Modulation of Baroreflex Sensitivity by Walnuts Versus Cashew Nuts in Subjects With Metabolic Syndrome

Aletta E. Schutte, Johannes M. Van Rooyen, Hugo W. Huisman, Janine Mukuddem-Petersen, Welma Oosthuizen, Susanna M. Hanekom, and Johann C. Jerling

Background: Impaired baroreflex sensitivity (BRS) is associated with cardiovascular diseases and the metabolic syndrome. Because lipid abnormalities have been associated with impaired BRS, this study aimed to determine whether diets known to improve the lipid profile, namely a diet high in polyunsaturated fatty acids (walnuts) or monounsaturated fatty acids (cashew nuts), would improve BRS in subjects with metabolic syndrome (MS).

Methods: A controlled feeding trial with a randomized, controlled, parallel study design was undertaken, which involved 62 subjects with MS. Subjects were stratified according to gender and age and were randomized into three groups receiving a control diet, or a diet high (20% energy) in walnuts or unsalted cashew nuts for 8 weeks while maintaining body weight. The BRS, C-reactive protein (CRP), and MS components were measured before and after the intervention.

Results: After the intervention, BRS in the walnut-fed study group decreased ($P = .038$) and that in the cashew-fed study group increased ($P = .036$), but the BRS in the control group did not change ($P = .56$). The percent change of the walnut versus cashew group differed ($P = .019$). Body mass index, waist circumference, blood pressure, high-density lipoprotein cholesterol, and triacylglycerol did not change. The fasting glucose concentrations of the cashew group increased ($P = .03$).

Conclusions: The significant improvements in BRS obtained by a diet rich in cashew nuts underline the beneficial cardiovascular effects of nuts. However, the opposite result was obtained with a diet rich in walnuts. These significant changes observed might indicate that BRS is particularly sensitive and influenced by changes in diet without changes in obesity. Am J Hypertens 2006;19:629–636 © 2006 American Journal of Hypertension, Ltd.

Key Words: Baroreflex, polyunsaturated fatty acids, monounsaturated fatty acids, nuts.
(including α-linolenic acid), have been shown to significantly reduce plasma cholesterol, and to improve the LDL: HDL ratio, without changing BP.11,12 Another major nutrient of the Mediterranean region’s food supply is monounsaturated fatty acids (MUFA)13 found in cashew nuts. Similarly to PUFA, MUFA have also been strongly linked with favorable effects on serum lipids.14,15

There have, however, been studies that showed that MUFA did not affect total cholesterol levels,16 and other studies found greater reductions in total cholesterol levels with PUFA versus MUFA.17

Because lipid abnormalities have been associated with impaired BRS5, the aim of this study was to determine whether diets that are known to improve the lipid profile, namely a diet high in PUFA (walnuts) or MUFA (cashew nuts), would improve spontaneous BRS of subjects with the MS.

**Methods**

This study formed part of a larger study with the main aim to investigate the effect of high cashew and walnut diets on markers of the MS. A report by Pieters et al18 focused on the effect of high-nut diets on hemostatic parameters, based on the results of this larger study.

**Study Population**

A total of 68 volunteers with the MS were recruited to take part in a controlled feeding trial at the North-West University, Potchefstroom, South Africa. In all, 62 subjects with complete BRS datasets were included in the present study. A power calculation was done based on the results of Dessein et al.19 To provide 80% power at 5% significance and taking a 15% change in quantitative insulin sensitivity check index as the main outcome variable (because of the original research question of this study), as significant, a total number of 22 subjects were needed per group. Inclusion criteria were 21 to 65 years of age, and the presence of the MS according to the criteria of the Adult Treatment Panel III.20 Exclusion criteria were pregnancy or lactation, thiazide (>25 mg/day) or β-blocker (nonspecific, β1 and β2) use, nut allergies, and diagnosed diabetes.

