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# The effects of atenolol and zofenopril on plasma atrial natriuretic peptide are due to their interactions with target organ damage of essential hypertensive patients

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**The effects of 10 weeks of treatment with atenolol ($n$ = 9) or the converting enzyme inhibitor zofenopril ($n$ = 25) on plasma atrial natriuretic peptide (ANP) were studied in 34 essential hypertensive patients. After 4 weeks on placebo, pretreatment ANP, 56 ± 7 pg/ml, was slightly but not significantly higher than that of 29 controls (41 ± 4) and correlated with age ($r$ = 0.44), ECG score for left ventricular hypertrophy (LVH) ($r$ = 0.51) and serum creatinine ($r$ = 0.67), and negatively with creatinine clearance ($r$ = –0.39). Atenolol reduced blood pressure (BP) by 0 ± 6/8 ± 2 mm Hg (ns/$P < 0.01$), and zofenopril by 14 ± 4/6 ± 2 ($P < 0.01$/$P < 0.01$), not significantly different between the two agents. Heart rate was decreased by atenolol (–16 ± 4 bpm, $P < 0.01$) but not by zofenopril (+1 ± 2 bpm, ns). Atenolol increased ANP in all patients but one (Δ = +42 ± 9 pg/ml, $P < 0.01$), while zofenopril did not change it significantly (–6 ± 6 pg/ml), due to 15 patients exhibiting decreases and 10 increases in plasma ANP. The effect of atenolol on ANP positively correlated with duration of hypertension ($r$ = 0.74), ECG score for LVH ($r$ = 0.73) and serum creatinine ($r$ = 0.68). Individual changes in ANP by zofenopril negatively correlated with pretreatment ANP ($r$ = –0.69), ECG score for LVH ($r$ = –0.44) and serum creatinine ($r$ = –0.41). No correlations were found between BP, heart rate or their changes by treatment and the effect of either agent on plasma ANP. Multiple linear regression showed that the change in ANP was explained by the therapeutic agent used, the pretreatment plasma level of ANP, and the ECG score for LVH ($F$ = 12.5, $P < 0.001$, $r^2$ = 0.56). We conclude that the effect of antihypertensives on plasma ANP is independent of their action on BP, but dependent on an interaction between the type of drug employed and those clinical characteristics of the patient that reflect pre-existing hypertensive target organ damage.**

**Keywords:** hypertension, humans; converting enzyme inhibitors; beta blockers; atrial natriuretic peptide; target organ damage

## Introduction

The effects of beta-blockers and angiotensin-converting enzyme (ACE) inhibitors on the circulating levels of plasma atrial natriuretic peptide (ANP) are highly variable. A frequent response to beta-blockers is an increase in plasma ANP, which has been observed in spontaneously hypertensive rats,[1] normal human volunteers,[2] and hypertensive patients.[3] It has been proposed that this effect of beta-blockers may play a role in mediating their antihypertensive action.[3,4] However, the ANP response to beta-blockade is far from consistent. There are many reports of unaltered plasma levels of ANP after use of beta-blockers in patients with heart disease,[5] hypertension,[6] renal replacement therapy[7] and cardiac transplantation.[8] An explanation for the presence or absence of a stimulatory effect of beta-blockers on plasma ANP is not readily apparent; both effects have been reported with the same drug,[2,8] with agents sharing the same pattern of cardioselectivity,[3,7] and in the same disease state.[3,6] Post-exercise ANP levels, before and after atenolol or carteolol, are predicted by pretreatment left ventricular function of hypertensives.[9] It is therefore conceivable that individual ANP responses to beta-blockers are determined by an interaction between these drugs and pre-existing clinical characteristics of the patients.

