β Adrenergic blockers lower renin in patients treated with ACE inhibitors and diuretics

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Abstract

***Objective*—To examine the effect of concomitant intake of β blockers with angiotensin converting enzyme (ACE) inhibitors, diuretics, or both on plasma renin concentrations in a population based sample (MONICA survey, Augsburg, Germany).**

***Subject and methods*—728 individuals were studied, of whom 171 were treated using monotherapy (ACE inhibitor (n = 21), diuretic (n = 10), or β blocker (n = 72)), or combination treatment (ACE inhibitor + diuretic (n = 32), ACE inhibitor + β blocker (n = 7), diuretic + β blocker (n = 22), ACE inhibitor + diuretic + β blocker (n = 7)). The remaining 557 individuals were untreated. Indications for treatment were hypertension (75%), coronary artery disease with (12%) or without (3%) hypertension, or unknown (10%).**

***Results*—Mean (SEM) renin concentrations in individuals treated with an ACE inhibitor (41 (8) mU/l), a diuretic (41 (10) mU/l), or the combination of an ACE inhibitor and a diuretic (54 (10) mU/l) were raised compared with untreated individuals (17 (1) mU/l; $p < 0.05$ each). Monotherapy with a β blocker, however, decreased mean renin concentrations (12 (1) mU/l; $p < 0.01$ *v* untreated). Renin concentrations in individuals taking a β blocker with either an ACE inhibitor (21 (8) mU/l), or a diuretic (22 (4) mU/l), or with both an ACE inhibitor and a diuretic (21 (7) mU/L), were significantly lower compared with renin concentrations in groups not receiving β blocker treatment ($p < 0.05$ each).**

***Conclusion*—These data suggest that the upregulation of renin by treatment with ACE inhibitors, diuretics, or both can be largely prevented by concomitant β blocker treatment.**

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Keywords: adrenergic β receptor blocker; angiotensin converting enzyme inhibitor; renin; hypertension

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The use of angiotensin converting enzyme (ACE) inhibitors and diuretics is of established value for prognostic or symptomatic treatment of hypertension or heart failure. In addition to their effects on volume homeostasis, preload, and afterload, both drugs interact with the renin-angiotensin system in a complex fashion. Diuretics are known to stimulate renin secretion indirectly via negative sodium balance, decreased blood pressure, and reflex stimulation of the sympathetic nervous system.[1] ACE inhibitors inhibit the renin-angiotensin system via blockade of the conversion of angiotensin I into angiotensin II, the effector peptide of the system. At the same time, secondary to the removal of negative feedback inhibition, renin secretion is stimulated by ACE inhibitors.[2] Thus, patients treated with ACE inhibitors, diuretics or both are characterised by high renin and angiotensin I concentrations.[2] As long as the inhibition of ACE is complete, angiotensin II concentrations should remain suppressed. It has been shown, however, that angiotensin II (and aldosterone) may return to pretreatment concentrations in patients treated chronically with ACE inhibitors, suggesting a functional escape from effective ACE inhibition.[3] Indeed, recent data show that combined angiotensin II receptor blockade and chronic ACE inhibitor treatment may result in enhanced effects on blood pressure as well as feedback controlled renin release.[4]

β Receptor blockade, on the other hand, is known to inhibit renin expression and secretion.[5] Recent studies demonstrate possible beneficial clinical effects of β blockers when administered in combination with ACE inhibitors and diuretics in patients with heart failure.[6–8] The underlying mechanisms are incompletely understood. In addition to a number of cardiac effects, the suppression of sympathetic activity by β blockade may affect renin release in individuals receiving ACE inhibitors and diuretics.

It is not known whether the adaption of the renin system to different treatment modalities has an effect in patients receiving these drugs in various combinations as prescribed by their general practitioners. We therefore studied the implications of monotherapy or combined treatment on circulating renin levels in a population based sample.

Methods

STUDY POPULATION

In 1994, the subjects of this study participated in a second follow up examination of the 1984–85 MONICA (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) general population survey in the study region of Augsburg, Germany.[9 10] Subjects responded to a standardised questionnaire including cardiovascular history and medication. The information on current medication was verified by inspection of prescription forms or packages. This population based sample included untreated individuals as well as individuals receiving treatment with an ACE inhibitor, a diuretic, or a β blocker,