The study was approved by the Ethics Committee of North-West University (Potchefstroom Campus) and all participants signed informed consent before entering the study.

**Study Design**

A randomized, controlled parallel study design was used. All subjects first underwent a 3-week run-in period in which all subjects received the control diet. Afterward the subjects were stratified according to gender and age and then randomized into three groups receiving either the control diet or a diet high in walnuts or unsalted cashews for 8 weeks. All baseline measurements (fasting blood samples, BP, anthropometric measurements, and BRS) were taken at the end of the run-in period, and at the end of the 8-week intervention. Subjects were weighed twice weekly.

**Diet**

The subjects ate lunches at a Metabolic Ward facility of the Nutrition Department under the supervision of a registered dietician. Weekend meals, breakfasts, and dinners were weighed to the nearest gram and were pre-packed in take-away format for the subjects to eat at home. Food frequency questionnaires were completed to determine the habitual diet of each participant, which were used to determine energy requirements for each subject to maintain body weight. The habitual diets were analyzed and the experimental meal compositions planned using the computer programme FoodFinder 2 (Medical Research Council, Tygerberg), based on the South African Food Composition Tables.21

Five different kilojoule diets were developed ranging from 8,000 to 14,000 kJ with 1,500-kJ increments. The calculated energy distribution of the 14-day menus for all three groups is shown in Table 1. The control, walnut, and cashew nut diets were identical except for 20% of the energy (63 to 108 g/day) provided by the nuts in the nut diets. The control diet did not contain any nuts or nut-based ingredients. Homogenized samples of all three diets, for each day of a 14-day menu cycle, were collected for macronutrient (Specialized Protein Products, Potchefstroom, South Africa) and fatty acid analysis as described by Van Jaarsveld et al.22

The calculated and analyzed nutrient distributions of the three diets are shown in Table 1. Subjects were requested to keep to their normal activity levels, and to keep a diary of illness, medication use and medication change (if absolutely necessary) and any deviation from their experimental diets. Compliance was measured by weighing returned leftover food portions and checking the food diaries.

**Blood Sampling**

The subjects were required to fast overnight (12 h). A nursing sister collected venous blood samples from the antecubital vein using a sterile winged infusion set and syringes. Samples were drawn with minimal stasis between 7 and 10 AM to avoid effects of diurnal variation. For lipid measurements blood was drawn and left to clot. For determination of glucose concentrations blood was collected in tubes containing sodium fluoride. The clotted and fluoride-treated blood were centrifuged at 2000 g for 15 min at 10°C. Aliquots were stored at −82°C until analyses.

**Experimental Methods**

Serum triacylglycerol (TG), high-density lipoprotein cholesterol (HDL-C), and fasting glucose were measured using a Vitros DT60 II Chemistry Analyzer (Ortho-clinical Diagnostics, Rochester, NY). Serum high sensitivity C-reactive protein (hs-CRP) was measured rate turbidimetrically...
(immunoassay) using a Synchron LX System (Beckman Coulter Inc., Fullerton, CA). Before fasting blood samples were taken systolic (SBP) and diastolic BP (DBP) were measured by a 7-min continuous measurement using the Finometer device\textsuperscript{23} (Finapres Medical Systems, Amsterdam, the Netherlands), after subjects rested for at least 10 min. These measurements were taken between 6 and 9 AM while subjects were lying in the Fowler position. Spontaneous baroreflex sensitivity (BRS) was determined by the validated cross-correlation baroreflex sensitivity (xBRS) method,\textsuperscript{24} derived from the continuous BP measurement. xBRS computes the correlation between beat-to-beat SBP and R-R interval, resampled at 1 Hz, over 10-sec sliding windows—a time-span sufficient to accommodate fully a 10-sec variability in rhythm, or several cycles at ventilatory frequencies.\textsuperscript{24} It has been suggested that this method be used in clinical and experimental settings because of its lower within-patient variance than other BRS methods.