An approximately equal number of studies reporting effects of ACE inhibitors on plasma ANP have found either decreased or unchanged levels of the natriuretic peptide. They include observations in patients[10,11] or rats[12,13] with left ventricular dysfunction, humans[14,15] or rats[16,17] with hypertension, and normal subjects.[18,19] A few authors have described increased plasma ANP or ANP/pulmonary capillary wedge pressure ratios after ACE inhibition, both in hypertensive subjects and cardiac patients.[20,21] In those studies in which mean ANP levels are unmodified by ACE inhibitors, the variance of ANP is usually very large, reflecting responses of opposite direction (ie, increases and decreases) among the subjects studied.[19] The reason for these highly variable results is unknown, but there are observations suggesting that patients' characteristics may interact with or modulate the action of ACE inhibitors on synthesis or release of

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ANP. For example, post-exercise ANP levels of hypertensives given cilazapril depend on pretreatment left ventricular function,[22] the decrease in plasma ANP produced by ramipril in patients with congestive heart failure depends on the reductions in pulmonary and right atrial pressures,[23] and the changes in ANP by lisinopril in patients with ischaemic heart disease correlate with observed changes in renal function due to this agent.[24]

To investigate our hypothesis that ANP responses to antihypertensives depend on an interaction between the type of agent used and clinical characteristics of the patients, we randomized 34 essential hypertensive subjects to receive either the $\beta$1-selective beta-blocker atenolol, or the ACE inhibitor zofenopril. These patients had enough variability in their clinical characteristics to permit investigation of the possible clinical correlates of the ANP response to these antihypertensives.

## Patients and methods

Thirty-nine essential hypertensive patients were recruited for double-blind, randomized studies of the efficacy of atenolol and/or zofenopril as antihypertensive agents. The projects were approved by the Institutional Review Board of the Mount Sinai School of Medicine in New York, and informed consent was obtained from all patients. After an initial evaluation to exclude secondary forms of hypertension, all previous medications were discontinued and a 4-week run-in period on placebo was begun. Patients were advised to restrict their salt intake but no specific diet was given. Five patients did not meet the criteria for sustained hypertension (mean of three seated diastolic BPs >95 mm Hg on two consecutive visits), and were therefore discontinued from the study. At the end of the placebo phase, the remaining 34 patients had: (a) an electrocardiogram scored for left ventricular hypertrophy (LVH) by use of Estes' criteria; (b) routine blood and urine laboratory tests; (c) 24-h urine collection for measurement of sodium and creatinine excretion; (d) blood specimens for plasma renin activity (PRA) and plasma ANP; and (e) baseline blood pressure (BP) measurements.

Patients were then randomized to receive either atenolol 50–100 mg/day ($n$ = 9) or zofenopril 15–60 mg/day ($n$ = 25). The randomization was double-blind and designed to obtain approximately two patients on zofenopril for each one on atenolol. This decision was made due to the reported larger variability of ANP responses to ACE-inhibitors compared to beta-blockers (see Introduction). The dosages of both agents were titrated according to a pre-specified schedule with a goal diastolic BP (DBP) of 92 mm Hg or less. After 10 weeks on therapy, all studies described above were repeated, with the exception of the 24-h urine collection.

Blood samples for PRA and ANP were obtained between mid-morning and noon, after the patients had been at least 2 h in the upright position. Blood for PRA was collected in EDTA-containing, chilled tubes which were immediately centrifuged. Plasma was separated into plastic vials and kept frozen at –20°C until measurement. PRA was measured by radioimmunoassay of angiotensin I generation (2 h incubation at 37°C, pH 5.5) using a rabbit antibody raised in our laboratory. Blood samples for ANP were collected in chilled tubes containing EDTA, aprotinin and PMSF. They were processed in similar fashion and kept frozen until measurement. The radioimmunoassay has been previously described in detail.[25] In brief, acidified plasma (pH 4) was extracted with Sep-Pak C-18 cartridges (recovery 78%), eluted, freeze dried and resuspended in buffer at pH 7.4. The tracer, $^{125}$I-labeled human ANP, was prepared by the lactoperoxidase method and the antibody was purchased from Peninsula (Belmont, CA, USA). The lowest detectable concentration of ANP was 3 pg per tube. Displacement of 50% of the bound tracer was obtained with 28 pg. The coefficients of variation were: intra-assay 12.7% and interassay 6.7%.

BPs were measured with a mercury sphygmomanometer and the appropriate size cuff. All measurements were carried out by two of the authors (FE & CL), the same observer for each patient whenever possible. Korotkoff phase V was used as the DBP. Values reported are the average of three seated readings obtained after 10 min rest and separated by 2 min intervals.

