and 60% \(\dot{V}O_2\) peak workloads and augmented CO at the workloads of 30% and 60% of \(\dot{V}O_2\) peak \((P < 0.05)\) (Fig. 4). No differences in HR were found between the two conditions at rest or across any workload (Fig. 3).

**DISCUSSION**

An important new finding of this investigation is that chronic supplementation with dietary BRJ (i.e., 15 days) in healthy males increased baseline concentrations of plasma NOx and decreased SBP, DBP, and MAP at rest and during exercise. It appears that these \(NO_3^-\)-induced attenuations in blood pressure were associated with concomitant attenuations of TPR, suggesting that the afterload on the heart was reduced, a contention that is supported by the fact that our index of myocardial oxygen consumption, RPP, was also attenuated. In the rat model, BRJ supplementation has been reported to increase blood flow and conductance in the kidney in resting conditions. During exercise, this effect dissipates but appears to be compensated for by augmentations in blood flow and conductance in exercising skeletal muscle compared with control animals (15, 16). Such responses to BRJ supplementation in the current study might also account for the subsequent reductions in TPR.

In our subjects, it was unclear how \(NO_3^-\) supplementation caused attenuations in TPR during exercise. This effect may have been related to an increase in NO bioavailability associated with a greater storage of \(NO_3^-\) for conversion to NO (5). Supporting this possibility is the observation that acute administration of \(NO_3^-\) increases plasma concentrations of \(NO_2^-\) available for conversion to NO (2). Data from both human and animal studies have found that endothelium-based, NO-dependent vasodilation contributes to exercise-induced vasodilation in contracting skeletal muscle (19, 44). Coupled with our findings that BRJ supplementation markedly enhanced endothelial function (i.e., increased FMD), it seems reasonable to speculate that NO-induced vasodilation in contracting skeletal muscle was enhanced to the point where it affected subsequent reductions in TPR.

Another explanation for the potential influence of \(NO_3^-\)-induced increases in NO on skeletal muscle TPR relates to effects on sympathetic nerve activity. During exercise, in-

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**Fig. 2.** Cardiac output (CO), stroke volume (SV), total peripheral resistance (TPR), and rate pressure product (RPP) at rest and during exercise before (Pre) and after (Post) supplementation with BRJ. *\(P < 0.05\), vs. presupplementation-supplementation.
creases in sympathetic nerve activity occur that are capable of causing vasoconstriction in contracting skeletal muscle (4, 40). However, this vasoconstriction can be reduced by NO-evoked functional sympatholysis that is associated with a direct inhibitory effect on $\alpha_1$-receptor responsiveness to norepinephrine (4, 34). This phenomenon could lead to a scenario where BRJ supplementation causes increases in NO bioavailability that, in turn, enhance the release of NO from the vascular endothelium of contracting skeletal muscle and subsequently reduce local vasoconstriction and TPR.

A recent study investigated the effect of acute dietary nitrates (500 ml, 1,500 mg/l) on physiological responses in healthy women during graded cycling exercise (40%, 60%, 80% $\dot{V}O_2$ peak) (1). They reported that BRJ treatment did not change CO at rest or across workloads. This is an important consideration, since it is not known whether there are similar effects following chronic supplementation. Our study found that BRJ supplementation augmented exercise-induced increases in SV and CO at the two lower workloads compared with NDBRJ treatment. These increases in SV were probably due to a reduction in the inhibitory effects of afterload associated with concomitant reductions in MAP and TPR. It is not clear why increases in SV and CO and reductions in TPR were not augmented at the highest workload. However, the blood pressure response was greatest during this workload, while the absolute reduction in MAP evoked by NO$_3^-$ supplementation was not different from that seen at the lower workloads. Thus, the corresponding reduction in afterload at the highest workload may not have been sufficient to allow SV to increase.

Additional findings from the present study also differ from those reported by Bond et al. (1, 2), who assessed acute effects of a single dose of BRJ on the cardiovascular response to cycling. Chronic supplementation with our dose of NO$_3^-$, which was approximately half of the acute dose used by Bond et al. (1, 2), caused modifications in the cardiovascular responses to cycling at similar work intensities that were not seen following acute administration of BRJ. They included reductions in DBP and MAP at all workloads compared with NDBRJ and increases in CO at the two lower workloads. The pattern of effects on SBP and TPR was similar. Thus, our results indicate that effects of an acute dose of NO$_3^-$ on cardiovascular function during exercise cannot only be maintained via dietary supplementation with a smaller dose but also can be extended such that cardiac function (i.e., SV and CO) is enhanced and afterload on the heart is reduced further (i.e., reductions in DBP and MAP). However, because the subjects in the Bond et al. studies (1, 2) were females, we cannot rule out possible intervening effects of sex differences.

