Enhanced Pressor Responsiveness to Norepinephrine in Type II Diabetes

Effect of ACE inhibition

ADOLFO CIAVARELLA, MD
ANNA MUSTACCHIO, MD
CRISTINA RICCI, MD
MAURIZIO CAPELLI, MD
PIETRO VANNINI, MD

OBJECTIVE — To evaluate the effect of angiotensin-converting enzyme (ACE) inhibition on the pressor responsiveness to norepinephrine in type II diabetes.

RESEARCH DESIGN AND METHODS — Eight normotensive subjects, eight mild-to-moderate hypertensive type II diabetic patients, and eight nondiabetic patients with essential hypertension were studied before and after 4 weeks of being administered enalapril. The pressor response to norepinephrine was assessed by infusing the hormone in an antecubital vein at incremental doses of 30 ng · kg^{-1} · min^{-1} for periods of 5 min until reaching an increase of 20 ± 2 mmHg in mean arterial pressure (MAP) measured by an automatic device at 1-min intervals. An effective dosage of norepinephrine that increased MAP by 20 mmHg (EDNE 20) was thereafter calculated. Before and during the last minute of norepinephrine infusion at maximum dosage, a venous blood sample was drawn to determine plasma renin activity (PRA), aldosterone, and norepinephrine levels.

RESULTS — In the three groups of patients, blood pressure and aldosterone were reduced while PRA was raised following ACE inhibition. Basal and maximum post-infusion levels of norepinephrine were not modified by enalapril. The EDNE 20 was basally lower in diabetic patients and remained unchanged after ACE inhibition, contrary to that observed in nondiabetic patients with essential hypertension.

CONCLUSIONS — Both normotensive and hypertensive type II diabetic patients have an increased pressor responsiveness to norepinephrine that is not modified by therapeutic doses of enalapril, contrary to what is observed in nondiabetic patients with essential hypertension.

From the Department of Metabolic Diseases (A.C., A.M., P.V.), the Department of Clinical Pharmacology (C.R.), and the Department of Clinical Pathology (M.C.), St. Orsola University Hospital, Bologna, Italy.

Address correspondence and reprint requests to Adolfo Ciavarella, MD, Servizio di Malattie del Ricambio e Diabetologia, Policlinico S. Orsola via Massarenti 9, 40138 Bologna, Italy.

Received for publication 16 December 1993 and accepted in revised form 26 May 1994.

ACE, angiotensin-converting enzyme; BMI, body mass index; UAE, urinary albumin excretion; HPLC, high-performance liquid chromatography; MAP, mean arterial pressure; EDNE 20, effective dose of norepinephrine increasing mean blood pressure by 20 mmHg; PRA, plasma renin activity.

Increased vascular sensitivity to agonists, such as norepinephrine or angiotensin II, has been found in both type I and type II hypertensive diabetic patients (1–4), but it may already occur at the normotensive stage of diabetes (5). The hyperresponsiveness to the pressor effect of norepinephrine is thought to be a consequence of Na^+ retention (6) or an expression of morphological or functional alteration in resistance vessels that is already present in the early, uncomplicated stage of diabetes (7–9). Altered cation metabolism in the smooth muscle cells is also thought to play a key role in this exaggerated vasoconstrictive response in diabetes (2,10–12).

Angiotensin-converting enzyme (ACE) inhibition reduces the pressor response to norepinephrine in hypertensive nondiabetic patients (13–15); however, this effect had not yet been thoroughly studied in patients with diabetes. Our purpose was to evaluate the effect of the ACE inhibitor enalapril on the pressor responsiveness to norepinephrine in normotensive and hypertensive type II diabetic patients compared with nondiabetic patients with essential hypertension.

RESEARCH DESIGN AND METHODS

— Eight normotensive (two men and six women; age range 42–62 years; body mass index [BMI] 26.8 ± 0.8 kg/m^2) and eight mild-to-moderate hypertensive (three men and five women; age range 44–60 years; BMI 27.2 ± 1.1 kg/m^2; supine diastolic blood pressure 90–110 mmHg) type II diabetic patients (National Diabetes Data group criteria) (16) were studied. Eight nondiabetic patients with mild-to-moderate uncomplicated essential hypertension (three men and five women; age range 35–65 years; BMI 27.0 ± 0.9 kg/m^2) were also recruited for the study as a comparison group. The diabetic patients were randomly selected from the diabetes outpatient clinic, and nondiabetic hypertensive patients were randomly selected from the Department of Clinical Pharmacology,

