Regulation of the Renin-Angiotensin-Aldosterone System in Fibromyalgia

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ABSTRACT. ***Objective.*** To assess the function of the renin-angiotensin-aldosterone (RAA) system in women with fibromyalgia (FM) compared to healthy women.

Methods. Women with FM [n = 14, age 41.0 ± 7.2 yrs, body mass index (BMI) 26.4 ± 5.4 kg/m^2] and healthy women (n = 13, age 40.0 ± 7.7 yrs, BMI 25.0 ± 5.0 kg/m^2) were placed on a low sodium diet (10 mEq sodium/day) for 5 days. After being supine and fasting overnight, subjects received an intravenous infusion of angiotensin II at successive doses of 1, 3, and 10 ng/kg/min for 45 min per dose. Blood pressure (BP), plasma renin activity (PRA), aldosterone, and cortisol were measured at baseline and after each dose of angiotensin II. Prior to sodium restriction, women with FM completed the Hopkins Symptom Checklist-90, which included a question grading the extent of dizziness/faintness on a scale of 0 (none) to 4 (extremely).

Results. After dietary sodium restriction, baseline PRA, aldosterone, and supine BP were similar in healthy women and women with FM. Aldosterone and BP rose in response to infused angiotensin II; these responses did not differ significantly between healthy women and women with FM. In women with FM, symptoms of dizziness correlated inversely with BMI ($r = –0.81$, $p < 0.001$) and the systolic BP response to 10 ng/kg/min angiotensin II ($r = –0.81$, $p < 0.001$).

Conclusion. The functioning of the RAA system, including the vascular response to angiotensin II, was intact in women with FM compared to healthy women. However, women with FM who complained of dizziness had a blunted vascular response to angiotensin II. This blunted vascular response may indicate intravascular volume depletion in women with symptoms of dizziness. (J Rheumatol 2002;29:1482–7)

Key Indexing Terms:
FIBROMYALGIA BLOOD PRESSURE
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Fibromyalgia syndrome (FM) is a chronic disorder characterized by widespread, nonarticular, musculoskeletal pain and generalized tender points that affects between 3 and 6 million Americans[1,2]. It is seen 4–8 times more frequently in women than men and the prevalence increases with age[3]. The pathophysiological basis of FM is uncertain, but does not appear to be due to a primary abnormality of peripheral tissues[4,5]. Patients with FM have lowered thresholds for pain elicited by pressure and temperature[6,7], altered activity of autonomic nervous system[8-14], and altered functioning of several hypothalamic-pituitary axes[15-20], including a reduced adrenocorticotropic hormone (ACTH) response to hypoglycemia[8]. These observations have led to the hypothesis that in FM, central nervous system dysfunction results in abnormal central processing of pain, altered autonomic nervous system activity, and altered neuroendocrine function[21-23].

In addition to pain, patients with FM often experience other symptoms including fatigue, malaise, gastrointestinal discomfort, irritable bladder, dizziness, and faintness. The etiology of dizziness and faintness is unknown. Several studies have examined aspects of cardiovascular regulation in FM. Compared to healthy women, women with FM had an increased incidence of positive tilt table testing[9,10]. Furthermore, upright tilt table testing for more than 10 minutes elicited worsening or provocation of widespread FM pain[9]. Patients with FM also had a blunted vasoconstrictor response to the cold pressor test[11]. In another study, individuals with FM had an appropriate increase in heart rate upon standing upright, but a decrease in power spectral density of the 0.05–1.5 Hz band that was not observed in healthy controls[12]. This suggested that there was an

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impaired sympathetic surge in response to orthostatic stress in patients with FM.

The renin-angiotensin-aldosterone (RAA) system, a major regulator of blood pressure and blood volume, has not been studied in FM. In response to a low sodium diet or to hypotension, there is activation of the RAA system that is mediated in part by the sympathetic nervous system[24]. Plasma renin activity increases, resulting in increased conversion of angiotensinogen to angiotensin I. Angiotensin I is converted by angiotensin converting enzyme to angiotensin II. In turn, angiotensin II stimulates vasoconstriction and stimulates zona glomerulosa cells of the adrenal cortex to increase aldosterone secretion. Aldosterone stimulates sodium and water retention and potassium excretion by the kidney. These combined effects of angiotensin II on blood volume and vascular tone serve to increase blood pressure.