BRJ contains vasoactive factors other than nitrates (i.e., polyphenols, flavonoids, and quercetin) (22) that may have contributed to the attenuations in blood pressure, resistance, and work of the heart that we observed following our supplementation period. However, since our alternative to a placebo (i.e., NDBRJ) consisted of BRJ that had been selectively

![Fig. 3. SBP, DBP, MAP and HR at rest and during exercise following supplementation with NO$_3^-$-depleted beetroot juice (NDBRJ) or BRJ. *P < 0.05, vs. NDBRJ.](http://ajpregu.physiology.org/)
removed of only NO$_3^-$, any effects of other vasoactive factors would have been present in equal amounts in both conditions (BRJ and NDBRJ). Consequently, we feel confident that differences observed between the two conditions were due to specific effects of NO$_3^-$.

We selected a dose of NO$_3^-$ of 400 mg/day for dietary supplementation because it is within the lower range of acute and chronic doses that have been shown to lower resting MAP (1, 2, 38, 45). In addition, this dose was chosen because there is evidence suggesting that high intakes of dietary NO$_3^-$ may have harmful effects on health (e.g., cancer), which has led to some regulation of nitrate concentrations in food and drinking water (43). Consequently, we opted to use a lower dose to limit exposure of NO$_3^-$ beyond that received from routine dietary sources and to minimize safety issues that might arise compared with supplementation with higher doses of this ion. That being said, it should be noted that the traditional diet of the Japanese people is high in nitrates (1,300 mg/day for a 73-kg individual) (32), yet they have the highest longevity in the world and a low occurrence of heart disease and cancer (46). This observation and other emerging evidence showing that dietary nitrates have beneficial cardiovascular effects suggests that the risk-to-benefit ratio associated with dietary intake of nitrates and nitrites should be reevaluated.

**Limitations of the study.** A limitation to our study is the fact that we measured NOx, which represents values of both NO$_2^-$ and NO$_3^-$ As a result, specific effects of BJR supplementation on plasma concentrations of NO$_3^-$ were not quantified. This is an important distinction because conversion of NO$_3^-$ to NO$_2^-$ is necessary for biological effects to occur (42).

**Conclusions.** The results of our study demonstrate that chronic dietary supplementation with BRJ (containing a daily dose of 400 mg of NO$_3^-$) increases NOx in the plasma, lowers blood pressure and vascular resistance at rest and during exercise, and reduces RPP during exercise. It also profoundly augments endothelial function, particularly compared with effects of other nutraceuticals, such as polyunsaturated fatty acids and flavonoids (18, 41).

Supplementation additionally enhanced cardiac function via augmented exercise-evoked increases in SV and CO at our lower workloads. The cardiovascular effects seen during exercise were most likely due to reductions in the afterload on the heart and to diminished peripheral vasoconstriction (most likely in the exercising skeletal muscle).

These findings suggest that BRJ can act as a dietary ergogenic supplement capable of enhancing oxygen delivery and reducing work of the heart, allowing exercise to be performed at a given workload for a longer period of time before the onset of fatigue. BRJ supplementation may also represent an alternative, more natural intervention for individuals that suffer from reductions in functional capacity and exercise tolerance.
related to cardiovascular diseases, such as hypertension, heart failure, and cardiovascular ischemia.

**Perspectives and Significance**

Compared to acute effects of BRJ, the relevance of our results relates to the ability of NO$_3^-$ to act chronically as a dietary nutraceutical that is capable of maintaining or enhancing its acute effects on oxygen delivery at a given level of exercise, while also causing reductions in blood pressure and work of the heart. Consequently, the onset of fatigue may be delayed in healthy individuals and athletes, allowing for exercise to be performed for longer periods of time.

These effects of chronic dietary supplementation with NO$_3^-$ also have clinical implications. It is well known that functional capacity and exercise tolerance are reduced in pathological conditions, such as hypertension, heart failure, coronary heart disease, and diabetes, which can limit the ability to perform work and participate in activities of daily life (10, 23, 27). Because such limitations are related to endothelial dysfunction, increases in vascular resistance, and reductions in skeletal muscle blood flow (10, 14, 27, 39), regular treatment with dietary NO$_3^-$ may at least partially offset these debilitating effects.

It is also of note that cardiac events, such as myocardial infarction, can be precipitated by physical exertion (29, 35) and that high levels of blood pressure may play a role (17, 24). Thus, dietary BRJ may provide a nonpharmacological intervention that reduces the risk of cardiac events during exercise, especially in conditions where cardiovascular function is compromised (e.g., hypertension, heart failure, and ischemic heart disease).

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors. All authors have no competing financial interests in relation to the work described.

**AUTHOR CONTRIBUTIONS**


**REFERENCES**