Table 1—Humoral and hemodynamic changes before and after enalapril administration in the three groups of patients

	Diabetic patients				Nondiabetic patients	
	Normotensive (n = 8)		Hypertensive (n = 8)		Hypertensive (n = 8)	
	Before	After	Before	After	Before	After
HbA_{1c} (%)	7.6 ± 0.25	7.5 ± 0.25	7.8 ± 0.28	7.8 ± 0.25	4.2 ± 0.28	4.2 ± 0.25
Serum creatinine (mg/dl)	0.8 ± 0.07	0.8 ± 0.11	0.9 ± 0.07	0.9 ± 0.07	0.9 ± 0.07	0.9 ± 0.11
Plasma sodium (mmol/l)	138 ± 0.9	137 ± 0.8	139 ± 0.9	138 ± 0.8	139 ± 0.7	139 ± 0.9
Plasma potassium (mmol/l)	4.10 ± 0.10	4.30 ± 0.13	4.08 ± 0.12	4.20 ± 0.11	4.13 ± 0.09	4.20 ± 0.13
Urinary sodium (mmol/24 h)	153 ± 29	161 ± 23	147 ± 23	153 ± 27	145 ± 18	149 ± 24
Urinary potassium (mmol/24 h)	63 ± 11	61 ± 13	64 ± 9	61 ± 12	64 ± 7	66 ± 9
Mean blood pressure (mmHg)	93 ± 2.4*	84 ± 2.8*†	104 ± 3.2	96 ± 3.4†	101 ± 4.4	92 ± 3.5†
PRA ($ng \cdot ml^{-1} \cdot h^{-1}$)	0.6 ± 0.22	7.1 ± 2.57†	0.5 ± 0.2	2.5 ± 1.1†	0.7 ± 0.26	2.4 ± 1.32†
Aldosterone (pmol/l)	158.1 ± 41.6	124.8 ± 24.9†	149.8 ± 30.5	144.2 ± 27.7	249.7 ± 33.3	163.7 ± 22.2†
EDNE 20	96 ± 12	97 ± 8	93 ± 13	96 ± 15	129 ± 15*	156 ± 18*†
Norepinephrine (nmol/l)						
Basal	2.48 ± 0.27	2.25 ± 0.32	2.21 ± 0.24	2.38 ± 0.21	2.64 ± 0.34	2.43 ± 0.37
Postinfusion	6.86 ± 0.48	7.11 ± 0.41	6.17 ± 0.44	6.81 ± 0.53	7.91 ± 0.57*	9.35 ± 0.63*

Data are means ± SE. *$P < 0.05$ vs. corresponding value of other patient groups. †$P < 0.05$ vs. corresponding basal value.

where they were receiving treatment for hypertension. By inclusion criteria, no patients had evidence of renal impairment, atherosclerotic coronary, cerebral, or peripheral vascular disease, or neuropathy as evidenced by normality of serum creatinine, ECG, ultrasonic Doppler measurement, big toe thermal, and vibratory perception threshold and of autonomic function tests. All diabetic patients had mild background retinopathy (microaneurysms or dot hemorrhages) at fluorangiography and urinary albumin excretion (UAE) <300 mg/24 h (Albumine-RIA, Pharmacia, Uppsala, Sweden). Metabolic control (HbA_{1c} levels of 7.7 ± 0.8% analyzed by high-performance liquid chromatography [HPLC], Bio-Rad, Richmond, CA) was maintained with sulfonylureas (5 patients) or with sulfonylureas plus metformin (11 patients), except for one hypertensive patient who also required insulin treatment. Before the start and at the end of the study, after at least 30 days of washout from previous antihypertensive drugs (ACE inhibitors, calcium antagonists, or α_1-receptor blockers), blood pressure, metabolic control (fasting blood glucose, HbA_{1c}, and fructosamine), renal function (4-h timed UAE, creatinine clearance), and plasma and urinary Na and K were evaluated in all patients. Enalapril was then given at an initial dosage of 10 mg daily, doubled after 10 days, and continued for a further 4 weeks. The pressor response to norepinephrine was assessed before the study and 6 h after the last intake of enalapril by infusing norepinephrine in an antecubital vein at incremental doses of 30 $ng \cdot kg^{-1} \cdot min^{-1}$ for periods of 5 min until an increase was reached of 20 ± 2 mmHg in mean arterial pressure (MAP), measured by an automatic device at 1-min intervals (Dynamap 845, Critikon, Tampa Bay, FL). An effective dosage of norepinephrine that increased MAP by 20 mmHg (EDNE 20) was thereafter evaluated. Immediately before infusion, a venous blood sample was obtained to determine plasma renin activity (PRA), plasma aldosterone, and norepinephrine levels. An additional blood sample was obtained during the last minute of norepinephrine infusion at maximum dosage to measure the level that the pressor hormone had reached. Plasma aliquots were kept frozen until assay, which was performed within 1 month. PRA and aldosterone levels were determined by radioimmunoassay (Renkit & Aldokit, Sorin, Saluggia, Italy). Plasma norepinephrine levels were measured by HPLC with the electrochemical method (17). Paired Student's t test and analysis of variance were used for statistical analysis, as appropriate. Data are shown as means ± SE, and the level of statistical significance was taken as $P < 0.05$. Informed consent was obtained from all patients.