**Statistical Analyses**

Statistica version 7 software (Statsoft Inc., Tulsa, OK) was used for the data analyses. Variables that were not normally distributed were logarithmically transformed. Repeated measures analysis of variance (ANOVA) was performed to determine whether there were significant time–group interactions. Changes within each subject group were tested for significance by using the \( t \) test for dependent samples only for fasting glucose and BRS, which showed significant interactions: \( F(2,59) = 3.634 \) (\( P = .032 \)) and \( F(2,59) = 3.186 \) (\( P = .048 \)), respectively. Percentage change in variables (from baseline to after intervention) within groups was determined with the formula: \([\text{after intervention} - \text{before intervention}] / \text{before intervention}] 	imes 100\%\). Differences between baseline values of the three groups were determined by ANOVA, and unequal N HSD post hoc comparisons were made if differences between groups were indicated. Differences in percent change among the three groups were determined with the analysis of covariance while adjusting for baseline values. Bonferroni post hoc comparisons were performed for variables that showed an overall effect of the group. Only percent fasting glucose levels and percent BRS showed a significant overall effect: \( F(2,58) = 3.342 \) (\( P = .042 \)) and \( F(2,58) = 3.440 \) (\( P = .038 \)), respectively. Forward stepwise two-group discriminant analysis was used to determine the best predictors (nine independent variables listed in Table 2) for the two nut diets. Homogeneity of variances of independent variables across groups was confirmed with the Box M test indicating \( P = .25.\)

**Results**

Dietary compliance with the control, walnut, and cashew diets was calculated to be approximately 90%. The macronutrient composition of the calculated and analyzed diets compared well (Table 1). The analyzed total fat content of the walnut diet was higher than calculated because the actual fat content of the walnuts were higher
than that indicated in the food composition tables. The test meals were also similar to the subjects’ reported habitual diets. As expected the walnut and cashew nut diets were high in PUFA and MUFA, respectively.

To determine whether BRS is associated with the components of the MS, partial correlations were performed on all baseline measurements within the whole group while adjusting for age and gender (N = 62) (Table 3). Results show that impaired BRS was significantly associated (P < .05) with increased WC, BMI, SBP, and hs-CRP levels, but not with HDL-C or TG.

In Table 4 all baseline characteristics (Pre-) and after intervention values (Post-) for the components of the MS, hs-CRP, and BRS are shown, also showing the percentage of subjects fulfilling the Adult Treatment Panel III criteria for each variable. The ages of the three groups were similar with mean values ranging from 44.4 to 45.7 years. After the dietary intervention no statistically significant changes (P ≤ .05) were shown for most MS components including WC, BMI, TG, HDL-C, SBP, and DBP. The fasting glucose level of the cashew group increased (P = .03), and the percent change values (%) of the cashew group compared with the control group also differed (P = .04). The BRS of the control group did not change (P = .56), whereas the BRS of the walnut group decreased (P = .038) and the BRS of the cashew group increased (P = .036) (Fig. 1, Table 4). When comparing the BRS percent change values of the walnut versus cashew group, a value of P = .019 was obtained.

A discriminant analyses showed that of the nine independent variables entered, the change in BRS (%) was the strongest and only significant predictor of the two nut diets (F = 5.60; P = .02) (Table 2). Together with WC percent and fasting glucose percent, these three variables showed 1-Tolerance values ranging from 0.12 to 0.15, explaining 12% to 15% in the discrimination between the walnut or cashew diet.

### Discussion

The principal finding of this study is that a diet rich in cashew nuts (MUFA) significantly increased the BRS in subjects with the MS, whereas a diet rich in walnuts (PUFA) significantly decreased the BRS after an 8-week intervention. The two nut diets therefore showed opposite effects regarding BRS changes. Subjects given a control diet did not show any significant changes in BRS. The significant changes in the nut-fed subject groups were observed despite the absence of any marked changes in other components of the MS. It is furthermore interesting that percent BRS change emerged as the strongest discriminator between the walnut and cashew diet (ie, high PUFA versus high MUFA), even when percent change in BRS was included with percent change of all other MS components after the intervention. This confirms that BRS could be affected by changes in dietary intake.

