ORIGINAL RESEARCH

Nutrition in health and disease

CURRENT DEVELOPMENTS IN NUTRITION

Interactions of the DASH Diet with the Renin-Angiotensin-Aldosterone System

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ABSTRACT

Background: The Dietary Approaches to Stop Hypertension (DASH) diet is widely recommended to lower blood pressure, but its mechanisms of action are unclear. Lines of evidence suggest an interaction with the renin-angiotensin-aldosterone system (RAAS).

Objective: We conducted a randomized, controlled, cross-over feeding trial to test RAAS-related mechanisms underlying the DASH diet in patients with isolated systolic hypertension.

Methods: Participants entered a 1-wk run-in period on a control (CON) diet and then consumed the DASH or CON diets for 4 wk each in randomized sequence. Calorie content was controlled to maintain weight, and sodium intake was set at 3 g daily. After each diet, participants had hormonal and hemodynamic assessments obtained at baseline, in response to RAAS inhibition with captopril (CAP) 25 mg, and to graded angiotensin II (AngII) infusions (1 ng/kg and 3 ng/kg × 45 min). Primary outcomes were mean arterial pressure (MAP) and renal blood flow (RBF), and secondary outcomes were diastolic function, pulse wave velocity (PWV), plasma renin activity (PRA), and aldosterone (ALDO) responses by diet.

Results: In total, 44 (19 female) participants completed the study. DASH + CAP significantly lowered MAP compared with CON + CAP (83 ± 11 mmHg compared with 88 ± 14 mmHg, $P < 0.01$). RBF was increased with DASH + CAP compared with CON + CAP (486 ± 149 cc/min compared with 451 ± 171 cc/min, $P < 0.001$). Study diet did not change PWV but CAP reduced diastolic function on the DASH diet ($P < 0.05$). DASH + CAP significantly increased PRA compared with CON + CAP (1.52 ± 1.78 ng/mL/min compared with 0.89 ± 1.17 ng/mL/min; $P < 0.001$). ALDO sensitivity to AngII infusion was greater with DASH when compared to CON (17.4 ± 7.7 ng/mL compared with 13.8 ± 6.2 ng/dL, $P < 0.05$) as was DASH + CAP compared with CON + CAP (15.1 ± 5.3 ng/dL compared with 13.1 ± 5.9 ng/mL, $P < 0.05$).

Conclusions: The DASH diet interacts with the RAAS resulting in vascular and hormonal responses similar to a natriuretic effect, which appears to augment the hypotensive effect of angiotensin-converting enzyme (ACE) inhibition in individuals with isolated systolic hypertension. This trial was registered at clinicaltrials.gov as NCT00123006. *Curr Dev Nutr* 2019;3:nzz091.

Introduction

It has been proposed that lifestyle interventions improve blood pressure (BP) and can often be an alternative to pharmacologic management in patients with stage 1 hypertension (1–3). One of the most frequently prescribed lifestyle interventions for hypertension is the Dietary Approaches to Stop Hypertension (DASH) diet (3). The DASH diet is rich in fruits, vegetables, nuts, and lean meats that overall lead to increased calcium, potassium, and protein intake (3, 4). The DASH diet has been shown to reduce BP, improve LDL-cholesterol, and improve insulin sensitivity (3–8). Although the DASH diet is a well-established, effective nutritional intervention to lower BP, the mechanisms behind its effects are unknown (9–14).

Keywords: blood pressure, DASH diet, nutrition, mechanism, renin-angiotensin-aldosterone system, lifestyle intervention, intervention, clinical trial

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Supplemental Table 1 is available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/cdn/.
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Abbreviations used: ACE, angiotensin-converting enzyme; ALDO, aldosterone; AngII, angiotensin II; BP, blood pressure; CAP, captopril; CON, control; DASH, Dietary Approaches to Stop Hypertension; E, peak early mitral inflow Doppler; e', peak early lateral mitral annulus tissue Doppler; MAP, mean arterial pressure; PAH, para-aminohippurate; PRA, plasma renin activity; PWV, pulse wave velocity; RAAS, renin-angiotensin-aldosterone system; RBF, renal blood flow.