RESULTS— All patients concluded the study at maximum dosage of enalapril without side effects. Results are reported in Table 1. Blood pressure was significantly reduced in the three groups of patients. PRA and aldosterone levels, which were in the normal ranges before therapy, were uniformly modified by the ACE inhibitor, with rises in PRA and falls in aldosterone. Basal levels of norepinephrine were similar in the three groups of patients and were not modified by treatment. The maximum postinfusion levels of norepinephrine were significantly lower in diabetic patients compared with nondiabetic patients, and, in all groups,

they were not modified by enalapril. The EDNE 20 before treatment was significantly lower in both groups of diabetic patients. After ACE inhibition, it increased only in patients with essential hypertension and remained unchanged in diabetic patients. Metabolic data, BMI, electrolyte balance, and UAE were not modified after enalapril.

CONCLUSIONS — This study confirms that type II diabetic patients, apart from the presence or absence of hypertension, have an increased pressor responsiveness to norepinephrine infusion when compared with hypertensive nondiabetic patients. The results of this study indicate, above all, that a prolonged administration of therapeutic dosage of enalapril does not modify the pressor responsiveness to norepinephrine in diabetic patients, contrary to what occurs in patients with essential hypertension.

On the basis of our measured parameters, we can only offer a hypothesis for this divergent effect. In nondiabetic patients, it has been shown that subpressor doses of exogenous angiotensin II enhance (18) or restore to normal the pressor responsiveness previously depressed by ACE inhibitors (13). These and other observations (19,20) suggest a potentiating interaction of angiotensin II with the sympathetic system at the level of post-synaptic α-receptors. They also point to the depression of plasma angiotensin II levels as a possible causal factor in the decrease of responsiveness to norepinephrine after ACE inhibition. In this study, basal PRA and aldosterone levels, which are indirect indexes of angiotensin II levels, were similar in the three groups and uniformly modified by enalapril, suggesting an analogous decrease of circulating angiotensin II concentration after the ACE inhibitor. Thus, the different results observed in diabetic and nondiabetic patients cannot be explained by a different effect of enalapril on the circulating renin-angiotensin-aldosterone system.

Locally generated angiotensin II may enhance vascular reactivity to sympathetic stimuli (21), but only a tissue study could clarify whether enalapril inhibits vascular ACE in diabetic and nondiabetic patients to a different extent.

In our study, no differences were found among the patient groups in preinfusion norepinephrine levels, which, as with postinfusion levels and in agreement with previous data (22), were unaltered after ACE inhibition. On this basis, the enhanced vascular response to the vasopressor hormone can be ascribed neither to a different basal norepinephrine concentration nor to a different effect of enalapril in diabetic compared with nondiabetic patients. Thus, the effect of ACE inhibitors seems to differ from that of diuretics, which in diabetic patients restore the pressor reactivity to norepinephrine to normal, possibly through the removal of excess body sodium (6). Because enalapril may induce a sodium loss and reduce pressor reactivity in patients with essential hypertension (22), it may be surmised that in diabetic patients, the treatment with ACE inhibitors may not be able to correct the expanded body sodium that characterizes diabetic patients with or without hypertension (3), thus leaving unchanged the pressor reactivity to sympathetic stimulation.

Acknowledgments — We are grateful to Maria E. Muscolini for assistance with this study and to Mary D. Cook for helping to improve the English translation.