Data are given as means ± s.e.m. (range) unless otherwise indicated. Paired and unpaired Student's $t$-tests, Pearson correlation analyses, single linear regression analyses and $\chi^2$ testing were carried out by use of a statistical package (SAS Institute Inc, Cary, NC, USA). For all these analyses, a probability value of $<0.05$ was used to reject the null hypothesis. The STEPWISE (FORWARD) and RSQUARE procedures of the general linear model in the SAS package were used for model fitting. Dummy variables were used to represent atenolol and zofenopril. In the STEPWISE FORWARD selection procedure, variables were entered in the model if the significance level for their F statistic was $<0.05$. In the RSQUARE procedure, the goodness of fit of the model was assessed with Mallows' Cp statistic[26] and Akaike's information criterion.[27]

## Results

Our study population consisted of 34 middle-aged subjects (57 ± 2 years, range 33–76) with a history of essential hypertension for 13 ± 1 (2–28) years. There were 25 Hispanic and 9 black patients; 88% were female. All subjects had been previously treated with a variety of antihypertensive agents. Creatinine clearance was 1.48 ± 0.08 (0.72–2.65) mL/s, retinopathy (Keith-Wagener grades I or II) was present in 91% and electrocardiographic evidence for LVH (Estes' score ⩾5) in 21%.

BP and heart rates, 4 weeks after discontinuation of treatment and maintenance on placebo, were 173 ± 4 (130–214)/103 ± 1 (95–110) mm Hg and 79 ± 2 (50–108) bpm, respectively. PRA was 0.19 ± 0.03 (0.00–0.94) ng$A_I$/L/s and the prevalence of low renin essential hypertension (by indexing PRA to urine sodium excretion according to Laragh *et al*[28]) was 58%. Plasma level of ANP at the end of the placebo

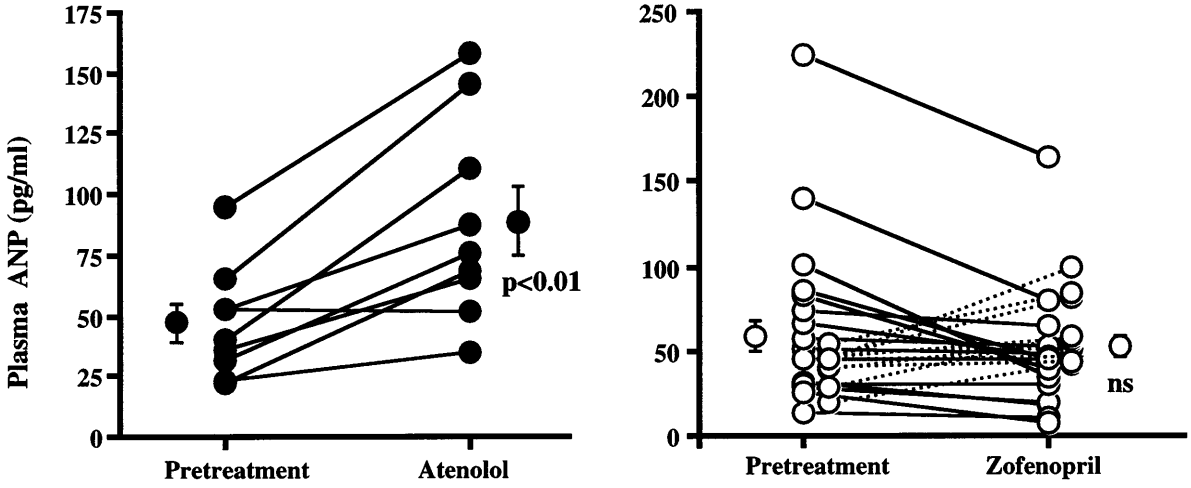


**Figure 1** Effects of atenolol and zofenopril on individual plasma levels of atrial natriuretic peptide (ANP) in 34 essential hypertensives. Each patient is represented by a pre- and post-treatment circle joined by a line. Data in zofenopril-treated patients (right panel) is presented with offset points to separate those subjects in whom there were increases *vs* decreases in circulating ANP. The means and standard errors for the groups are shown by the circles with bars. $P < 0.01$ and ns = not significant, are for the paired *t*-tests assessing the change in ANP by each treatment.