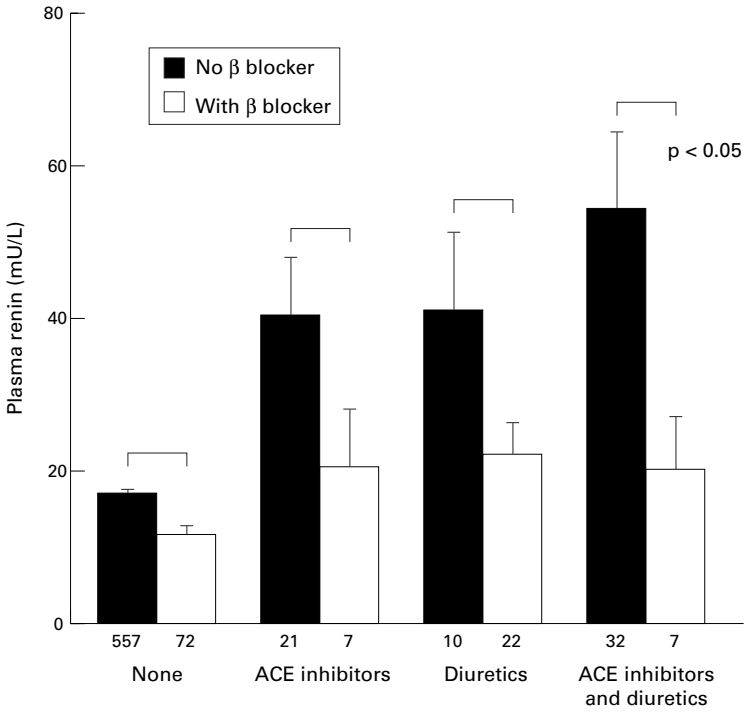

Figure 1 Mean (SEM) renin concentrations in subjects on no medication or on chronic treatment with ACE inhibitors, diuretics, or both (closed bars), and concentrations in subjects receiving β blocker monotherapy or β blocker with an ACE inhibitor, a diuretic, or both (open bars). Numbers indicate individuals receiving the respective treatments.

or any combination of these agents. Some forms of monotherapy or antihypertensive combination treatments were infrequent in this population based sample. We therefore also included 56 subjects of the 1995 MONICA survey that was carried out according to the same protocol. The predominant indication for treatment with β blockers, ACE inhibitors, and diuretics (alone or in combination) was hypertension (75%) followed by coronary heart disease with (12%) or without (3%) hypertension. Ten per cent of the participants were unable to provide the indication for medication and were not aware of any history of hypertension or coronary heart disease. This relation was similar in all groups studied. Patients with congestive heart failure were not included in this study. Biometric (body weight, height), haemodynamic (blood pressure and heart rate), and echocardiographic assessment (fractional shortening) of participants followed a uniform protocol.[9]

Table 1 Demographic and haemodynamic data

	No medication	*ACE inhibitor*	*Diuretic*	*ACE inhibitor+ diuretic*
Sex (male/female)				
Without β blocker	264/293	12/9	3/7	12/20
With β blocker	30/42	2/5	9/13	5/2
Age (years)				
Without β blocker	57.0 (0.2)	60.8 (1.9)	59.7 (2.5)	61.7 (1.3)
With β blocker	58.7 (0.7)*	55.7 (2.4)*	60.3 (1.4)	63.5 (2.6)
Indication for treatment (HTN/CAD)				
Without β blocker		18/0	10/2	30/4
With β blocker	62/15	7/0	20/2	7/0
Systolic blood pressure (mm Hg)				
Without β blocker	146 (1)	157 (5)†	151 (8)	154 (3.7)†
With β blocker	147 (2)	154 (5)	153 (5)	148 (7)
Heart rate (beats/min)				
Without β blocker	71 (0.5)	69 (2.4)	80 (3)	74 (2)
With β blocker	67 (2)*	67 (4)	66 (2)*	70 (3)
Fractional shortening (%)				
Without β blocker	36.3 (0.3)	34.5 (1.9)	33.0 (3.3)	35.7 (1.8)
With β blocker	36.5 (0.9)	33.7 (3.1)	38.6 (2.3)	36.3 (2.6)

Absolute numbers are given for men and women, and indication for treatment. Means (SEM) are given for other demographic and haemodynamic parameters.
*$p < 0.05$ *v* respective treatment group without β blocker; †$p < 0.05$ *v* no medication.
HTN, arterial hypertension; CAD, coronary artery disease.

DETERMINATION OF RENIN

Blood was drawn from non-fasting subjects who were in a supine resting position for at least 30 minutes. Determinations were carried out in duplicate using an immunoradiometric assay (Nichols Institute, Wychen, the Netherlands), as proposed by Derkx *et al.*[11]

STATISTICS

Data are presented as mean (SEM). The distribution of renin concentrations was slightly skewed to the right. Thus, the non-parametric Mann-Whitney U test was used for statistical comparisons between the untreated group and groups taking ACE inhibitors, diuretics or the combination of ACE inhibitors and diuretics, as well as respective groups that, in addition, received β blockers (Stat View SE+Graphics 1.03). To test further whether β blockers have an independent effect on renin concentrations in patients taking ACE inhibitors, diuretics, or both, a multivariate analysis was performed (Super ANOVA 1.11); all untreated subjects or those on β blocker monotherapy were excluded. Covariates included age, sex, systolic blood pressure, history of myocardial infarction, fractional shortening, and β blocker treatment—that is, factors that may affect plasma renin concentrations. Significance was accepted at $p < 0.05$.