The difficulty in discussing results of whole-food interventions is that it is not clear which component included in

### Table 2. Forward stepwise two-groups discriminant analysis with the dependent variable being a walnut-rich versus cashew nut–rich diet

<table>
<thead>
<tr>
<th>Variables in model (%)</th>
<th>Step</th>
<th>F to enter/remove</th>
<th>P value</th>
<th>1-Tolerance (R²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baroreflex sensitivity</td>
<td>1</td>
<td>5.60</td>
<td>.02</td>
<td>0.13</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>2</td>
<td>3.41</td>
<td>.07</td>
<td>0.12</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>3</td>
<td>2.55</td>
<td>.12</td>
<td>0.15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variables not in model</th>
<th>F to enter</th>
<th>P value</th>
<th>1-Tolerance (R²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index</td>
<td>0.13</td>
<td>.72</td>
<td>0.21</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>0.31</td>
<td>.57</td>
<td>0.07</td>
</tr>
<tr>
<td>Triacylglycerol</td>
<td>0.39</td>
<td>.53</td>
<td>0.13</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>1.02</td>
<td>.31</td>
<td>0.03</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.03</td>
<td>.87</td>
<td>0.02</td>
</tr>
<tr>
<td>hs-C-reactive protein</td>
<td>0.14</td>
<td>.71</td>
<td>0.05</td>
</tr>
</tbody>
</table>

% = Percent change from before to after intervention in each respective variable; HDL-cholesterol = high-density lipoprotein cholesterol; hs-C-reactive protein = high-sensitivity C-reactive protein.

### Table 3. Partial correlations of baroreflex sensitivity with baseline measures of the metabolic syndrome components in study subjects (n = 62)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Correlation r value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference (cm)</td>
<td>−0.37</td>
<td>.003</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>−0.34</td>
<td>.008</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>−0.14</td>
<td>.30</td>
</tr>
<tr>
<td>Triacylglycerol (mmol/L)</td>
<td>−0.18</td>
<td>.17</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>−0.07</td>
<td>.58</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>−0.36</td>
<td>.005</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>−0.18</td>
<td>.17</td>
</tr>
<tr>
<td>hs-C-reactive protein (mg/L)</td>
<td>−0.30</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 2.
Data adjusted for age and sex.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group (N = 21) Mean (95% CL)</th>
<th>Walnut group (N = 20) Mean (95% CL)</th>
<th>Cashew group (N = 21) Mean (95% CL)</th>
<th>Differences between groups (P values) * ANCOVA (pre-values) ANCOVA (post-values, adjusted for pre-values)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/Women</td>
<td>10/11</td>
<td>10/10</td>
<td>8/13</td>
<td>0.91</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
<td></td>
<td>.52</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>Pre 44.4 (40.2; 48.6) Post 107.7 (101.8; 113.6)</td>
<td>Pre 45.5 (40.3; 50.7) Post 108.6 (101.6; 115.7)</td>
<td>Pre 45.7 (40.7; 50.7) Post 107.2 (98.5; 111.8)</td>
<td>.52</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>Pre 35.5 (33.1; 37.8) Post 35.3 (32.9; 37.7)</td>
<td>Pre 35.9 (33.1; 38.7) Post 35.8 (33.0; 38.5)</td>
<td>Pre 34.7 (32.2; 36.6) Post 34.3 (32.0; 36.5)</td>
<td>.64</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>Pre 92.9 (88.2) Post 92.9 (88.2)</td>
<td>Pre 92.9 (88.2) Post 92.9 (88.2)</td>
<td>Pre 92.9 (88.2) Post 92.9 (88.2)</td>
<td>.91</td>
</tr>
<tr>
<td>Triacylglycerol (mmol/L)</td>
<td>Pre 53.2</td>
<td>Pre 53.2</td>
<td>Pre 53.2</td>
<td>.59</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>Pre 4.89 (4.48; 5.31) Post 4.60 (4.00; 5.21)</td>
<td>Pre 4.77 (4.42; 5.11) Post 4.97 (4.32; 5.61)</td>
<td>Pre 4.75 (4.43; 5.07) Post 5.80 (4.72; 6.88)</td>
<td>.81</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>Pre 130.9 (125.4; 136.5) Post 132.7 (128.1; 137.3)</td>
<td>Pre 128.4 (125.6; 131.1) Post 130.2 (126.4; 133.9)</td>
<td>Pre 130.7 (125.9; 134.5) Post 128.4 (122.8; 137.3)</td>
<td>.78</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>Pre 78.9 (75.8; 82.1) Post 79.4 (76.2; 82.8)</td>
<td>Pre 78.7 (76.3; 81.2) Post 79.5 (76.2; 82.8)</td>
<td>Pre 77.8 (74.0; 80.0) Post 76.4 (73.1; 79.7)</td>
<td>.53</td>
</tr>
<tr>
<td>High-sensitivity C-reactive protein (mg/L)</td>
<td>Pre 1.82 (1.77; 5.41)</td>
<td>Pre 1.99 (1.76; 5.76)</td>
<td>Pre 1.82 (1.77; 5.41)</td>
<td>.53</td>
</tr>
<tr>
<td>Baroreflex sensitivity (msec/mm Hg)</td>
<td>Pre 25.9 (4.06; 55.9)</td>
<td>Pre 25.9 (4.06; 55.9)</td>
<td>Pre 25.9 (4.06; 55.9)</td>
<td>.038a</td>
</tr>
</tbody>
</table>