We examined the functioning of the RAA system in women with FM compared to healthy women. In contrast to regulation of cortisol secretion by adrenal zona fasciculata cells, in which there is one major regulator of steroid secretion, ACTH, aldosterone secretion by adrenal zona glomerulosa cells is stimulated by multiple factors including low dietary sodium intake, angiotensin II, potassium, and ACTH[24]. To examine the RAA system, subjects were placed on a controlled low (10 mEq/day) dietary sodium intake, a diet known to activate the RAA system in healthy individuals. Plasma renin activity and serum aldosterone levels were determined and the adrenal and vascular responsiveness to a graded infusion of angiotensin II were examined. Further, activity of the RAA system was examined in women with FM with respect to their symptoms of dizziness and faintness.

MATERIALS AND METHODS

Subject selection. Adult normotensive premenopausal women between the ages of 21 and 51 years were studied. Fourteen women who met the 1990 American College of Rheumatology criteria for the diagnosis of FM[1] were recruited from the clinical practice of one author (DLG). Thirteen healthy women were recruited using advertisements in local newspapers. All subjects underwent a detailed history and physical examination, including assessment of blood and urine chemistries and thyroid function studies. During this visit, blood pressure (BP) was assessed while the subject was seated. Subjects with a medical problem other than FM were excluded. Subjects who had used any form of glucocorticoids within one year prior to the initiation of the study procedures, or estrogen/progesterone within the previous 6 months, were excluded. All individuals underwent a Structured Clinical Interview from the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition, Revised (DSM-IIIR), to identify past and present psychiatric diagnoses. Control subjects with a history of psychiatric problems were excluded, except for one woman who had a history of substance abuse. FM subjects with current major depression were excluded except for one individual.

All studies were reviewed and approved by the Committee for the Protection of Human Subjects of Brigham and Women's Hospital. Informed written consent was obtained for each subject before participation. Studies were performed at the General Clinical Research Center (GCRC) at Brigham and Women's Hospital.

Study protocol. All subjects completed the FM Impact Questionnaire (FIQ)[25]. The questionnaire consists of 10 items measuring pain, stiffness, fatigue, sleep, physical functioning, work status, depression, anxiety, and well being. The Hopkins Symptom Checklist-90 was completed by patients with FM while on an *ad lib* diet. In one question, patients were asked how much they were bothered by faintness/dizziness over the prior week and responded 0: not at all; 1: a little bit; 2: moderately; 3: quite a bit; or 4: extremely. Control subjects did not complete the Hopkins Symptom Checklist. Twenty-four hour urine was collected for assessment of urinary sodium and creatinine excretion in all women on an *ad lib* diet. An average of 2.0 ± 0.66 urine collections were obtained from each subject. All subjects discontinued the use of caffeine, alcohol, vitamins, and herbal remedies at least 2 weeks prior to the initiation of the study procedures. Prescription and nonprescription medications were also discontinued for 2 weeks prior to the study procedures except for acetaminophen, which was allowed up to 48 h prior to hospitalization.

Subjects were placed on a constant isocaloric diet with a daily intake of 10 mEq sodium and 100 mEq potassium per day starting 5 days prior to performance of an angiotensin II study. Twenty-four hour (8:00 AM to 8:00 AM) urine collection was obtained the day before the angiotensin II infusion. The angiotensin II study began at about 9:00 AM after the subjects had been supine and fasting since midnight. Subjects received a continuous intravenous infusion of angiotensin II-amide (Hypertension, Ciba Geigy, Summit, NJ, USA) at successive doses of 1, 3, and 10 ng/kg/min for 45 min each. Baseline blood samples were obtained prior to starting the angiotensin II infusion and after each incremental dose of angiotensin II. Blood was analyzed for aldosterone, cortisol, plasma renin activity (PRA), sodium, and potassium. Blood pressure was measured using a Dinamap Vital Sign Monitor (Critikon, Tampa, FL, USA) every 5 min for 30 min prior to the angiotensin II infusion (baseline BP) and every 2 min during the angiotensin II infusion. The average BP measured during the last 20 min of each 45 min angiotensin II infusion was considered to be the BP induced by that dose of angiotensin II. Due to a robust BP response to angiotensin II, the 10 ng/kg/min angiotensin II infusion was not initiated in one control subject and was stopped after 8 min in one FM subject. The BP response during this 8 min infusion was included in the data analysis for Table 2 and Figure 4. One day prior to the angiotensin II study, 11 of the 14 FM subjects and all 13 control subjects participated in a hypoglycemic-hyperinsulinemic clamp protocol to assess hypothalamic-pituitary function[8]. Analysis of the data with and without the 3 FM subjects who did not complete the clamp protocol yielded similar results. Therefore, all 14 FM subjects were included in the study.