Several hypotheses have been proposed to explain the BP lowering effects of the DASH diet, but to date, the mechanisms are poorly characterized or observational in nature (9–14). Some of these mechanisms could be associated with *1*) physiological effects similar to a natriuretic or angiotensin-converting enzyme (ACE) inhibition, or *2*) how the DASH increases potassium, calcium, magnesium, and/or protein (3–14). Understanding these physiologic relations could provide insight into whether some individuals may preferentially benefit from the DASH diet either alone or in combination with antihypertensive medications.

Lines of evidence suggest that the DASH diet interacts with the renin-angiotensin-aldosterone system (RAAS) (9–14). Prior reports describe a shift in the BP-natriuresis curve and higher plasma renin activity in response to the DASH diet (12, 13). Genetic studies report an association of the DASH BP effect with angiotensinogen and B2 adrenergic receptor polymorphisms, which are associated with salt sensitivity (11). In addition, the DASH diet enhances the BP response to the angiotensin receptor blocker, losartan (12). Collectively, these observational data suggest that the DASH diet may be acting through a natriuretic effect or interruption of the RAAS, though no prospective studies have yet provided a detailed physiologic evaluation of the DASH diet effects in hypertensive patients.

We designed a feeding trial in patients with isolated systolic hypertension to compare hemodynamic and RAAS responses to the DASH diet compared with a control (CON) diet. We hypothesized that the DASH diet would cause alterations in the RAAS that would be indicative of a natriuretic/diuretic effect and synergize with ACE inhibition.

Methods

We conducted a randomized, double-blind, controlled, cross-over study to test RAAS-related mechanisms underlying the DASH diet effect in patients with isolated systolic hypertension. This study design was similar to the DASH-Sodium trial and the original DASH study (4, 14) and was chosen to have subjects serve as their own control to enhance statistical power and reduce variability. The research protocol was reviewed and approved by the Partners Healthcare Institutional Review Board, and all study participants provided written informed consent prior to participation. The study was registered at clinicaltrials.gov as NCT00123006.

We recruited community-dwelling individuals to participate in a 10-wk intervention study. All participants were required to have a diagnosis of isolated systolic hypertension as defined by a systolic BP >140 mmHg and a diastolic BP <90 mmHg without antihypertensive medications, measured on 2 occasions separated by ≥2 wk. Individuals could either be antihypertensive drug-naïve or undergo a medication washout period in order to minimize drug effects on outcome measures. For those requiring medication washout, home BP readings were reported daily over a 3-wk period for safety monitoring. The study included 2 initial screening visits, the first of which included informed consent and BP measurements. The second screening visit included confirmation of the hypertension diagnosis and initial blood work. All screening and eligibility BP recordings were measured using an automated monitor (Model BP786N; Omron Healthcare) after a minimum of 5 min of rest. The mean of 3 consecutive readings on each occasion was recorded.

Additional inclusion criteria included a normal estimated glomerular filtration rate (>60 cc/min), serum electrolytes, resting electrocardiogram, fasting glucose, and normal physical exam. History of diabetes, illicit drug or tobacco use, and use of possible confounding medications, such as psychiatric medications, oral contraceptives, or hormone replacement therapy, were exclusion criteria.

Diet protocol

Participants underwent a 1-wk diet run-in period on the CON diet to monitor adherence to the study diets and procedures. Initial caloric requirements were calculated to estimate resting energy expenditure and an activity correction factor, derived from the Stanford 7-d physical activity questionnaire, which is used to obtain an estimate of total energy requirements (15). All meals were prepared by the Brigham and Women's Hospital Center for Clinical Investigations (CCI) Dietary Research Core. Participants were required to eat one meal per day under direct observation by a research dietitian (typically lunch or dinner) and completed daily dietary questionnaires reporting food intake. After successfully completing the diet run-in period, participants were randomly assigned to start either the DASH or CON diet. The randomization was carried out in block format ($n = 6$) accounting for race and sex, and the assignment was delivered in a sealed envelope under control of the study nutritionist. Diet assignment continued for 4 wk followed by cross-over to the alternate diet, with a washout period that averaged 2 wk in duration between diets where participants consumed an ad libitum diet. Research staff that collected outcome measures were blinded to diet assignment and dietary staff were masked to outcome measures.