period was 56 ± 7 (14–224) pg/ml. This value was slightly but not significantly higher than that of 29 controls in our laboratory (41 ± 4, $P = 0.07$). The individual pretreatment levels of plasma ANP correlated with age (r = 0.44, $P < 0.01$), ECG score for LVH ($r = 0.51$, $P < 0.002$), and serum creatinine ($r = 0.67$, $P < 0.001$), and exhibited a negative correlation with creatinine clearance ($r = -0.39$, $P < 0.03$).

Atenolol increased plasma ANP in eight out of nine patients and did not change it in the ninth (Figure 1, left). Plasma concentration of ANP was 47 ± 8 pg/ml before, and 89 ± 14 after atenolol. The average increase for the group, 42 ± 9, was significant ($P < 0.002$). In contrast with this observation, plasma ANP levels before, 59 ± 9, and after treatment with zofenopril, 53 ± 6, were not significantly different (Δ = −6 ± 6 pg/ml, Figure 1, right). This occurred as a result of 15 patients exhibiting a decrease and 10 patients sustaining an increase in ANP due to zofenopril. To make apparent the existence of these two subgroups, data of zofenopril patients are plotted with offset points in the Figure.

The different effects of atenolol and zofenopril on ANP, and the opposite effects of zofenopril on the subgroups of patients who exhibited increases and decreases of ANP due to this agent, were not due to unwanted differences in patients' characteristics introduced by the randomization. This was assessed by $\chi^2$ or unpaired *t*-tests for comparisons between all atenolol and all zofenopril patients, and by $\chi^2$ tests or one-way analyses of variance for comparisons between the atenolol group and the zofenopril subgroups with increases and decreases in plasma ANP. These analyses failed to detect significant differences in age, duration of hypertension, gender or ethnic distribution, pretreatment body mass index, BP, heart rate, ECG score for LVH, serum creatinine, creatinine clearance, PRA, or ANP among the groups.

BP was reduced by atenolol from 170 ± 9/103 ± 2 mm Hg to 170 ± 8/96 ± 3 and by zofenopril from 174 ± 5/103 ± 1 to 160 ± 6/97 ± 2 mm Hg. Figure 2 (left) shows that all BP reductions were statistically significant with the exception of systolic BP (SBP) in the atenolol patients (perhaps due to titration of dosage to DBP or to high prevalence of low-renin hypertension). There was no significant difference in the magnitude of BP reduction in patients with an increase against those with a decrease in plasma ANP by zofenopril (Figure 2, right). Moreover, there were no correlations between changes in plasma ANP and changes in BP (systolic, diastolic or mean) in either the atenolol or the zofenopril groups.

Heart rates before and after atenolol were 76 ± 5 bpm and 60 ± 4 (Δ = −16 ± 4, $P < 0.01$). The respective values for zofenopril were 81 ± 3 and 82 ± 2 (Δ = +1 ± 2, ns). Changes in heart rate did not differ between patients who sustained increases *vs* decreases in plasma ANP by zofenopril; +3 ± 2 *vs* −

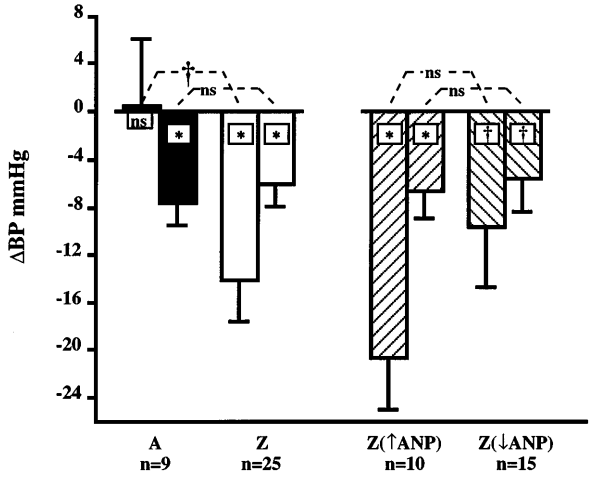


**Figure 2** Changes in blood pressure (ΔBP) represented by pairs of equally-shaded bars (systolic, diastolic). Results in atenolol (A) *vs* zofenopril (Z) treated patients are on the left, while those in zofenopril-treated patients with increases (↑) *vs* decreases (↓) in plasma atrial natriuretic peptide (ANP) are shown on the right. Symbols within bars are for the significance of ΔBP in each group. Symbols outside the bars are for unpaired comparisons between the groups as indicated. ns = not significant, $*P < 0.01$, $\dagger P < 0.05$.