Pre- = before intervention; Post- = after intervention; % = mean individual percentage change from Pre- to Post-, adjusted for pre-values (before intervention); 95% CL = 95% confidence limits; ATP III = Adult Treatment Panel III; MS = metabolic syndrome.

P values of within-group changes: Fasting glucose: * 0.34; † 0.49; ‡ 0.03; baroreflex sensitivity: § 0.56; ¶ 0.038; †† 0.036.

P values of differences in percent change values between three diet groups:
A: Fasting glucose: between control and walnut group: P = 1.00; between control and cashew group: P = .04; between cashew and walnut group: P = .31.
B: Baroreflex sensitivity: between control and walnut group: P = .28; between control and cashew group: P = .78; between cashew and walnut group: P = 0.019.
FIG. 1. Individual changes in baroreflex sensitivity during the 8-week dietary intervention of a control diet or a diet rich in walnuts or cashew nuts. *P < .038. Overall effect of group: F(2,59) = 3.186 (P = .048); results of dependent t test shown.

the composition of the diet is responsible for the significant changes in BRS. The most obvious component would be the high percentage of MUFA in cashews and PUFA in walnuts, suggesting that diets richer in MUFA might be more beneficial than diets rich in PUFA. However, nuts are also a good source of plant sterols, dietary fiber, folic acid, antioxidants, flavonoids, and L-arginine—all of which have been shown to have possible beneficial effects on endothelial function. It has also been shown that dietary lipid quality may influence cardiac adrenoceptor density and function. The fatty acids and other bioactive substances in nuts could therefore alter the distensibility of large arteries. The improvement in BRS in subjects consuming the cashew diet might have been brought about by improved arterial compliance and distensibility. Ros et al recently published results showing that a walnut diet was associated with improved endothelial function and reduced cholesterol levels. The current study did not find cholesterol reductions and found decreased BRS after a walnut diet, which could have been caused by the unexpectedly high analyzed fat content of the walnut diet or the extremely high percentage of PUFA (21%) in the diet (as most dietary recommendations state that PUFA intake should not exceed 10%). Furthermore, the participants in the study by Ros et al were asymptomatic subjects with only moderate hypercholesterolemia who were otherwise healthy, whereas the subjects in the present study had the MS, which might have influenced the results.