The macronutrient and micronutrient composition of the diets are shown in **Supplemental Table 1** (based on 2100 kcal/d intake) and was modeled directly after the original DASH diet study (4). The DASH diet emphasizes fruits, vegetables, and low-fat dairy products, whereas the CON diet is consistent with a more typical Western diet composition (4, 13). Specifically, the CON diet was representative of the 25th percentile of USA consumption for calcium, potassium, and magnesium. In contrast, the experimental DASH diet was representative of the 75th percentile of USA consumption for calcium, potassium, and magnesium (4). Given the main outcome measures of RAAS activity, particular attention was paid to matching dietary sodium composition in both study diets. Caloric intake was adjusted for a given individual to maintain their diets as isocaloric.

Outcome measurements

During the last week of each 4-wk study diet period, all participants spent 1 night and 1 day on the Inpatient CCI Unit to participate in physiological assessments. Participants arrived at ~17:00 and ate their evening study meal, then remained fasting and supine from midnight until outcome assessments were completed the next day at ~14:00. To further examine potential effects of the DASH diet on the RAAS, sequential responses to an AngII (AngII; Bachem) infusion followed by ACE inhibition were examined at the end of the feeding period. After obtaining baseline measurements, AngII was infused at doses of 1 and 3 ng/kg/min for 45 min at each dose. BP was monitored every 2 min using an automated BP device (Dynamap) with specific cut-off limits

for termination of infusion. Blood sampling was obtained prior to and at the end of each dose of AngII. After completing the AngII infusion, participants were given an oral dose of 25 mg captopril (CAP). This was followed 90 min later by a second AngII infusion as described above. The primary outcome variables of this study were BP and renal blood flow (RBF), and secondary outcomes included arterial stiffness, diastolic function, and measures of RAAS function (i.e. plasma renin activity [PRS] and aldosterone [ALDO] secretion).

BP reported as mean arterial pressure (MAP) was measured throughout the inpatient phase using an automated device (16). The average of 5 BP measurements obtained at 08:00 after overnight supine posture and at the end of each AngII infusion period were used for outcome measures. RBF was assessed by the para-aminohippurate (PAH) clearance method. PAH was administered intravenously as a loading dose of 8 mg/kg followed by a continuous infusion (12 mg/min) for ≥60 min, which has been shown previously to estimate renal function (17). Blood samples were drawn in triplicate and assayed via radioimmunoassay, as previously reported (18). Results were adjusted for body surface area and reported as an RBF rate (cc/min). Peak early mitral inflow Doppler (E), peak early lateral mitral annulus tissue Doppler (e'), and their ratio (E/e') were used to assess diastolic function (19). Pulse wave velocity (PWV) was obtained through arterial tonometry at brachial, radial, femoral, and carotid artery sites (19–21).

To evaluate the activity of the RAAS, PRA and plasma ALDO concentrations were measured by radioimmunoassay. Timed urine collections (24 h) were obtained on the last day of each diet and assayed for creatinine, potassium, and sodium to monitor differences in electrolyte excretion on each diet.

Statistical analysis

Analyses were conducted for all participants who completed both study diets. Data are presented as mean values with corresponding SDs for continuous values and percentages for categorical data. A repeated measures analysis of variance (ANOVA) was conducted for each outcome variable with significance set at 0.05 for prespecified primary analyses and a Bonferroni adjustment for secondary analyses due to multiple comparisons. Analysis of AngII response curves was conducted using a repeated measures regression analysis model along with an interaction analysis to determine if diet condition influenced the response to AngII infusion. Analyses were conducted on STATA software with the addition of GraphPad for graphic creation (Stata/IC 15.0, StataCorp).

Results

Baseline demographics of the 44 participants who completed the study are provided in **Table 1**. All participants had isolated systolic hypertension at screening (systolic BP 148 ± 8 mmHg, diastolic BP 82 ± 7 mmHg); 15 participants were antihypertensive drug-naïve and the others completed a medication washout period without complications. **Figure 1** displays the participant flow from screening to study completion including the 2 screening visits. Results are presented as diet contrasts in response to AngII, before and after ACE inhibition.

TABLE 1 Baseline characteristics of study participants[1]

N	44
Age, y	55.7 ± 13.6
Gender, % female	19 (43)
Race or ethnic group, %	
Black	22 (50)
Non-Hispanic White	18 (41)
Asian or others	4 (9)
Weight, kg	84.5 ± 16.6
Height, m	1.69 ± 0.10
Body mass index, kg/m^2	29.7 ± 5.2
Blood pressure, mm Hg	
Systolic	148 ± 8
Diastolic	82 ± 7

[1]Data summarized as means ± SD.