Laboratory assays. All blood samples were withdrawn through an indwelling catheter placed at least 1 h prior to the start of the study. Samples for plasma were collected on ice, centrifuged immediately at 4°C, and the plasma separated and frozen until time of assay. Serum samples were allowed to clot for 1 h at room temperature, centrifuged, and the serum collected and frozen until assay. Serum aldosterone was measured using Coat-A-Count radioimmunoassay (Diagnostic Products Corp., Los Angeles, CA, USA). Lower limit of detection was 1.6 ng/dl with intraassay coefficient of variation (CV) of 2.7–8.3% and interassay CV of 4–10.5%. Plasma renin activity was measured using Diasorin RIA (INCStar Corp., Stillwater, MN, USA). Lower limit of detection was 0.1 ng/ml/h with intraassay CV of 7–10% and interassay CV of 7–10%. Serum cortisol was measured using the Gammacount Cortisol RIA kit (INCStar). Lower limit of detection was 1.0 μg/dl with intraassay CV of 5–8% and interassay CV of 8–11%. Serum and urine sodium and potassium measurements were performed on a Nova Analyzer 1 (Nova Biomedical, Waltham, MA, USA) with an ion selective electrode with a CV of 0.5% for serum samples and 2% for urine. Urine creatinine was measured on a Beckman creatinine analyzer (Model II, Beckman, Somerset, NJ, USA). If any urinary creatinine level was < 75% of the mean 24 h urinary creatinine level for that subject, the urine collection was considered incomplete and was not used.

Statistical methods. Standard descriptive statistics were presented. The FM and control groups were compared with the t test when variables were

normally distributed. The natural log transform was used to normalize the 24 h urinary sodium and potassium and the PRA at baseline. The hormonal and blood pressure responses to the angiotensin II, which involved multiple measurements over time, were analyzed using repeated measures analysis of variance. The Spearman rank correlation was used to assess the association in FM patients between the dizziness score and baseline hormones, blood pressure, aldosterone change, and the maximum change in blood pressure. Data were presented as mean ± standard deviation.

RESULTS

Subject characteristics. There were no significant differences between patients with FM and control subjects for age (41.0 ± 7.2 and 40.0 ± 7.7 yrs, respectively) or body mass index (BMI) (26.4 ± 5.4 and 25.0 ± 5.0 kg/m^2, respectively). The average disease duration of FM was 8.7 ± 5.4 years (range 2–19). As anticipated, the FM Impact Questionnaire score was significantly higher in women with FM: 65.0 ± 17.1, than in healthy women: 3.2 ± 7.0 ($p < 0.0001$).

FM patients were more likely to have a past or current psychiatric diagnosis than controls as determined by the Structured Clinical Interview for DSM-III-R. Several subjects with FM were found to exhibit one or more psychiatric diagnoses. Four subjects with FM had a history of major depression and one individual had a current major depression. Four FM subjects had a history of alcohol or polysubstance abuse; 2 had had eating disorders and 2 were found to have a history of anxiety/panic disorder. Six subjects with FM and 12 controls had no current or past Axis I diagnosis. One control subject had a history of substance abuse.

