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AN INDIRECT EVALUATION OF THE EFFECT OF THE AUTONOMIC NERVOUS SYSTEM FOLLOWING CONVERTING ENZYME INHIBITION IN HYPERTENSION

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ABSTRACT

Common carotid blood flow and cold pressor test were evaluated in 16 patients with sustained essential hypertension before and after 30 days treatment with the converting enzyme inhibitor Enalapril (20 mg). Enalapril decreased blood pressure and carotid vascular resistance with no significant change in heart rate. After treatment, despite a wide range of the responses, the changes in systolic blood pressure to cold test were significantly attenuated, whereas the heart rate responses were not. Acute random and double blind administration of either Cadralazine or Nitrendipine, two vasodilating drugs which are known to cause an activation of the

autonomic nervous system, were performed before and after long term treatment by Enalapril. Whereas the blood pressure and heart rate responses to cold test was unmodified by these compounds before Enalapril treatment, significant changes were observed after converting enzyme inhibition : Cadralazine reduced the heart rate response wheareas Nitrendipine increased it significantly. The study provides evidence that converting enzyme inhibition causes sympatho-inhibitory influences which are principally observed in stress conditions, with heterogeneous responses depending on the nature and the type of stimulation. .

INTRODUCTION

It has been known for many years that converting enzyme inhibition have a sympatho-inhibitory influence, probably due to a peripheral or central interaction between the sympathetic and the renin-angiotensin system (1-4). In contrast with other vasodilating anti-hypertensive agents , converting enzyme inhibitors do not cause any classical baroreflex response, as elicited by an increase in cardiac output and heart rate (5-10). Experimental studies have shown that converting enzyme inhibition affect the baroreflex by shifting it to the left (9). It affect also the release of noradrenaline, as indicated in various reviews (2-4,10). However, the contribution of the sympathetic nervous system blockade in the mechanism of the blood pressure reduction following converting enzyme inhibition remains controversial in clinical hypertension (11-14).

Theorically, the inhibitory influence of converting enzyme inhibition on sympathetic nervous system might occur either at rest or in the presence of sympathetic stimulation (1-15). In the

present investigation, the latter situation is particularly taken into consideration, using two different procedures. The response to cold pressor test (16-18) was evaluated before and after converting enzyme inhibition.The acute haemodynamic effect of vasodilating antihypertensive drugs producing sympathetic stimulation was evaluated before and after long-term treatment with the converting enzyme inhibitor Enalapril. In this double blind, randomized design, two vasodilating drugs were used in acute administration : the calcium-entry blocker, Nitrendipine (19), and the dihydralazine-like substance, Cadralazine (5). The non-invasive determination of carotid blood flow and vascular resistance was used as an index of vasodilation.

MATERIALS

Patients :

Sixteen patients with sustained essential hypertension (12 males and 4 females) were included in the study. Their age range was between 29 and 59 years (mean : 49 years). Mean weight and height were respectively 76 ± 16 kg and 172 ± 11 cm (± 1 standard deviation). The patients had no signs, symptoms or history of cardiac or renal failure, coronary insuffiency or major diseases other than hypertension. After extensive screening as previously described (20), all patients were diagnosed as having sustained essential hypertension, with diastolic blood pressure superior or equal to 95 mmHg (korotkow phase five) measured

by a mercury sphygmomanometer in the supine position at the end of the placebo wash out period.

Previous treatments, including diuretics or beta-blocking agents or any other anti-hypertensive treatment, were discontinued in all patients at least a month before the study. Placebo was administered during 15 days after the wash out period. Sodium intake, estimated by urinary sodium output was between 80 and 140 mmol/day. Informed consent was obtained from each patient after a detailed description of the procedure. The study protocol was approved by INSERM (Institut National de la Santé et de la Recherche Médicale) and the Broussais Ethical Comittee

METHODS

Hemodynamic investigations were performed in the morning during a clinic day (DO), in a controlled room temperature of 20 ± 2°C, the patients having rested for 30 minutes in the recumbent position. At 9 a.m., arterial blood pressure and heart rate were measured automatically every three minutes in the left arm with an oscillometric blood pressure recorder, the DINAMAP TYPE 845 apparatus (21). The same values of blood pressure were recorded in the left and right arms. Mean arterial pressure, calculated as the sum of the diastolic pressure and one third of the pulse pressure, was shown to be identical to mean arterial pressure evaluated directly

from the Dinamap apparatus. In all hypertensive patients, hemodynamic measurements were carried out first, on the right common carotid artery, second, using cold pressor test.