1 ± 2 bpm, respectively. In addition, changes in plasma ANP did not correlate with changes in heart rate in either the atenolol or the zofenopril groups.

Figure 3 depicts the relationships between changes in plasma ANP produced by atenolol and zofenopril and pretreatment ECG score for LVH (left) and serum creatinine (right). It is apparent from the Figure that these statistically significant correlations exhibit slopes of opposite sign for atenolol and zofenopril. The changes in ANP produced by atenolol were positively correlated with ECG score for LVH ($r = 0.73$, $P < 0.03$) and serum creatinine ($r = 0.68$, $P < 0.05$), while those produced by zofenopril were negatively correlated with the same pretreatment variables ($r = -0.44$, $P < 0.05$ and $r = -0.41$, $P < 0.05$, respectively). Not shown in the Figure is a significant positive correlation between increases in plasma ANP produced by atenolol and the duration of hypertension ($r = 0.74$, $P < 0.03$).

Finally, a negative correlation was found between the change in ANP produced by zofenopril and the pretreatment plasma levels of this peptide ($r = -0.69$, $P < 0.001$, not shown). Because this correlation involves interrelated variables, its validity was confirmed by use of their orthogonal polynomials.[29] The linear regression, ΔANP due to zofenopril = 22 – [0.5 × Pretreatment ANP], predicts that zofenopril will reduce ANP of hypertensives with pretreatment plasma ANP ⩾45 pg/ml.

Atenolol did not change PRA (0.22 ± 0.08 $ngA_I/L/s$, before and after treatment), probably due to inability to detect inhibition of very low baseline PRA in five patients, while zofenopril increased PRA from 0.17 ± 0.06 to 0.42 ± 0.11 (ΔPRA = +0.25 ± 0.11, $P < 0.02$). When the data for all atenolol and zofenopril patients were combined, the changes in ANP and PRA by these agents were negatively correlated ($r = -0.47$, $P < 0.01$) but this observation was not sustained for the atenolol and zofenopril groups analyzed separately. Moreover, neither PRA before treatment nor the renin status of the patients (normal *vs* low), predicted the response of ANP to drug therapy.

Multiple linear regression showed that 56% of the variability of the change in ANP produced by treatment was explained by: (1) the therapeutic agent (dummy variables for atenolol = 0 and zofenopril = 1); (2) the pretreatment plasma concentration of ANP; and (3) the ECG score for LVH. The model was ΔANP = 59.2 – [42.2 × Drug] – [0.5 × ANP] + [2.3 × ECG score], F = 12.5, $P < 0.001$. Serum creatinine, creatinine clearance and the dosages of atenolol and zofenopril did not contribute to the explanatory power of this model.

## Discussion

Changes in plasma ANP during antihypertensive therapy cannot be explained by BP reduction, because they vary depending on the pharmacologic agent employed. This is not surprising, in view of the fact that there is no relationship between the degree of BP elevation and plasma ANP in untreated mild hypertensives.[30,31] Plasma ANP is only consistently elevated in patients with severe hypertension, probably reflecting established target organ damage.[32] Consistent with these observations, in our patients there was no correlation between plasma ANP and pre- or post-treatment BPs. Also, changes in ANP by atenolol and zofenopril were different, despite similar reductions of BP by both agents.