Effect of dietary sodium restriction and angiotensin II on adrenal activity. Twenty-four hour urinary sodium excretion was low during the 5th day of the restricted dietary sodium intake, indicating compliance with the low sodium diet. There was no significant difference ($p > 0.70$) in amount of sodium excreted in the urine between patients with FM, 15.7 ± 8.6 mEq/TV, and control subjects, 21.0 ± 10.3 mEq/TV (Table 1).

After 5 days of restricted sodium intake, baseline plasma renin activity and serum aldosterone were similar in the 2 study groups (Table 1). In response to the angiotensin II infusion, there was a significant ($p < 0.001$) dose dependent increase in serum aldosterone that did not differ between subject groups ($p > 0.25$) (Figure 1). With 10 ng/kg/min angiotensin II, serum aldosterone increased to 86.2 ± 33.8 ng/dl in women with FM and to 71.8 ± 13.5 ng/dl in healthy women. During the angiotensin II infusion, PRA decreased to similar levels in FM subjects (2.0 ± 2.0 ng/ml/h) and controls (1.2 ± 0.7 ng/ml/h) and serum cortisol levels fell consistent with the normal decrease in endogenous ACTH during the late morning (Figure 2).

Table 1. Baseline hormone and blood pressure measures after 5 days of dietary sodium restriction.

Measure	Control, n = 13	FM*, n = 14
24 hr urinary sodium, mEq/TV**	21.0 ± 10.3	15.7 ± 8.6
Plasma renin activity, ng/ml/h**	3.5 ± 2.2	4.5 ± 4.2
Aldosterone, ng/dl	19.8 ± 7.1	22.7 ± 17.7
Cortisol, μg/dl	9.7 ± 2.4	9.2 ± 2.7
Sodium, mmol/l	139.8 ± 1.4	139.3 ± 1.8
Potassium, mmol/l**	4.2 ± 0.3	4.4 ± 0.4
BP systolic, mm Hg	107.4 ± 9.4	109.4 ± 11.4
BP diastolic, mm Hg	65.8 ± 8.0	68.6 ± 8.3

* $p > 0.15$ for all subject group comparisons; **log-transformed data analyzed.

Effect of dietary sodium restriction and angiotensin II on blood pressure. With dietary sodium restriction, subjects with FM had supine baseline systolic and diastolic BP that did not differ from those of healthy women (Table 1). Infusion of angiotensin II stimulated similar dose dependent increases in BP in both study groups (Figure 3). With the 10 ng/kg/min angiotensin II infusion, systolic BP increased to 128 ± 15.0 mm Hg and diastolic BP to 80 ± 12.0 mm Hg in women with FM and to 125 ± 13.0 and 75 ± 9.0 mm Hg in healthy women ($p > 0.5$ for comparisons between groups).

RAA system in women with FM and complaints of dizziness. The Hopkins Symptom Checklist assesses symptoms of faintness/dizziness in women with FM using a scale from 0 (none) to 4 (severe) symptoms. On an *ad lib* sodium diet, 5 women reported a score of 0, 3 a score of 1, 2 a score of 2, and 3 a score of 3.

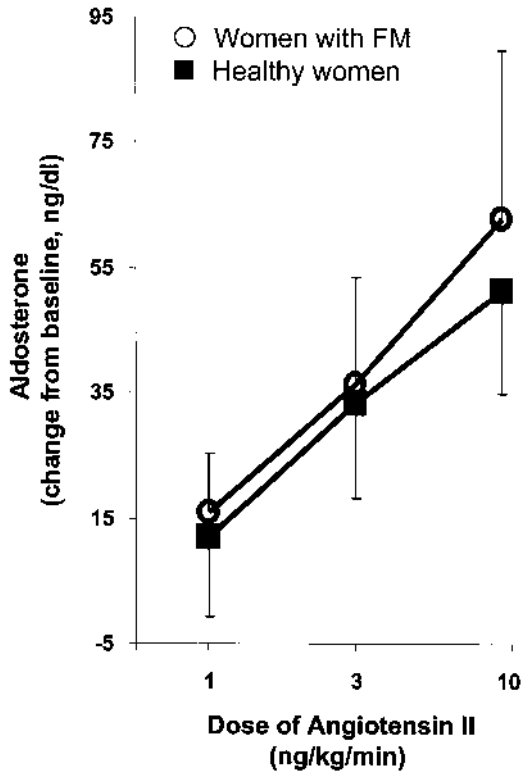


Figure 1. Change in serum aldosterone from baseline in response to angiotensin II infused at sequentially increasing doses of 1, 3, and 10 ng/kg/min for 45 min per dose. There is no significant difference comparing aldosterone response between 14 women with FM and 13 healthy women ($p > 0.25$).