Carotid arterial hemodynamic measurement :

Carotid hemodynamic measurements were obtained using a bidimensional pulsed Doppler system, the probe being maintened over the course of the carotid artery, as previously described and validated (22). This zero-crossing apparatus allowed the diameter and the blood velocity of the artery to be measured using two fundamental characteristics : a bidimensional recording of the Doppler signals, and a range-gated time system of reception. For the former, a probe containing two transducers was used, forming between them an angle of 120 degrees, so that when the Doppler signals recorded by each transducer were equal in absolute value, the ultrasonic incidence with the vessel axis was 60 degrees. Using the latter value, it was possible to select the delay from the emission and the duration of the reception, and to convert this time echographically into the depth and width of the Doppler measurement volume. To determine the arterial diameter, the width of the measurement volume was reduced to the smallest convenient value with a sufficient reflected energy (about 0.4 mm), and its depth from the transducer was progressively increased. This was continued across the lumen of the artery,

with a small measurement volume, and allowed the recording of velocities of the different stream lines involved in the arterial flow. Thus, the first and last Doppler signals recorded when crossing the vessel corresponded to the position of the vessel walls, and the difference in depth beetween these two signals, to the internal arterial diameter. To take into account the ultrasonic incidence angle, a correction was made by multiplying this difference by sine 60 degrees, this being the angle used in the measurement. Since the arterial diameter was determined, the velocity of the whole arterial blood column could be adequately measured, as previously described (22). The arterial blood velocity was expressed in centimeters per second and mean arterial blood velocity was electronically integrated. Common carotid blood flow (ml/min) was calculated as the product of mean blood velocity and cross sectional area (S), the latter value being derived from the arterial diameter (D), using a cylindrical representation of the artery ($S = 3.14D^2/4$). Vascular resistance ($mmHg.min.ml^{-1}$) was calculated as the ratio between simultaneous mean blood pressure and mean blood flow. The variability of the Doppler measurements was studied in six subjects (independently of the 16 patients in the present study). After 30 minutes of rest, repeat measurements of artery diameter and blood flow velocity were performed through-out at 9, 10, 11 and 12 AM (two or three determinations at each hour) to evaluate short-term variability (20). The measurements were

repeated 7 days later, under the same conditions and in the same patients, to evaluate long-term variability. All measurements were made by the same researcher (RA). Three-way analysis of variance did not demonstrate any interaction between day and hour nor were there any hour or day effects. Short-term and long-ter variability was approximately 2.2% for the arterial diameter and 18.7% for blood flow velocity.

Cold pressor test (16-18)

In each subject, blood pressure and heart rate response to cold pressor test were evaluated by immersion of the right hand just above the wrist in ice water (4°-5°C) for 90 secondes. Blood pressure and heart rate were automatically (DINAMAP 845 P) recorded before, during (at the 30th and 90th seconds) and for 5 minutes after the end of the cold test. For this test, baseline parameters were considered as the mean of the three last measurements just before the cold test. The difference between peak value of blood pressure and heart rate during hand immersion (i.e. almost always at the 90th second) and baseline values was considered as the response to cold pressor test and the degree of magnitude of vascular reactivity. Individual average variation of blood pressure and heart rate response from test to test, evaluated in other studies (16-18) was confirmed to be less than 10%. The reproducibility of the response to the cold pressor test was evaluated in 10 normotensive and 12

hypertensive patients. Blood pressure variability from one day to another was 8 ± 3%.