Influence of the DASH diet compared with CON diet on vascular function

MAP following the DASH diet may have been slightly lower than on the CON diet (96 ± 11 mmHg compared with 98 ± 14 mmHg, $P = 0.07$). However, during AngII infusion, MAP was significantly lower on the DASH diet when compared to the CON diet ($P < 0.01$) (**Figure 2**). Similarly, CAP produced a greater reduction in MAP following DASH compared with the CON diet (83 ± 10 mmHg compared with 88 ± 14 mmHg, $P < 0.01$) (**Figure 3**). These differences in MAP were significant with AngII infusion in the setting of CAP exposure ($P < 0.05$). There were no significant changes in diastolic function (E/e') or aortic stiffness in response to the DASH diet (**Table 2**). With the addition of CAP, E/e' was significantly reduced on the DASH diet compared with the CON diet (6.53 ± 1.65 compared with 6.88 ± 1.62, $P < 0.05$). There were no significant changes in PWV across any diet conditions ($P > 0.05$).

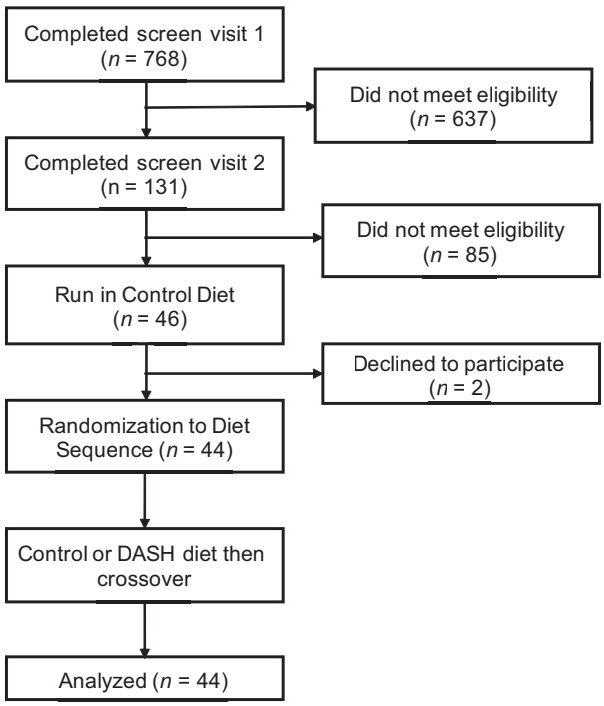

FIGURE 1 Flow diagram of participants through the study.