Contradictory to expectations there were no changes in the lipid profiles after the walnut and cashew diets. Thus the goal of determining the relationship of this specific dietary intervention to lipid lowering was not met. Baseline lipid and BRS values of all subjects also failed to show a significant correlation. It is difficult to interpret these results, but a possible explanation might be that many studies that have shown the lipid-lowering effect of nuts, MUFA, and PUFA have involved healthy individuals, and other studies made use of whole-food interventions such as diets high in vegetables, fruit, and nuts or the Mediterranean-type diet. It is possible that a nut-rich diet would have different effects in subjects with the MS (compared with healthy individuals), and it is also not certain which components in the whole-food interventions such as the Mediterranean diet were responsible for the beneficial effects of these diets. De Lorgeril et al concluded that it is likely that certain nutrients characteristic of the Mediterranean diet (omega-3 fatty acids, oleic acid, antioxidant vitamins) have specific cardioprotective effects, but it is not certain which specific components have such effects.

Although serum lipids failed to show an association with BRS, obesity showed strong correlations with impaired BRS in the whole group, which could possibly be explained by an autonomic shift towards sympathetic nerve activity by high levels of leptin in the obese subjects. This association is emphasized by the correlation between impaired BRS and hs-CRP, which underline the effect of the atherogenic and inflammatory states as found in obese subjects on BRS. This association of impaired BRS and hs-CRP are further underlined, as it has recently been shown that arterial baroreflex dysfunction promotes the development of atherosclerosis in rats and that inflammation may be involved in this process.

Apart from the significant increase in BRS of the cashew nut group, this group also showed an impaired fasting glucose level after the intervention, differing significantly from the percent change in the control group. There is very limited literature available regarding the content and cardiovascular effects of cashew nuts, and it is not clear why this diet improved BRS but was also associated with increased fasting glucose levels. It is possible that the increased glucose levels could be related in part to the unusually high total (36.5%) and MUFA (15.9%) fat intake. It should be taken into consideration that the participants of this study had MS, and whether similar effects (both on BRS and fasting glucose levels) would be observed if this diet were consumed by a large population or to a more moderate degree is currently unknown. It is therefore suggested that future studies involve healthy as well as high-risk patients, and that measures of arterial distensibility (such as pulse wave velocity and carotid-intima-media thickness) be performed. Because it has been shown that insulin levels are associated with impaired BRS, it is also suggested that an oral glucose tolerance test (including insulin measurements) and more detailed measurements of insulin sensitivity and insulin secretion using clamp studies or the frequently sampled intravenous glucose tolerance test be performed.

In conclusion, the results of this study underline the beneficial cardiovascular effects of nuts by significant improvements in BRS obtained by a cashew nut diet (an autonomic shift towards the parasympathetic side) in subjects with MS. However a walnut diet that was very high in PUFA (21%) had detrimental effects on BRS in these
subjects. An overwhelming body of evidence has demonstrated the beneficial effects of nuts, but this study suggests that intake of large quantities of walnuts and cashews may have detrimental effects on the BRS and glycemia, respectively, at least in individuals with MS. Further research defining the potential benefits and harmful effects of nuts, especially when consumed in large quantities, is therefore needed. In addition it remains to be established whether smaller amounts of nuts resulting in a lower total fat and unsaturated fatty acid content of the diet would still have these negative effects. It can be speculated that the significant changes observed in BRS found in this study might indicate that this cardiovascular parameter is particularly sensitive and is influenced by changes in diet without any changes in obesity level, whereas improvements in other components of MS might be more dependent on weight loss.

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References