Therapeutic design

Following baseline hemodynamic determination (DO ; TO), the patients were randomized into groups : an acute random double blind administration of either Cadralazine (10 mg p.o.) or Nitrendipine (20 mg p.o.) was performed. According to the known pharmacodynamic characteristics of the drugs (5,18), a second hemodynamic study was performed 4 hours after the oral administration (D0 ; T4). One day after this acute, randomized and double blind study, long term treatment with Enalapril given in monotherapy was performed for 30 days. Enalapril was given each day (20 mg p.o.) around 8 a.m. in the 16 patients. At the 30th days (D30), a second clinic day was performed in the same condition as at TO. Again, the same acute oral administration of either Cadralazine or Nitrendipine was performed in the same condition as in D0 (D30 ; T4). The same drug was given at D0 and D30 to the same patient.

Statistical methods (23-25)

The NCSS statistical package (U.S.A) was used for the calculations. Statistical analysis of data were performed with a repeated-measures analysis of variance : the between subject factor was the treatment group (Cadralazine or Nitrendipine), the

within-subject factor was the measurement. Two independant analyses were made for the comparison of the parameters at D0, D30, at baseline and 4 hours after administration of the treatment and for the cold-test. Planned contrasts were used to test the hypotheses that : 1) value at D0 differed at T0 from that 4 hours after the acute administration of the treatment ; 2) same hypothesis but at D30 ; 3) value at T0 D0 differed from that at T0 D30. Differences between the initial value and the value 90 secondes after the beginning of the cold-test were calculated for each variable, each subject and each cold-test. The delta values were introduced in the repeated-measures analysis of variance for the cold-test. Spearmen rank correlation coefficient was used for non-parametric regression analysis.

RESULTS

Effect of Enalapril

Table I shows that following Enalapril (D0 T0 versus D30 T0) blood pressure significantly decreased ($P<10^{-3}$). No significant change in heart rate occured. Following Enalapril, common carotid blood flow significantly increased ($P=0.04$) while vascular resistance decreased ($P<10^{-2}$).

Table II shows the pressor and heart rate response to cold pressor test. After 30 days treatment, the systolic pressure response to cold pressor test was attenuated ; despite a wide

TABLE I

SYSTEMIC BLOOD PRESSURE AND CAROTID HEMODYNAMIC CHANGES

		D0		D30		p value		
		T0 (1)	T4 (2)	T0 (3)	T4 (4)	(1)-(2)	(1)-(3)	(3)-(4)
SBP (mmHg)	Cadra	161 ± 22	155 ± 21	140 ± 18	137 ± 19	NS	0.001	NS
	Nitren	162 ± 17	150 ± 17	139 ± 24	138 ± 23			
DBP (mmHg)	Cadra	99 ± 15	93 ± 14	84 ± 10	80 ± 10	0.02	0.001	NS
	Nitren	103 ± 6	95 ± 7	88 ± 13	87 ± 14			
MBP (mmHg)	Cadra	120 ± 17	114 ± 16	103 ± 12	100 ± 10	0.03	0.001	NS
	Nitren	122 ± 10	113 ± 12	105 ± 16	103 ± 17			
HR (beats/mn)	Cadra	79 ± 14	80 ± 14	76 ± 14	75 ± 13	NS	NS	NS
	Nitren	76 ± 11	78 ± 9	72 ± 7	68 ± 4			
Flow ($ml.min^{-1}$)	Cadra	287 ± 60	370 ± 115	369 ± 146	405 ± 124	0.03	0.04	NS
	Nitren	334 ± 96	356 ± 104	350 ± 114	340 ± 121			
Resistance ($mmHg.min.ml^{-1}$)	Cadra	26.34 ± 7.25	20.10 ± 6.98	18.73 ± 5.85	16.05 ± 4.95	0.02	0.01	NS
	Nitren	24.04 ± 8.80	20.81 ± 6.66	20.28 ± 8.77	20.55 ± 8.44			

± 1 standard deviation

Change in blood pressure and carotid hemodynamics between the beginning (D0) and the end (D30) of the study. TO and T4 represents the acute hemodynamic study before (TO) and after (T4) administration of either Nitrendipine of Cadralazine. The effect of Enalapril is evaluated from D0 TO to D30 TO.
Cadra : Cadralazine ; Nitren : Nitrendipine ; SBP : systolic blood pressure ; DBP : diastolic blood pressure ; MBP : mean blood pressure ; HR : heart rate

range of response, the improvement predominated on systolic pressure ($P < 0.05$) (Fig. 1). The change in blood pressure and heart rate was not correlated with baseline values. No attenuation of the heart rate response was observed following cold test.

