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A MECHANISM FOR SALT SENSITIVE HYPERTENSION: ABNORMAL DIETARY SODIUM MEDIATED VASCULAR RESPONSE TO ANGIOTENSIN II

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Abstract

Objectives—Several mechanisms have been proposed for salt-sensitive hypertension with most focusing on impaired renal sodium handling. We tested the hypothesis that abnormalities in peripheral vascular responsiveness to angiotensin-II might also exist in salt-sensitive hypertension because of the interplay of the renin-angiotensin system and dietary sodium.

Methods—Blood pressure response to angiotensin-II infusion was studied in 295 hypertensives and 165 normotensives after 7 days of high (200 mEq/day) and low (10 mEq/day) dietary sodium.

Results—Normotensives demonstrated higher blood pressure response to angiotensin-II on high-salt than low-salt diet whereas hypertensives had similar responses on both diets, i.e., the high-salt response was not enhanced compared to low-salt. Additionally, hypertensives had a significantly greater high-salt blood pressure response to norepinephrine than to angiotensin-II. There was no correlation between the high-salt hormone levels and the difference in blood pressure response to angiotensin-II between the two diets. When stratified by blood pressure response to dietary salt restriction, individuals with salt sensitivity of blood pressure demonstrated abnormal high-salt blood pressure responsiveness to angiotensin-II. To assess if this represented increased tissue renin-angiotensin system activity in the vasculature, blood pressure responses to angiotensin were compared before and after captopril in 20 hypertensives on a high-salt diet. Subjects with the greatest blood pressure lowering effect to captopril had similar high and low-salt blood pressure responses to angiotensin-II at baseline and a significant increase in the high-salt response after captopril.

Conclusion—Hypertensives have an abnormal vascular response to angiotensin-II infusion on a high-salt diet. Dysregulated tissue renin-angiotensin system activity may play a role in this abnormal response. These findings raise an intriguing novel possibility for the pathophysiologic mechanism of salt-sensitive hypertension.

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Keywords

hypertension; salt sensitivity; salt-sensitive; sodium; angiotensin II response; tissue renin-angiotensin system

Introduction

Salt-sensitivity of blood pressure (BP) is present in approximately half of the population with essential hypertension (HTN) [1]. The pathophysiologic mechanisms leading to salt-sensitivity are complex and only partially understood. Most studies have focused on the pathogenic role of the kidney. Abnormal renal hemodynamic responses to high dietary salt intake and alterations of renal sodium handling have been suggested as potential causal mechanisms for the variation in BP responses to salt [2-8]. Dietary sodium is known to modulate renal vascular and adrenal responsiveness to exogenous angiotensin-II (ANGII) [9]. In normal subjects, restriction of sodium intake enhances adrenocortical sensitivity and decreases renal vascular sensitivity to infused ANGII [9]. Among hypertensives (HTves), it has been shown that a substantial fraction fail to modulate adrenal and renal responses to ANGII in response to changes in dietary sodium [10,11]. The classical reasoning had been that responsiveness to ANGII was mediated by the circulating levels of ANGII [12,13]. However, there is evidence suggesting that the activity of the renin-angiotensin-aldosterone system (RAAS) at the tissue level, particularly in the kidney, has importance beyond what is apparent from measures of circulating RAAS [14-17]. We have previously reported evidence of increased intra-renal RAAS activity in African Americans and diabetics, which has been suggested as the explanation for their low circulating renin levels [14,18,19]. While renal vascular responses to ANGII have been extensively studied, it is not known whether there are similar variations in the general peripheral vasculature, which may also contribute directly to BP regulation and salt-sensitivity.

The overall aim of this study was to test the hypothesis that the observed salt sensitivity of BP described in HTN is in part related to altered tissue RAAS activity in the vasculature.

Methods

Subjects and protocol

Data from a total of 295 HTve and 165 normotensive (NTve) individuals in whom all study-specific outcome variables were available and who had participated in the International Hypertensive Pathotype study were analyzed. Subjects had been recruited from the general populations of Boston, Massachusetts, Salt Lake City, Utah, Nashville, Tennessee, Rome, Italy and Paris, France. The institutional review board of each institution approved the original study protocol. All subjects gave written informed consent before enrollment and underwent identical protocols at each study site. Some characteristics of subsets of this population have been reported previously [10,11,20]. However, the present analyses are original.