Results

STUDY POPULATION

The study population comprised 728 middle aged men and women (table 1). Chronic monotherapy with an ACE inhibitor, a diuretic, or a β blocker was received by 21, 10, and 72 individuals, respectively. The combination of an ACE inhibitor and a diuretic was used in 32 individuals. A β blocker was used in conjunction with an ACE inhibitor, a diuretic, or both in 7, 22, and 7 individuals, respectively. Most frequently used β blockers were metoprolol (34%), bisoprolol (23%), and atenolol (20%) with a mean (SEM) dose of 42 (3)% of the recommended maximal dose. The dosages of ACE inhibitors and diuretics were similar in patients with and without concomitant β blockade and vice versa (data not shown). The remaining 557 individuals were not treated medically for hypertension or coronary heart disease.

PLASMA RENIN

Chronic intake of an ACE inhibitor, a diuretic, or both was associated with increased renin concentrations when compared with untreated individuals (fig 1; $p < 0.05$ each *v* untreated). In contrast, β blocker monotherapy was associated with decreased renin concentrations when compared with untreated individuals ($p < 0.01$). Patients taking a combination of a β blocker and an ACE inhibitor or a diuretic had significantly lower renin concentrations

Table 2 Multivariate analysis of covariates determining plasma renin in individuals treated with an ACE inhibitor and/or a diuretic

	β coefficent	*p value*
Sex (male *v* female)	+5.53	0.43
Age (per year)	+0.47	0.33
Systolic blood pressure (per mm Hg)	−0.39	0.02
Fractional shortening (per %)	+0.47	0.23
Myocardial infarction (yes *v* no)	+5.9	0.74
β Blocker (yes *v* no)	−20.23	0.007

Only subjects treated with ACE inhibitors, diuretics, or the combination of both were included. The addition of a β blocker was related to a substantial decrease of renin that was independent of all covariates tested.

than respective patient groups not taking a β blocker (fig 1; $p < 0.05$ each). The same effect was shown in individuals receiving a β blocker in conjunction with both an ACE inhibitor and a diuretic ($p < 0.05$).

We were unable to identify any haemodynamic or anthropometric parameters that might explain the profound association of lower renin concentrations with the use of β blockers in subjects taking an ACE inhibitor, a diuretic, or both (table 1). Notably, monotherapy with diuretics was found to be associated with an accelerated heart rate, an effect that was not observed in those receiving concomitant β blockers. The multivariate analysis performed on the individuals receiving an ACE inhibitor, a diuretic, or both revealed that β blocker treatment was a highly significant predictor of lower plasma renin concentrations despite the use of agents that stimulate renin release (table 2).

Discussion

The data corroborate the well documented suppression of plasma renin activity by β blockers in otherwise untreated individuals.[5] Furthermore, this observational study suggests that β blockers prevent the reactive increase of renin concentrations in individuals who are concomitantly treated with ACE inhibitors or diuretics, a notion that has initially been proposed by a few small intervention studies.[12–15] Finally, the data suggest that β blockers are sufficient to prevent completely the threefold renin induction observed in patients who receive the combination of ACE inhibitors and diuretics.

Our study does not elucidate the mechanism that enables β blockers to decrease plasma renin concentrations in patients receiving diuretics and ACE inhibitors. Experimental and molecular biological studies, however, have clearly documented the central role of the sympathetic nervous system in the regulation of renin expression and secretion, making such interaction very plausible.[16 17] Our observations extend these studies, suggesting that in man both the negative feedback loop (that is activated by low angiotensin II concentrations) as well as the salt sensitive renin regulation (that is activated by low sodium chloride at the macula densa) are modulated by the sympathetic nervous system.

The clinical implications of this apparent pharmacodynamic interaction of β blockers with ACE inhibitors, diuretics, or both remain to be demonstrated. However, there is substantial evidence suggesting that in the presence of counter regulatory renin and ACE induction[2–4 18] chronic ACE inhibition fails to block the renin-angiotensin system completely.[19] It may be speculated, therefore, that the profound β blocker associated renin suppression is of functional significance. In this regard, recent reports indicate that addition of β blockers to conventional treatment with ACE inhibitors and diuretics may improve survival and left ventricular ejection fraction, as well as reduce the need for hospitalisation and transplantation in patients with heart failure.[6–8] Reduction of the raised sympathetic activity is certainly one of the mechanisms mediating these benefits in patients with heart failure. This mechanism may also contribute to the apparent favourable effects of β blocker treatment in hypertension.[20 21] However, our study points to the well documented but complex interaction of various neurohormonal systems that might also confer some of the clinical effects seen when β blockers are used in conjunction with ACE inhibitors and diuretics.

A limitation of the present study is that the composition of respective medication groups is potentially confounded by treatment indications. However, we were unable to identify any significant differences of anthropometric parameters, indications for medical treatment, or respective dosages between groups with and without β blockers. Furthermore, a multivariate analysis carried out on patients who received ACE inhibitors, diuretics, or both identified β blocker treatment as an independent predictor of suppressed renin activity. Our analysis does not exclude patients with low renin hypertension. These patients more often require more than one antihypertensive drug and, therefore, may be overrepresented in groups with combination treatment; however, groups with and without β blocker treatment should be equally affected. Future trials should test the present findings prospectively and define the functional implications of renin suppression by β blockers in patients receiving these drugs in combination with ACE inhibitors and diuretics.

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