The available families of antihypertensive medications have distinct pharmacologic properties and reduce BP via different mechanisms of action; it would be reasonable to expect, therefore, that their actions on plasma ANP are family-specific. However, multiple observations in hypertensive patients have established that this is not the case; diuretics,[33] beta-blockers,[2,6] ACE inhibitors[18–21] and calcium channel blockers,[34,35] have each been reported to increase, decrease or not modify plasma ANP. These results could be explained on the basis of differ-

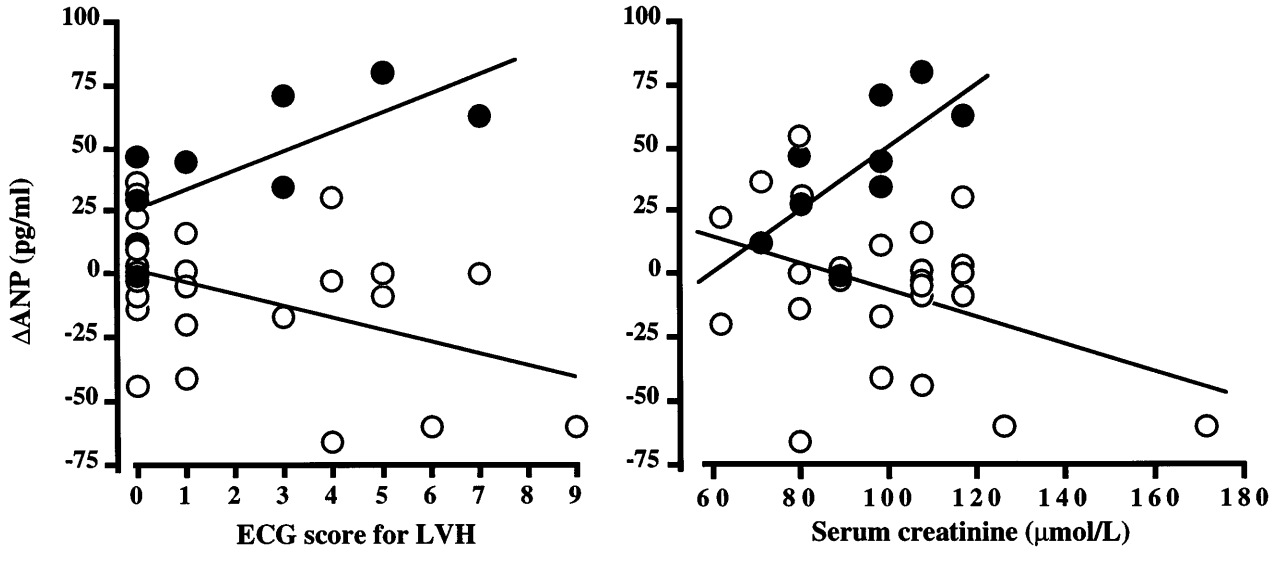


**Figure 3** Correlations between the changes in circulating atrial natriuretic peptide (ΔANP) induced by atenolol (●) and zofenopril (○) and the pretreatment Estes' electrocardiographic score for left ventricular hypertrophy (LVH, left panel) and serum creatinine (right panel). The Pearson coefficients and statistical significance for these four relationships are given in the text.

ences in the pharmacologic profiles of individual agents within the same family. However, this possibility has also been disproved by reports in which the same drug produces different effects on plasma ANP. For example, hydrochlorothiazide and the dihydropyridine calcium channel blocker nifedipine have been shown to increase or decrease circulating ANP.[33–35]

Because pharmacologic properties alone cannot account for the effect of antihypertensives on plasma ANP, we hypothesized that patient-related factors play a role in this response. Release of ANP reflects increased atrial stretch[36,37] in essential hypertensives. The latter may be caused by impaired relaxation associated with LVH, diastolic left ventricular dysfunction in the absence of LVH,[38] systemic volume overload (eg, renal insufficiency[39]) or increased venous return in patients with normal systolic and diastolic left ventricular function.[36] Results of laboratory tests routinely used to assess the presence of either cardiac (eg, CXR and ECG) or renal (eg, creatinine clearance) abnormalities have been previously shown to correlate with plasma ANP of essential hypertensives.[40,41] In the present study, pretreatment plasma ANP was positively correlated to age, ECG score for LVH and serum creatinine and negatively correlated to creatinine clearance. These observations confirm that routine laboratory tests are sensitive enough to detect hypertensive target organ damage linked to augmented release of ANP from the atria. Therefore, we used these tests to investigate possible patient-related determinants of the response of ANP to the administration of atenolol and zofenopril.