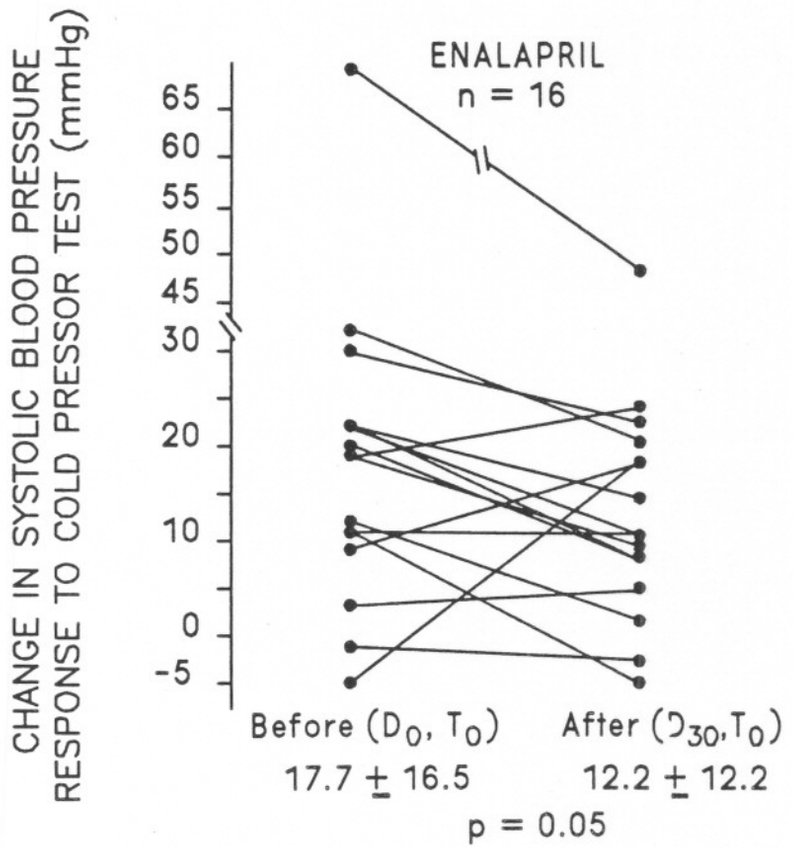

Figure 1 : Individual values of the change in systolic blood pressure response to cold pressor test before and after long term treatment by Enalapril. (n = 16 patients)

Effect of Cadralazine and Nitrendipine

Before Enalapril (D0 TO versus D0 T4), Cadralazine and Nitrendipine decreased significantly ($P<0.02$; $P<0.03$) diastolic and mean blood pressure (Table I) without significant change in heart rate. Both drugs caused an increase in carotid blood flow

(P = 0.03) with a decrease in vascular resistance (P = 0.02). Cadralazine and Nitrendipine did not affect the response to cold pressor test (Table II).

After long term treatment by Enalapril, Cadralazine and Nitrendipine caused no acute change in blood pressure and carotid hemodynamics (D30 T0 versus D30 T4) (Tables I). The only significant effect was the heart rate response to cold pressor test (Table II). In patients treated by Enalapril, the increase in heart rate following cold pressor test tended to decrease with Cadralazine (P = 0.06) and to increase significantly with Nitrendipine (P = 0.03) (Figure 2).

DISCUSSION

In the present investigation, the three vasodilating drugs, Enalapril, Cadralazine and Nitrendipine produced a significant decrease in blood pressure through arteriolo-dilation. In the three cases, indirect evidence for this mechanism was provided by the decrease in carotid vascular resistance. The sympatho-inhibitory influence of converting enzyme inhibition was principally investigated on the basis of blood pressure and heart rate responses to cold pressor test before and after acute administration of Cadralazine and Nitrendipine, two drugs which are known to cause an activation of the sympathetic nervous system.