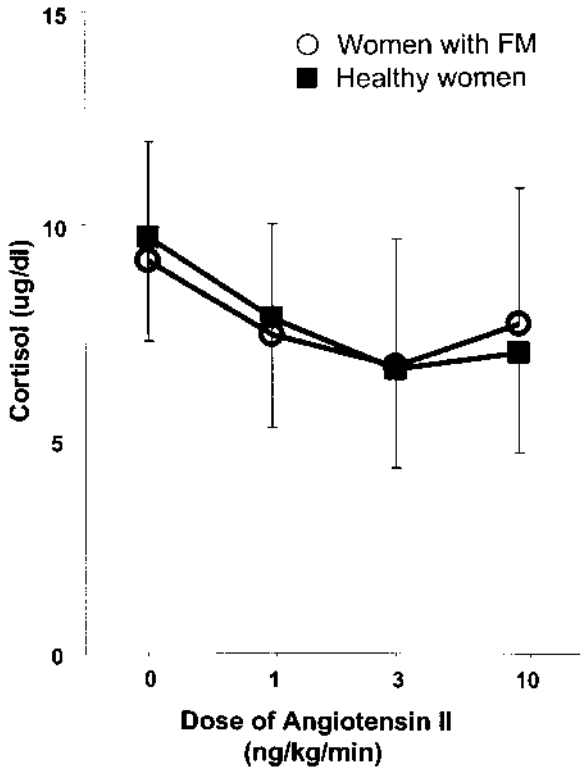
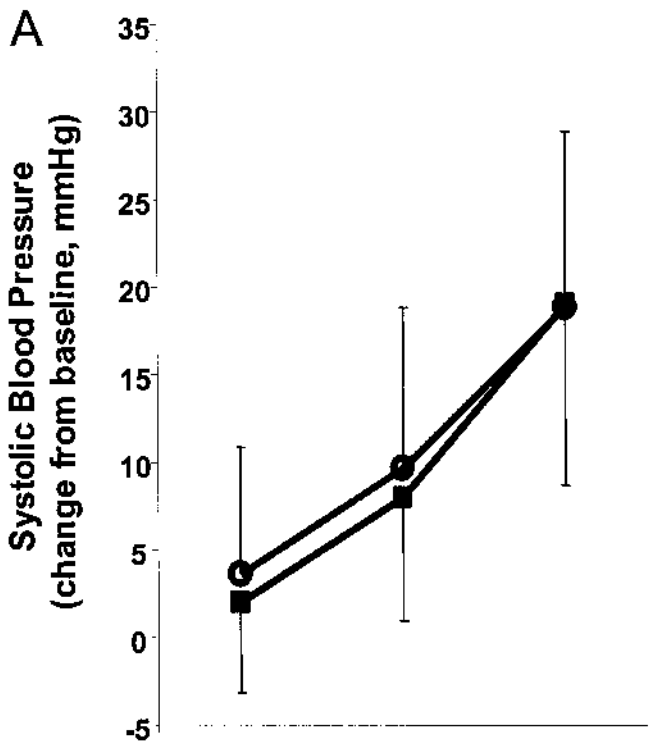


Figure 2. Serum cortisol levels in 14 women with FM and 13 healthy women at baseline and after each dose of angiotensin II (1, 3, and 10 ng/kg/min).