Atenolol doubled plasma ANP in our patients. This is consistent with the majority of studies on the effects of beta-blockers on plasma ANP.[1–3] Because noradrenaline infusion[42] and shortening of diastole by tachycardia[43] stimulate release of ANP, blockade of adrenergic beta-receptors or reduction of heart rate by atenolol cannot explain our results. The increase in ANP by atenolol was present in all patients but one. The longer the duration of hypertension, the higher the ECG score for LVH and the higher the serum creatinine, the larger was the magnitude of this increase. These data suggest that the negative inotropic action of atenolol results in increased atrial stretch despite BP reduction, and that the magnitude of this effect depends on the degree of pre-existing target organ damage in individual hypertensive patients. If such were the case, increased plasma ANP by beta-blockers would not be a primary mediator of their antihypertensive action[3,4] but only a compensatory response to increased atrial stretch by these agents. Decreases of plasma ANP by atenolol and other beta-blockers, reported in a few patients,[40,42] may be explained if these agents improved severely impaired diastolic relaxation or controlled severe hypertension. Improvement in atrial function by these effects may have overcome the untoward atrial consequences of negative inotropism by beta-blockers. These explanations are speculative and require direct echocardiographic or haemodynamic study for confirmation.

Angiotensin II stimulates gene expression of ANP in the rat.[44] Also, infusion of angiotensin II, at pressor[42] or subpressor[45] doses, increases plasma ANP in humans and dogs, respectively. If these direct actions of angiotensin II on ANP were the major determinants of the effect of ACE inhibitors, the latter should consistently reduce circulating levels of ANP. Neither previous studies,[11,13,15,19] nor our data with zofenopril support this contention. Only 60% of our patients experienced a reduction of ANP by zofenopril, the remainder sustaining the opposite effect.

In congestive heart failure, abnormally high levels of ANP due to increased atrial pressures are diminished by afterload reduction with ACE inhibitors.[10,12,17] In chronic renal insufficiency, abnormally high levels of ANP due to volume overload are also decreased by ACE inhibitors; in this case probably via increases in renal blood flow and blunting of aldosterone release, leading to enhanced natriuresis and decreased atrial stretch.[39] Our hypertensive patients as a group did not exhibit a significant change in ANP by zofenopril. However, there were relationships between individual changes in ANP and clinical markers of cardiac and renal involvement. The higher the ECG score for LVH or serum creatinine, the more the reduction in ANP by zofenopril. These observations suggest that in patients with pre-existing hypertensive target organ damage, the haemodynamic actions of zofenopril result in decreased atrial stretch concomitant with BP reduction. The observation that the higher the pretreatment level of ANP, the larger its reduction by zofenopril, is also consistent with this view, because pretreatment ANP of our patients correlated with cardiac and renal markers of hypertensive target organ damage. It is noteworthy that the latter relationship predicted a decrease in ANP by zofenopril in patients with pretreatment ANP $\geqslant$45 pg/ml, a value almost identical to mean plasma ANP in our normotensive controls.

A different explanation is required for the stimulation of ANP by ACE inhibitors in a subgroup of our patients. It is possible that in hypertensive patients with normal plasma ANP and no cardiac or renal involvement, the predominant effect of ACE inhibitors on ANP is the blunting of its natriuretic action, analogous to what is observed in normal humans.[46] Mild sodium retention may thus lead to subtle atrial stretch and compensatory release of ANP. Whether this accounted for increased plasma ANP in some of our patients cannot be ascertained in the present study.

We conclude that an interaction between the pharmacological properties of the therapeutic agent and the degree of pre-existing target organ damage of individual hypertensive patients determines the effects of treatment on plasma ANP. The multivariate model in our patients supports this view, and accounts for more than half the variability of the change in ANP due to treatment with atenolol or zofenopril. It is therefore possible that the explanation for the conflicting results of multiple studies on the actions of antihypertensive agents on plasma ANP can be found in the different clinical characteristics of the recruited patient samples.

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