All subjects had screening history, physical and laboratory examinations. Subjects with known or suspected secondary HTN, diabetes mellitus (DM), coronary artery disease, stroke, overt renal insufficiency (serum creatinine > 1.5 mg/dl), current tobacco or illicit drug use, alcohol intake > 12 ounces per week, or other significant medical or psychiatric illnesses were excluded. Subjects with abnormalities of baseline laboratory tests including electrolytes, thyroid and liver function tests or electrocardiographic evidence of heart block, ischemia, or prior coronary events at the screening exam were excluded from participation.

As per the original study protocol, HTN was defined as seated diastolic BP (DBP) ≥ 100 mmHg off antihypertensive medication, ≥ 90 mmHg with ≥ 1 medication, or treatment with ≥ 2 medications. HTves requiring more than four medications were excluded. NTves, in addition to having BP less than 140/90 mmHg, reported no first degree relatives diagnosed with HTN before age 60. Subjects taking an angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker, or mineralocorticoid receptor antagonist were transitioned to amlodipine with or without hydrochlorothiazide to control BP three months prior to study to minimize interference with assessment of the RAAS. All antihypertensive medications were then discontinued for a total of three weeks before hormonal and vascular assessment.

Subjects completed two controlled dietary phases; five to seven days of high-sodium (HS) diet (200 mmol Na/day) and seven days of low-sodium (LS) diet (10 mmol Na/day), prepared by each site's General Clinical Research Center (GCRC) kitchen. Each diet was isocaloric, contained 100 mmol/day potassium, 20 mmol/day calcium, and caffeine and alcohol-free. On the final day of each diet week a 24-hour urine collection for sodium, potassium and creatinine excretion was obtained. Only individuals whose urine sodium was ≥ 150 mmol/24hrs on HS diet and <30 mmol/24hrs on LS diet were included. All subjects were then admitted to a GCRC and remained fasting and supine overnight. The following morning they received an ANGII infusion at 3 ng/kg/min $\times$ 55 minutes (both LS and HS phases). To determine if BP responses to ANGII were affected by a BP "ceiling effect", all subjects underwent a separate graded norepinephrine (NE) infusion (10, 30, 60 ug/kg/min $\times$ 10mins each) on HS diet. A subset of HTves (n = 20) underwent an additional protocol on HS diet consisting of baseline 3ng ANGII infusion followed by captopril administration (25mg $\times$ 1 dose) followed by a second 3ng ANGII infusion 60-90 minutes later.

BP was measured using an automated device (DINAMAP; Critikon, Tampa, FL) and consisted of a mean of 3 consecutive readings separated by 5 minutes, each measured supine. Salt-sensitivity was defined as a change in systolic BP (SBP) between HS and LS diets; salt-sensitive ≥ 10 mmHg change in SBP, salt-resistant < 10 mmHg change in SBP. HTves were also classified as either low-renin (LR), if the PRA was < 2.5 ng/ml/hr (< 0.69 ng/L/s) on LS diet after 1-2 hours of upright posture, or as normal-renin (NR), if PRA was > 2.5 ng/ml/hr.

Laboratory Analyses

Blood samples were collected on ice and centrifuged for 20 minutes. Samples were stored at -20°C without preservatives until assayed. Plasma renin activity (PRA), serum aldosterone, sodium, potassium and creatinine were measured as previously described [20].

Statistical Analysis

Data are reported as mean $\pm$ standard error for continuous variables and percentages for discrete variables unless otherwise specified. Statistical significance was indicated by a p value of < 0.05 . Statistical analyses were performed using SPSS Version 15.0 (SPSS, Chicago, Illinois) statistical software package. Student's t-tests were used to compare means between independent populations. Paired t-tests were used to compare the means within subjects including comparison of the BP response to ANGII between HS and LS diets, BP response to captopril, BP response to ANGII before and after captopril, as well as the comparison of BP response to ANGII versus NE. Pearson correlation estimates were used to investigate the relationship between circulating measures of the RAAS (PRA, serum aldosterone and ANG II levels) and the BP responses to ANGII.