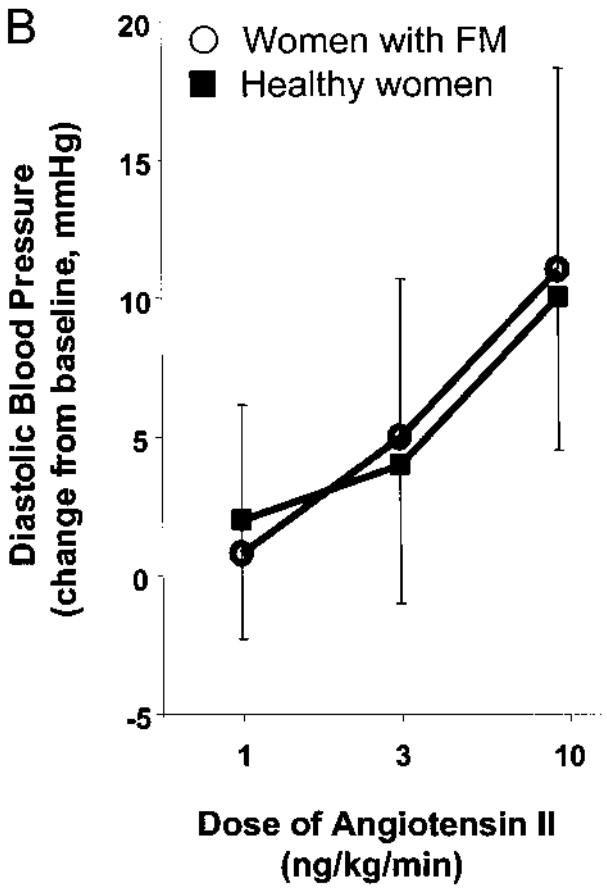


Figure 3. Increases in systolic BP (A) and diastolic BP (B) from baseline in response to angiotensin II infused at sequentially increasing doses of 1, 3, and 10 ng/kg/min for 45 min per dose were similar in 14 women with FM and 13 healthy women ($p > 0.5$).

Symptoms of dizziness correlated inversely with the increase in systolic BP, the level of systolic BP achieved with 10 ng/kg/min angiotensin ($p < 0.01$), BMI ($p = 0.001$), and age ($p = 0.01$) (Figure 4, Table 2). In a multiple variable model, the systolic BP achieved with angiotensin II accounted for 57.5% of the variance in dizziness ($p < 0.003$), with BMI accounting for an additional 12.2% of the variance ($p = 0.07$) and age accounting for only about 2%. Baseline PRA and systolic BP on a low sodium diet tended to be lower in those individuals with more dizziness ($r = 0.44$, $p = 0.14$ and $r = –0.46$, $p = 0.12$, respectively). Baseline and angiotensin II stimulated diastolic BP and aldosterone did not correlate with symptoms of dizziness.

DISCUSSION

This study revealed that the regulation of the RAA system was intact in women with FM compared to healthy female controls. Restricting dietary sodium intake resulted in similar elevations in baseline plasma renin activity and serum aldosterone in these 2 study populations. Further, the aldosterone and vascular responses to a graded angiotensin II did not differ between groups. These results complement our previous study showing an intact cortisol response to a graded ACTH infusion in women with FM[8]. Together these

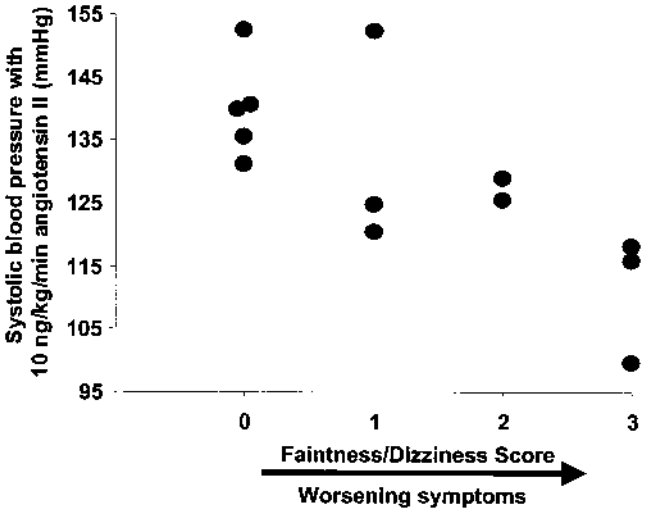


Figure 4. Relationship between systolic blood pressure achieved by 10 ng/kg/min angiotensin II infusion and dizziness score in 13 women with FM. The level of systolic blood pressure achieved with 10 ng/kg/min dose of angiotensin II correlated inversely with symptoms of dizziness (r = –0.81, p > 0.001).