References

1. Sowers JR, Zemel MB: Clinical implications of hypertension in the diabetic patient: a review. *Am J Hypertens* 3:415–424, 1990
2. Sowers JR: Relationship between hypertension and subtle and overt abnormalities of carbohydrate metabolism. *J Am Soc Nephrol* 1:S39–S47, 1990
3. Weidmann P, Beretta-Piccoli C, Trost BN: Pressor factors and responsiveness in hypertension accompaying diabetes mellitus. *Hypertension* 79 (Suppl. 2):33–42, 1985
4. American Diabetes Association: Consensus statement: treatment of hypertension in diabetes. *Diabetes Care* 16:1394–1401, 1993
5. Beretta-Piccoli C, Weidmann P: Exaggerated pressor responsiveness to norepinephrine in nonazotemic diabetes mellitus. *Am J Med* 71:829–835, 1981
6. Weidmann P, Beretta-Piccoli C, Keusch G, Gluck Z, Mujagic M, Grimm M, Meier A, Ziegler W: Sodium-volume factor, cardiovascular reactivity and hypotensive mechanism of diuretic therapy in mild hypertension associated with diabetes mellitus. *Am J Med* 67:779–784, 1979
7. Blumenthal HT, Goldenberg S, Berns AW: Pathology and pathogenesis of the disseminated angiopathy of diabetes mellitus: on the nature and treatment of diabetes. In *International Congress Series No. 84*. Leibel BS, Wrenshall GA, Eds. Amsterdam, Excerpta Med., 1965, p. 397–408
8. Vallance P, Calver A, Collier J: The vascular endothelium in diabetes and hypertension. *J Hypertens* 10 (Suppl. 1):S25–S29, 1992
9. Weidmann P, Boehlen LM, deCourten M: Pathogenesis and treatment of hypertension associated with diabetes mellitus. *Am Heart J* 125:1498–1513, 1993
10. Sowers JR, Levy J, Zemel MB: Hypertension and diabetes. *Med Clin N Am* 72: 1399–1414, 1988
11. Epstein M, Sowers JR: Diabetes mellitus and hypertension. *Hypertension* 19:403–418, 1992
12. Resnick LM, Gupta RK, Bhargava KK, Gruenspan H, Alderman MH, Laragh JH: Cellular ions in hypertension, diabetes, and obesity: a nuclear magnetic renonance spectroscopic study. *Hypertension* 17:951–957, 1991
13. Imai Y, Abe K, Seino M, Haruyama T, Tajima J, Yoshinaga K, Sekino H: Captopril attenuates pressor responses to norepinephrine and vasopressin though depletion of endogenous angiotensin II. *Am J Cardiol* 49:1537–1539, 1982
14. Fruncillo RJ, Rotmensch HH, Vlasses PH, Koplin JR, Swanson BN, Ferguson RK: Effect of captopril and hydrochlorothiazide on the response to pressor agents in hy-

pertensives. *Eur J Clin Pharmacol* 28:5–9, 1985
15. Malini PL, Strocchi E, Valtancoli G, Ambrosioni E: ACE-inhibition and pressor responsiveness to norepinephrine in hypertensive patients. *J Clin Pharmacol* 30: 422–424, 1990
16. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 28:1039–1057, 1979
17. Krstulovic AM, Dziedzic SW, Bertani-Dziedzig L, Dirico DE: Plasma catecholamines in hypertension and phaeochromocytoma determined using ion-pair reverse-phase chromatography with ampherometric section. *J Chromatogr* 217:523–537, 1981
18. Reams GP, Bauer JH: Angiotensin II potentiates the vasoconstrictive effect of norepinephrine in normotensive and hypertensive man. *J Clin Hypertens* 3:610–616, 1987
19. Zimmerman BG, Sybertz EJ, Wong PC: Interaction between sympathetic and renin-angiotensin system. *J Hypertens* 2:581–584, 1984
20. Seidelin PH, Coutie WJR, Morton JJ, Struthers AD: The interaction between noradrenaline and angiotensin II in man: evidence for a postsynaptic and against a presynaptic interaction. *J Hypertens* 5 (Suppl. 5):121–124, 1987
21. Okamura T, Miyazaki M, Inagami T, Toda N: Vascular renin-angiotensin system in two-kidney, one-clip hypertensive rats. *Hypertension* 8:560–565, 1986
22. Uehlinger DE, Ferrier CP, Matthieu R, Reuter K, Gnaedinger MP, Saxenhofer H, Shaw S, Weidmann P: Antihypertensive contribution of sodium depletion and the sympathetic axis during chronic angiotensin II converting enzyme inhibition. *J Hypertens* 7:901–907, 1989