Results

Baseline Characteristics and Primary Analyses

The baseline characteristics of the HTves and NTves are shown in Table 1. Age, BMI and BP were higher in HTves. Racial distribution was similar in both groups. As anticipated, baseline BP was higher on HS diet compared with LS diet in HTves and NTves. The levels of circulating RAAS hormones were similar in both groups except for mild differences in the aldosterone levels and a slightly lower LS PRA in HTves.

SBP increased in response to ANGII infusion in both HTves and NTves on HS and LS diets. NTves displayed a significantly higher ($p < 0.001$) HS SBP response to ANGII compared to the LS response (Figure 1). HTves on the other hand, did not show a higher SBP response to ANGII on HS relative to LS (Figure 1). The SBP response patterns in both HTves and NTves were consistent regardless of age and gender. The difference in the BP response to ANGII between the two diets i.e. HS minus LS response, was significantly less in HTves compared with NTves ($p < 0.001$). DBP response patterns were similar to the SBP responses.

We then assessed the relationship between circulating levels of the RAAS and SBP response to ANGII within each diet in HTves and NTves. As anticipated by the receptor occupancy theory, in both HTves and NTves, the SBP response to ANGII correlated with the baseline PRA and aldosterone levels on each diet (Table 2). However, when we examined this relationship with the change in SBP response to ANGII between diets, we no longer observed a significant correlation on the HS diet (Table 2), supporting that the defect in the BP response to ANGII was occurring on the HS diet.

Evaluation for the Mechanism(s) Underlying the Abnormal BP Response to ANGII on HS Diet

1) BP Response to Norepinephrine Infusion

To evaluate whether the abnormal response to ANGII on a HS diet in HTves represented a BP “ceiling effect” versus specific ANGII responsiveness we measured BP response to NE infusion on a HS diet. HTves were able to mount a significantly greater ($p = 0.002$) SBP response to NE than to ANGII on HS diet (Figure 2).

2) Salt-sensitivity and Vascular Response to ANGII

In the absence of a ceiling effect, we then assessed if the BP response to ANGII is related to salt-sensitivity of BP. We examined the relationship between the change in SBP between HS and LS diet, i.e. salt sensitivity, and the change in SBP response to ANGII between the two diets and found a strong correlation in HTves (Pearson correlation -0.44 , $p < 0.001$) and NTves (Pearson correlation -0.41 , $p < 0.001$), suggesting a relationship between salt-sensitivity and the BP response to ANGII. Subsequently, we stratified HTves and NTves into salt-sensitive (≥ 10 mmHg increase in SBP from LS to HS) and salt-resistant subgroups. Among hypertensives, subjects classified as having “salt-resistant” HTN had a normal response to ANGII relative to their salt intake. In contrast, the HTves who were “salt-sensitive”, which included two-thirds of the HTve cohort, had an abnormal response on the HS diet (Figure 3). Interestingly, NTve subjects displayed a similar pattern when divided into salt-sensitive and salt-resistant subgroups (Figure 3), although only one-third of the NTves had salt-sensitivity of BP by our criteria. The salt-sensitive individuals had higher baseline HS SBP and DBP among the HTves (151/91 in salt-sensitive versus 134/83 in salt-resistant, $p < 0.001$) and NTves (118/70 in salt-sensitive versus 108/65 in salt-resistant, $p < 0.001$) compared to the salt-resistant individuals within each group. There were no significant differences in baseline PRA and aldosterone levels between the salt-sensitive and salt-resistant subgroups of HTves, but among

normotensives, the salt-sensitive individuals had lower baseline PRA on LS diet (PRA 2.55 in salt-sensitive versus 3.32 in salt-resistant NTves; $p = 0.026$).

3) Renin status and BP Response to ANGII

When HTves were stratified based on renin status (LR or NR), both groups exhibited a significantly lower SBP response to ANGII compared to NE on a HS diet (Figure 4). The reduced HS SBP response to ANGII was more pronounced in the LR group compared to the NR group ($p < 0.001$), but the response to NE was similar in both groups ($p = 0.42$).