TABLE II

BLOOD PRESSURE AND HEART RATE CHANGES
FOLLOWING COLD PRESSURE TEST

		DO		D30		p value		
		T0 (1)	T4 (2)	T0 (3)	T4 (4)	(1)-(2)	(1)-(3)	(3)-(4)
SBP (mmHg)	Cadra	14 ± 9	14 ± 17	8 ± 10	8 ± 15	NS	0.05	NS
	Nitren	21 ± 21	20 ± 13	17 ± 13	16 ± 11			
DBP (mmHg)	Cadra	6 ± 9	10 ± 8	7 ± 8	9 ± 11	NS	NS	NS
	Nitren	13 ± 12	11 ± 8	10 ± 11	12 ± 8			
HR (beats/mn)	Cadra	0.8 ± 5.5	1.1 ± 3.1	2.6 ± 4.3	-0.54 ± 5.8	NS	NS	0.06
	Nitren	3.3 ± 5.9	4.3 ± 7.23	1.6 ± 6	5.6 ± 8	NS	NS	0.03

± 1 standard deviation

Change in blood pressure and carotid hemodynamics between the beginning (D0) and the end (D30) of the study.
TO and T4 represents the acute hemodynamic study before (T0) and after (T4) administration of either Nitrendipine of Cadralazine. The effect of Enalapril is evaluated from D0 T0 to D30 T0.
Abbreviations : Cadra : Cadralazine ; Nitren : Nitrendipine ; SBP : systolic blood pressure ; DBP : diastolic blood pressure ; MBP : mean blood pressure ; HR : heart rate

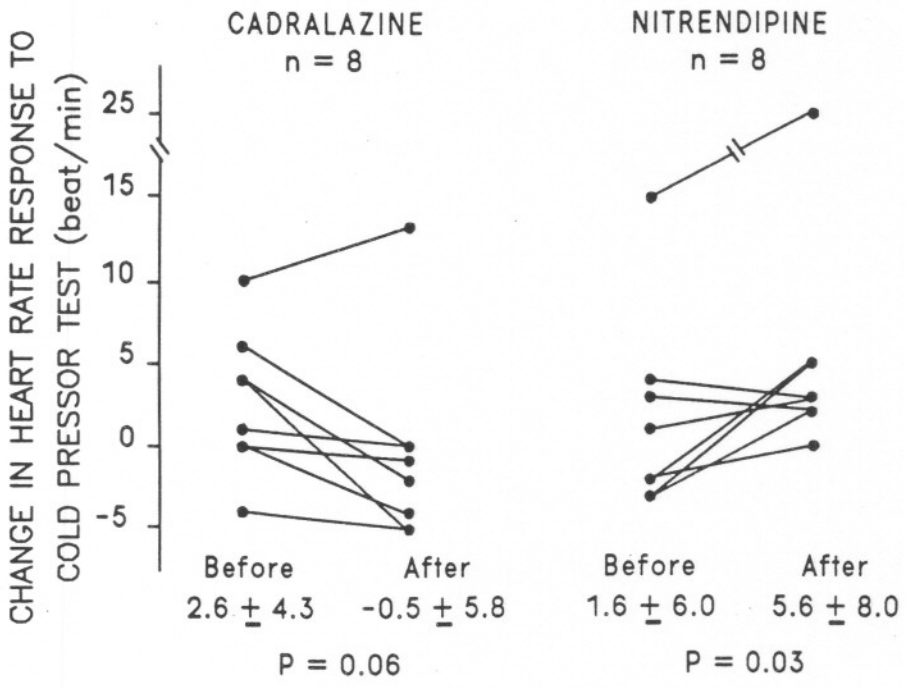

Figure 2 : Individual values of the change in heart rate response to cold pressor pressure in patients long term treated by Enalapril (D30). The left panel represents the effects of Cadralazine (n = 8 patients) whereas the right panel represents the effect of Nitrendipine (n = 8 patients).