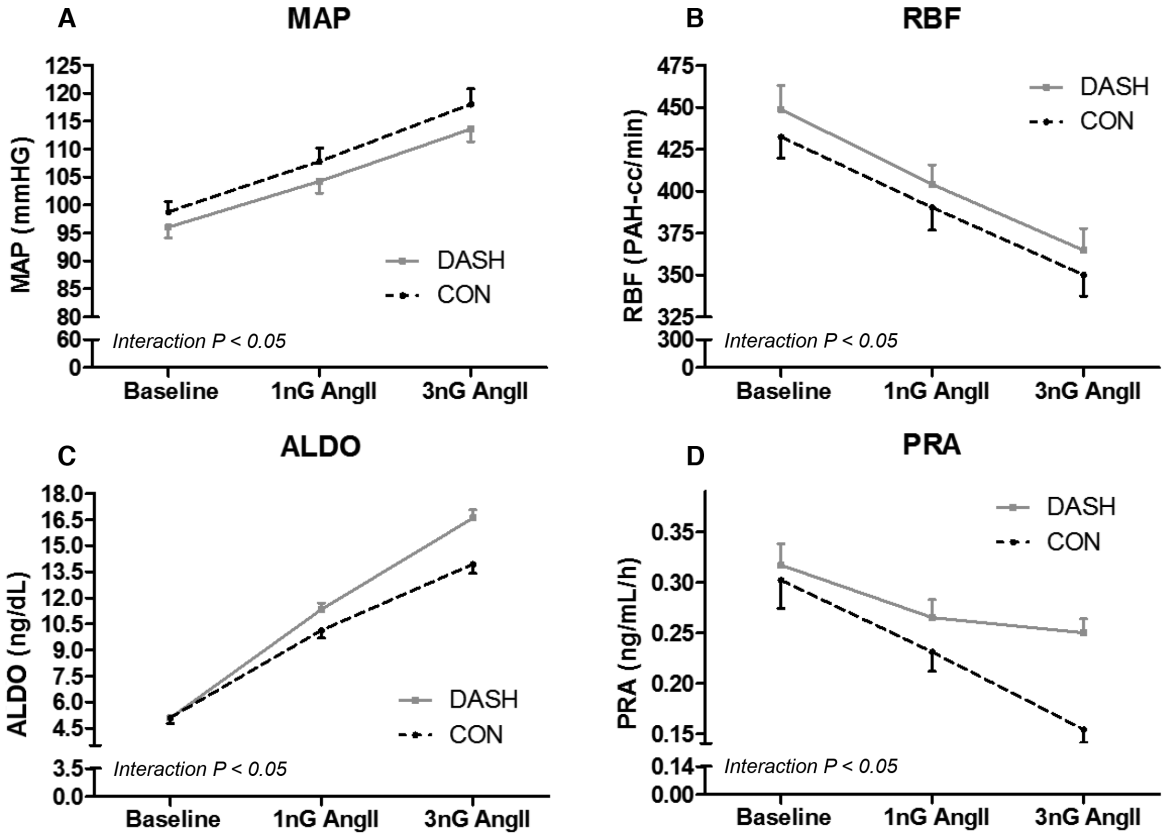

FIGURE 2 Differences in the 4 outcome measures between Dietary Approaches to Stop Hypertension (DASH) and control (CON) diet conditions prior to captopril (CAP) administration and in response to AngII (AngII). **A)** AngII infusion and mean arterial pressure **(**MAP), **B)** AngII infusion and renal blood flow (RBF) **C)** AngII infusion and aldosterone secretion (ALDO), **D)** AngII infusion and plasma renin activity (PRA). Data were analyzed by repeated measures ANOVA with an interaction term, $n = 44$.

RBF did not differ between the DASH and CON diets prior to AngII and CAP (Figure 2). However, CAP significantly enhanced RBF differences between the DASH and CON diets (486 ± 13 cc/min compared with 451 ± 10 cc/min, $P < 0.001$) (Figure 3). The subsequent response to AngII infusion was not different between diets ($P = 0.09$).

Influence of the DASH diet compared with CON diet on RAAS activity

Baseline PRA was not different between diets. In response to AngII infusion, PRA was significantly higher on the DASH diet compared with the CON diet ($P < 0.05$) (Figure 2). Specifically, the DASH diet had greater PRA than the CON diet at the 3 ng/kg/min dose (0.25 ± 0.01 ng/mL/h compared with 0.15 ± 0.02 ng/mL/h, $P < 0.05$). These responses were similar after CAP, with higher PRA on the DASH diet after the 3 ng/kg/min dose (1.52 ± 0.10 ng/mL/h compared with 0.89 ± 0.09 ng/mL/h, $P < 0.01$), but overall responses to the infusions across both diets were similar.

Baseline ALDO concentrations were similar between diets. In response to the AngII infusion, aldosterone secretion was significantly greater on the DASH diet compared with the CON diet (Figure 2), and particularly at the 3 ng/kg/min dose (17.4 ± 7.7 ng/mL compared with 13.8 ± 6.2 ng/dL, $P < 0.05$). After CAP, these differences persisted ($P < 0.05$) (Figure 3). During the post-CAP AngII infusion, the DASH

TABLE 2 Changes in vascular function after captopril in hypertensives[1]

	DASH diet		Control diet	
	Pre-CAP	Post-CAP	Pre-CAP	Post-CAP
Pulse wave velocity, m/s	9.14 ± 2.63	8.58 ± 2.36	9.43 ± 2.69	8.34 ± 1.99
Diastolic function, E/E′	6.81 ± 1.75	6.53 ± 1.65*	6.82 ± 1.85	6.88 ± 1.62*

[1]Data are presented as means ± SD. CAP, captopril. Data were analyzed by repeated measures ANOVA with Bonferroni correction.
*$P < 0.05$ for comparison between the post-CAP to DASH compared with control.