4) Assessment for a Potential Tissue ANGII Effect

To assess whether the inability of the HTves to mount a higher BP response to ANGII on HS diet reflected higher ambient tissue RAS that was not being appropriately suppressed by the HS diet, we pre-treated a subset of HTves on a HS diet with the ACE inhibitor captopril. BP response to captopril varied among HTves with 1/3rd of the subset (tertile 1; $n = 6$) showing minimal to no change (< 10 mmHg fall in SBP), 1/3rd (tertile 2; $n = 7$) with a 10-20 mmHg fall in SBP and 1/3rd (tertile 3; $n = 7$) with > 20 mmHg fall in SBP. As this variation in BP response to captopril suggested differences in endogenous RAAS activity within the hypertensive subset, subsequent analyses of the BP responses to ANGII were performed based on tertile of baseline SBP decrement with captopril. Individuals who had the least change in SBP after captopril (tertile 1) had a greater ($p = 0.005$) SBP response to ANGII on HS compared to LS diet (Figure 5) at baseline (before captopril) similar to the response pattern seen in NTves and salt-resistant HTves and had no significant change in the HS SBP response to ANGII after captopril. In contrast, in tertile 3, which comprised of individuals with the greatest change in SBP after captopril (tertile 3), the SBP response to ANGII on HS was not significantly different ($p = 0.69$) from their LS response at baseline (Figure 5), but after receiving captopril, these individuals had a significant increase ($p = 0.006$) in their HS SBP response to ANGII (Figure 6). These results suggest that tertile 3 subjects had higher tissue ANGII on the HS diet despite similarly suppressed circulating PRA levels. Individuals in tertile 2 showed no significant difference between their HS and LS SBP responses to ANGII at baseline ($p = 0.27$) and when tertiles 2 and 3 were combined ($n = 14$), there was again no significant difference in the HS and LS SBP responses to ANGII at baseline and a significant increase in the HS SBP response after captopril ($p = 0.025$), similar to the results in tertile 3.

Discussion

The results of this study demonstrate for the first time an abnormality in the relationship between dietary salt intake and BP responses to ANGII in HTN. They suggest an abnormality related to salt-sensitivity of BP and a possible mechanism involving increased intrinsic RAS activity within the peripheral vasculature. The abnormality in the dietary sodium-mediated BP response characteristics to ANGII is not explained on the basis of the circulating RAAS activity, therefore suggesting heightened RAAS activity at the tissue level. To support this mechanism we performed a pilot study to assess if ACE inhibition would correct the abnormality in the HS SBP ANGII responsiveness in HTves. ACE inhibition modified the HS BP response to ANGII only in those individuals who displayed an abnormality in dietary sodium-mediated change in BP response to ANGII. Furthermore, the “intact” SBP response to an alternate pressor (NE) indicates that the relative inability to appropriately increase the BP response to ANGII on a HS diet is not secondary to a “ceiling effect” of BP on the HS diet i.e. the abnormal response is not due to an already high baseline BP on a HS diet in HTves limiting the ability to further enhance the BP in response to a pressor.

The RAAS regulates sodium and volume homeostasis. The circulating measures of the RAAS such as the PRA and aldosterone levels are generally used as indicators of the activity of the

RAAS, but several lines of evidence suggest that in certain situations, there is an apparent disconnect between circulating concentrations of the RAAS and target organ function which may represent either altered tissue sensitivity at the receptor level or dysfunctional tissue RAAS activity [14,15,17-19]. It has been suggested that increased tissue RAAS in the kidney may be the underlying mechanism causing increased susceptibility to renal injury and nephropathy among blacks [18] and patients with DM [14,15,19], both groups that generally also tend to have salt-sensitive HTN. Blacks display a blunted renal vascular response to ANGII that is reversed with captopril [18]. In separate studies involving patients with type I [14,19] and type II DM [15], activation of intra-renal RAS was noted as evidenced by marked renal vasodilator responses to an ACE inhibitor and/or an angiotensin receptor blocker in the absence of an increase in PRA. Among patients with essential HTN, it has been documented that between 30-50% lack the normal sodium-mediated renal vascular responsiveness to ANGII [10,11]. Our study has expanded on the above concepts and provides evidence that a similar mechanism, i.e. dysregulation of tissue ANGII in response to high dietary sodium, occurs in the peripheral vasculature in many HTves and is associated with salt-sensitive HTN.