Numerous studies in humans have examined the effect of converting enzyme inhibitors on circulatory reflexes. Reflex vasoconstrictor, pressor, chronotropic, or catecholamine responses to test autonomic function have been shown to be little changed after converting enzyme inhibition, although some conflicting results have been reported (6,10,13,14,26). In that

condition, it is important to investigate the haemodynamic effects of cold pressor test, which represents a global response of the activation of the sympathetic nervous system involving both the afferent and the efferent components of the reflex. Since the change in blood pressure and heart rate following cold pressor test is not correlated to baseline values (16-18,27), only the delta values and not the absolute values are commonly taken into consideration. Benetos and al (27) using intravenous administration of Perindoprilat, did not elicit significant changes in cold test response in acute situations. In the present study, oral Enalapril was given chronically. Despite a wide range of responses, the pressor changes to cold test were slightly attenuated, indicating a reduction in the ability to alter peripheral vasomotor tone response to alteration in nerval drive (26-28). The result agrees with the recent finding that chronic treatment with captopril prevents the elevation of blood pressure in cold-induced hypertension in rats (29). Interestingly, in hypertensive humans, this inhibitory influence affected exclusively the vascular and not the heart rate response to cold test. Indeed, whereas the vascular response is exclusively influenced by the sympathetic nervous system, the heart rate response is influenced both by the sympathetic and the parasympathetic system. Pharmacological studies have previously shown that the control of heart rate following converting enzyme inhibition was

influenced more by parasympathetic than by sympathetic system (1, 6, 10, 30, 31).

Vasodilating anti-hypertensive agents, as Calcium entry blockers and Dihydralazine, are known to affect the baro reflex response with activation of the sympathetic nervous system and increase in heart rate. However, in the present investigation, this classical response did not appear or was significantly attenuated. Such a finding has been previously observed with the dihydropyridine derivative Nitrendipine which is known to produce only a modest sympathetic stimulation (19). In the case of Cadralazine, the present results contrast with previous investigations in our laboratory indicating a significant increase in heart rate both in normotensive and hypertensive subjects (5). However, in the present investigation, Cadralazine dosage was 10 mg whereas a 20 mg dosage was given in our previous study (5). Despite the lack of change in heart rate following arteriolar dilatation by Nitrendipine or Cadralazine, the response of cold pressor test to these drugs was substantially different before and after Enalapril treatment. Whereas before Enalapril, comparable responses to cold test were elicited following Cadralazine and Nitrendipine, a significant difference appeared after long term therapy by Enalapril. Whereas Cadralazine attenuated the heart rate response following hand immersion, a significant increase in the response was observed following Nitrendipine. Interestingly no difference occurred in the vascular (sympathetic) response,

suggesting that, following converting enzyme inhibition, parasympathetic tone acted differently with Cadralazine and Nitrendipine after hand immersion.

Nevertheless, such findings should be analyzed very cautiously. The effect of cold pressor test after chronical treatment with Enalapril and acute administration of either Cadralazine or Nitrendipine on heart rate are in a small range of less than 5 beats/minute with standard deviation larger than the effects. However, this finding precisely shows that it is principally the mean value and not the variance of the test which was modified. In addition, the P-values were calculated using sophisticated methods (23-25). Planned contrasts were used to test the hypotheses that : 1) value at D0 differed at T0 from that 4 hours after the acute administration of the treatment ; 2) same hypothesis but at D30 ; 3) value at T0 D0 differed from that at T0 D30. Differences between the initial value and the value 90 secondes after the beginning of the cold-test were calculated for each variable, each subject and each cold-test. The delta values were introduced in the repeated-measures analysis of variance for the cold test. Finally, the findings agree with those reported in hypertensive subjects either untreated (32) or following the calcium-entry blocker Felodipine (33).

In a previous study (11), it has been suggested that converting enzyme inhibition could prevent the increase in heart rate produced by Dihydropyridine derivatives. The present

investigation indicates that the sympatho-inhibitory influence of converting enzyme inhibition is more complex. It is too simple to say only that vasodilators as Cadralazine or Nitrendipine "activate le sympathetic nervous system". The autonomic influence is heterogeneous in nature, with responses depending on the reflex involved (cold pressor test), on the type (cardiac or vascular ; sympathetic or parasympathetic) of the response and also on the mechanism of action of the vasodilating drug involved.

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