Table 2. Relationship of dizziness score with blood pressure and hormone measurements in women with FM.

	Correlation	p
Age	–0.69	0.01
BMI	–0.81	0.001
Disease duration	0.02	0.95
FIQ	0.21	0.49
Outpatient systolic BP	–0.55	0.06
Outpatient diastolic BP	–0.16	0.63
After 5 days sodium restricted diet		
At baseline		
Urinary sodium	–0.50	0.08
Plasma renin activity	0.44	0.14
Aldosterone	0.29	0.34
Systolic BP	–0.46	0.12
Diastolic BP	–0.13	0.30
After 10 ng/kg/min angiotensin II		
Systolic BP	–0.81	0.001
Diastolic BP	–0.21	0.48
Change in systolic BP	–0.66	0.01
Change in diastolic BP	0.20	0.52
Change in aldosterone	0.02	0.96

studies rule out a primary defect in adrenal cortical function in FM.

There was a significant inverse correlation between the pressor response to angiotensin II and symptoms of dizziness in subjects with FM, with dizziness being associated with a blunted vascular response. This blunted response could be attributable to a primary defect in vascular responsiveness to angiotensin II or other pressors, possibly reflecting a hyporeactive stress response. Alternatively, the blunted response may indicate that FM subjects with symptoms of dizziness have intravascular volume depletion compared to those subjects without symptoms. In healthy individuals, intravascular volume depletion is associated with a blunted BP response to angiotensin II due to down-regulation of angiotensin II receptors in individuals with an activated RAA system[26]. The tendency for baseline PRA to be positively correlated with symptoms of dizziness was consistent with the idea of intravascular volume depletion. We did not perform a formal posture study to assess orthostatic intolerance, nor did we directly measure blood volume. However, there was an inverse relationship between symptoms of dizziness and seated systolic BP on an *ad lib* sodium intake, raising the possibility that FM subjects with dizziness may have orthostatic hypotension and volume depletion even without dietary sodium restriction.

If FM subjects who experience dizziness had intravascular volume depletion, it was not due to a lack of end organ responsiveness. With dietary sodium restriction, there was appropriate sodium retention by the kidney, an intact angiotensin II stimulated aldosterone secretion by the adrenal, and an angiotensin II stimulated pressor response appropriate for a volume depleted state. Possible etiologies for intravascular volume depletion include increased vascular compliance and/or a decrease in blood volume. Part of the relationship between BMI and dizziness may be related to changes in vascular compliance and blood volume associated with the lean/obese state[27].

If women with FM and dizziness have intravascular volume depletion, volume expansion may be beneficial. Increasing dietary sodium intake would be a relatively benign way to raise blood volume. Further, factors that deplete blood volume such as diuretics, caffeine, and alcohol potentially may exacerbate FM symptoms in susceptible individuals. The aldosterone analog fludrocortisone has been used in subjects with orthostatic intolerance to expand blood volume[28-30]. However, fludrocortisone did not have a beneficial effect on either fatigue or orthostatic symptoms when studied as a potential treatment in a disorder thought to be related to FM, chronic fatigue syndrome[30]. Recent studies suggest that under certain conditions aldosterone causes cardiovascular toxicity through mechanisms independent of aldosterone's classic effects on volume homeostasis and blood pressure[31-38]. Given the potential risks associated with excess mineralocorticoids and the normal functioning of the RAA system in FM, fludrocortisone should be used with caution in this disorder.

In summary, women with FM have intact functioning of the RAA system and intact angiotensin II mediated vasoconstriction compared to healthy women. Women with FM who complain of dizziness tend to be younger and leaner, and in response to dietary sodium restriction, display alterations in the vascular response to angiotensin II that are suggestive of intravascular volume depletion. The mechanisms for this proposed intravascular volume depletion remain to be elucidated.

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