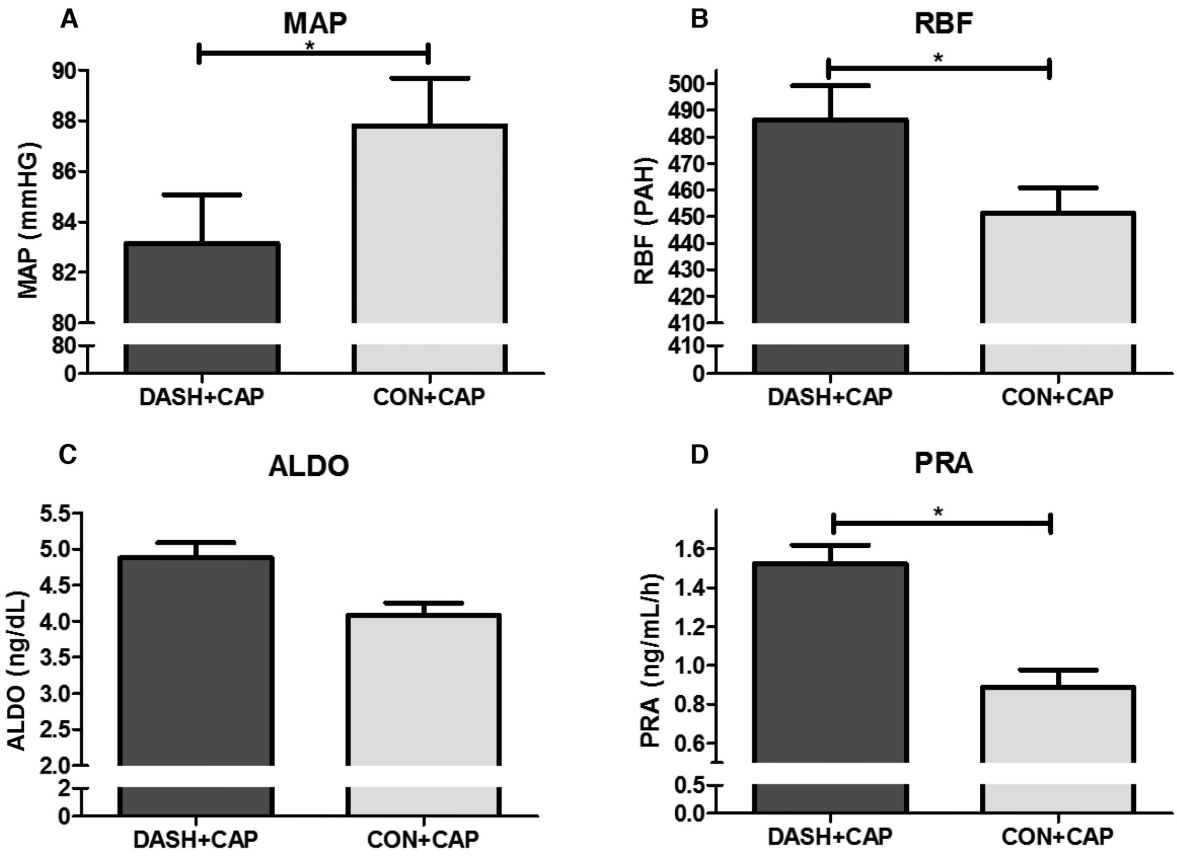

FIGURE 3 Differences in the 4 outcome measures between Dietary Approaches to Stop Hypertension (DASH) and control (CON) diet conditions with the addition of captopril (CAP). **A)** CAP and mean arterial pressure (MAP), **B)** CAP and renal blood flow (RBF), **C)** CAP and aldosterone (ALDO), **D)** CAP and plasma renin activity (PRA). * = P <0.05 in comparison to the CON diet. Data were analyzed by repeated measures ANOVA, n = 44.

diet showed greater ALDO secretion than the CON diet (15.1 ± 5.3 ng/dL compared with 13.1 ± 6 ng/dL, P <0.05).

Discussion

This clinical trial was designed to evaluate the RAAS mechanisms by which the DASH diet lowers BP and to address a series of observational associations suggesting an interaction between the DASH diet and RAAS activity. Deciphering such a physiologic basis may help identify individuals who will benefit from the diet and determine if certain pharmaceutical approaches may enhance the DASH diet effect.