The contribution of salt intake to the pathogenesis of HTN has been an area of longstanding interest. Individual BP responses to changes in dietary sodium are known to be highly variable and thought to be mediated by complex hormonal and genetic factors. Most previous studies that have tried to elucidate the mechanisms leading to the development of salt-sensitive HTN have focused on the kidney. Abnormalities in the regulation of sodium retaining hormones, renal tubular defects in sodium handling resulting in salt-retention as well as derangements in renal hemodynamic adjustments to high salt intake have been suggested as key mechanisms for salt-sensitive HTN [2-8]. Our study does not provide any further evidence in support of a renal mechanism but shifts attention to mechanisms outside of the kidney that may also be important determinants of the BP response to salt. The results of this study provide evidence for an abnormal interaction between dietary sodium and systemic vascular pressor responses, specifically to ANGII, that could potentially play an important role in the causation and maintenance of salt-sensitive HTN.

Interestingly, the results in NTves may provide a potential additional mechanism that may be present in some NTves that could predispose them to salt-sensitive HTN. Those NTves who had a ≥ 10 mmHg change in SBP with change in salt intake also had higher resting BPs than the salt-resistant subjects. These data support the hypothesis that in addition to any potential alterations in renal sodium handling leading to salt-sensitive HTN, there may also be changes in peripheral vascular pressor responsiveness.

Our findings should be interpreted in the context of the retrospective study design. HTves in our database had mild/moderate HTN. Hence, these findings may not be applicable to more severe HTN. Our subjects were under the age of 66 and therefore the results may not be applicable to older individuals. The strengths of this study are the large sample size and ability to control for relevant confounders by carefully controlled experimental conditions including dietary sodium intake, medication washout, and use of a GCRC. We attempted to provide supporting evidence of a specific role for ANG II through use of replacement/ablation experimentation and a control pressor (NE) infusion. However, while our findings are strongly suggestive of dysregulation of vascular tissue ANGII resulting in abnormal BP regulation in response to high dietary sodium intake as a plausible contributor for salt-sensitive HTN, these indirect assessments of RAS involvement at the target tissue do not definitively prove a causal relationship. In addition, the kidney may also be modulating the blood pressure responses to ANGII.

In summary, these data demonstrate an alteration in the peripheral vascular response to dietary sodium intake related to ANGII responsiveness and salt-sensitivity of BP in HTves. The

mechanism appears to involve dysregulated tissue ANGII thus providing additional important clues to the underlying pathophysiology of salt-sensitive HTN. These findings may also have important pharmacological implications related to specific antihypertensive agent selection in hypertension.

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Fig. 1. SBP response to ANGII on HS versus LS diet in HTve and NTve subjects. Each subject received ANGII infusion on both HS and LS diet. Error bars represent standard error of the mean.

Fig. 2.
Comparison of SBP response to NE (60ug/kg/min) and ANGII (3ng/kg/min) infusions in the same HTve subjects. Error bars represent standard error of the mean.

Fig. 3. SBP response to ANGII infusion on HS versus LS diet in the same HTve and NTve subjects stratified by salt-sensitivity of BP (salt sensitive and salt resistant). Error bars represent standard error of the mean.

Fig. 4. SBP response to ANGII and NE infusions on HS diet in hypertensives classified by renin status (low-renin and normal-renin). Each subject received both infusions. Error bars represent standard error of the mean.

Fig. 5.

SBP response to ANGII infusion on HS versus LS diet. Subjects are those who received captopril and are divided into those who had a minimal BP response to captopril (tertile 1) or a maximum response (tertile 3) [see text for definition of tertiles]. The results indicate the SBP responses to ANGII on HS versus LS diet in the two groups at baseline, before receiving captopril. Error bars represent standard error of the mean.

Fig. 6.

SBP response to ANGII infusion on HS diet before and after captopril (25mg) administration in HTves who had the greatest SBP response to captopril at baseline (tertile 3 individuals). These results suggest that tertile 3 subjects have higher tissue ANGII activity on a HS diet. Error bars represent standard error of the mean.

Table 1

Baseline Characteristics of the Hypertensive and Normotensive Subjects.