Our results show that the DASH diet enhances some of the physiologic effects of ACE inhibition; lowers BP, and increases PRA, ALDO, and RBF. This is consistent with a prior report showing a shift in the pressure-natriuresis curve with the DASH diet (9). Collectively, these results are consistent with the DASH diet having natriuretic/diuretic effects rather than ACE inhibition. Further, the enhanced physiologic and biochemical responses to CAP on the DASH diet are consistent with the well-described effects of ACE inhibition when coadministered with diuretics (22, 23).

Our use of AngII infusions and ACE inhibition to amplify RAAS activity provided the opportunity to detect differences by diet that were less pronounced at baseline. Previous studies have shown that salt/volume depletion are associated with reduced RBF and increases in both PRA and ALDO concentrations (23, 24). Conversely, when AngII concentrations are reduced via ACE inhibition, RBF and PRA increase whereas ALDO concentrations are reduced (24). AngII infusion in each setting may modulate the slope of these relations, respectively (24). The results of this study portray a combination of changes that indicate an interaction between the DASH diet and the RAAS, which may contribute to the BP lowering effects of the diet.

There was a greater BP response to CAP on the DASH diet compared with the CON diet, likely due to a priming effect of the DASH diet. This response is similar to the well-described observation in which the BP response to ACE inhibition is more effective in the setting of increased PRA (12). We previously reported that the DASH diet enhanced the BP response to losartan, and larger diet-induced increases in PRA were associated with greater BP changes (12). Of note in the present study, CAP significantly increased RBF on the DASH diet, which replicates the RBF response to ACE inhibition with salt depletion. Changes in RAAS activity with the DASH diet also support the hypothesis that the diet produces a natriuretic/diuretic effect (9, 12, 22). We observed

higher PRA and ALDO concentrations during AngII infusion on the DASH diet. Additionally, diastolic function was improved in response to CAP with the DASH diet, as evidenced by the reduction in E/e'. This is consistent with a prior study showing that the DASH diet improves diastolic function in patients with heart failure with preserved ejection fraction (2), an effect that was attributed to reduced afterload.

Calorie and sodium intake were similar between the 2 diets, so it is likely that other macro- or micronutrient differences may underlie these findings. In this regard, the DASH diet is enriched in potassium and calcium and both have been shown to affect RBF and PRA, as was observed in this study (25–29). Potassium specifically has been shown to significantly influence RAAS activity responses in the renal vasculature and the adrenal gland, 2 major sites of BP regulation (26). It may be assumed that the DASH diet is different in other ways and includes a variety of factors that could impact BP (4). The original DASH study included a separate dietary condition that was matched in potassium intake and the differences were still present, suggesting the possibility that potassium may not be the only impacting factor (4).

This study has several strengths. We used a rigorous feeding study protocol with randomized cross-over design and careful physiologic measurements to enhance our ability to detect small changes with statistical significance. Study diets were carefully constructed, and participants' weight and sodium intake were tightly controlled. We restricted enrollment to individuals with isolated systolic hypertension to provide a more homogeneous study population. Nevertheless, there are several limitations. The sodium composition of the DASH diet is only mildly reduced from average intake, and this makes it challenging to detect changes in the RAAS between diets. We did not directly measure natriuresis in this study to confirm that sodium excretion was enhanced as urinary sodium was not collected. In addition, the study was not designed to identify specific nutrients that lead to a DASH diet–RAAS interaction. Finally, we did not measure responses to other BP-regulating mechanism (e.g. sympathetic nervous system, endothelial function) to ascertain if the DASH diet also affects these systems.

These results do have potential clinical implications. Our data suggest that the DASH diet produces a priming effect on pathways affected by the RAAS, which results in a greater physiologic response when combined with CAP. This could imply that blocking the RAAS (e.g. ACE inhibition or angiotensin receptor blocker) may offer unique advantages when patients require escalation in antihypertensive treatment beyond the DASH diet alone. Indeed, this is consistent with our prior study showing that the DASH diet significantly enhanced the BP response to losartan (12).

In conclusion, the DASH diet induces physiologic and biochemical changes that may mimic a natriuretic/diuretic effect rather than ACE inhibition. Due to the priming response observed in the presence of CAP, we hypothesize that the DASH diet may not mimic effects similar to ACE inhibition. Many of the responses observed in this study were enhanced by CAP, suggesting an interaction of the DASH diet with the RAAS.

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