Characteristic	Hypertensives	Normotensives (n=165)
Age	48.6 ± 0.5 (44-55)	39.3 ± 0.9 (28-50) **
Gender (female%)	36.9	54.3 **
Race (white%)	88.5	84.8
Body Mass Index (kg/m ²)	28.2 ± 3.9 (23-31)	25.3 ± 3.9 (22-27) **
SBP (mm Hg), low salt	130.3 ± 0.95 (116-144)	105.4 ± 0.8 (98-111) **
DBP (mm Hg), low salt	80.2 ± 0.6 (73-86)	62.96 ± 0.6 (58-67) **
SBP (mm Hg), high salt	144.9 ± 1.1 (133-157)	110.9 ± 0.9 (103-118) **
DBP (mm Hg), high salt	88.4 ± 0.7 (80-96)	66.6 ± 0.6 (61-72) **
High Salt Diet		
Urine sodium (mmol/24-hrs)	234.5 ± 3.7 (188-269)	240.2 ± 5.3 (186-278)
Urine potassium (mmol/24 hrs)	72.5 ± 1.16 (61-85)	75.3 ± 2.05 (58-95)
Serum sodium (mmol/L)	141.96 ± 0.3 (140-145)	140.3 ± 0.4 (138-143) **
Serum potassium (mmol/L)	4.16 ± 0.02 (4-4.4)	4.14 ± 0.03 (3.9-4.3)
Plasma renin activity (ng/mL/hr)	0.47 ± 0.03 (0.2-0.5)	0.40 ± 0.03 (0.15-0.5)
Serum aldosterone (ng/dL)	5.1 ± 0.23 (2.5-6.2)	3.6 ± 0.16 (2.5-4) **
Serum ANGII (pg/mL)	28.1 ± 1.0(20-36)	25.8 ± 0.9 (17-32)
Low Salt Diet		
Urine sodium (mmol/24-hrs)	12.7 ± 0.4(7.5-18)	8.9 ± 0.6 (2-11) **
Urine potassium (mmol/24-hrs)	71.1 ± 1.2(57-84)	75.3 ± 1.7(60-91) *
Serum sodium (mmol/L)	140.4 ± 0.3 (138-143)	139.2 ± 0.4 (137-141) **
Serum potassium (mmol/L)	4.2 ± 0.02 (4-4.5)	4.1 ± 0.03 (3.9-4.3) **
Plasma renin activity (ng/mL/hr)	2.5 ± 0.1 (1-3.2)	3.1 ± 0.2(1.6-4.3) **
Serum aldosterone (ng/dL)	17.4 ± 0.65 (10-22)	20.3 ± 0.97 (12-26) *
Serum ANGII (pg/mL)	43.6 ± 2.2 (26.5-55.8)	43.3 ± 1.9(28.8-52.9)

Values reported as mean ± standard error of the mean with interquartile ranges in parenthesis. For categorical variables gender and race, percentage is used. Abbreviations: SBP - systolic blood pressure; DBP - diastolic blood pressure; ANGII – angiotensin II. Statistical significance is indicated by

* for p < 0.05

** for p < 0.01 and comparing HTves and NTves.

Table 2

A: Correlations between circulating RAAS levels and BP response to ANGII on each diet in HTves and NTves.

	Hypertensives		Normotensives	
	Pearson Correlation	P - value	Pearson Correlation	P - value
High Salt PRA	− 0.14	0.03	− 0.18	0.025
Aldosterone	− 0.18	0.005	− 0.02	0.76
Angiotensin II	0.13	0.21	− 0.035	0.69
Low Salt PRA	− 0.32	< 0.001	− 0.28	< 0.001
Aldosterone	− 0.25	< 0.001	− 0.24	0.002
Angiotensin II	− 0.24	0.013	− 0.073	0.40

B: Correlation between circulating RAAS levels and the difference in ANGII response between HS and LS diets in HTves and NTves.

Circulating RAAS	Hypertensives		Normotensives	
	Pearson Correlation	p-value	Pearson Correlation	p-value
High Salt PRA	< 0.001	1.0	−0.13	0.11
Aldosterone	− 0.11	0.07	0.09	0.24
Angiotensin II	0.16	0.11	−0.12	0.17
Low Salt PRA	0.27	< 0.001	0.13	0.11
Aldosterone	0.11	0.07	0.18	0.03
Angiotensin II	0.39	< 0.001	0.07	0.39