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Hemodynamic Effects of Long-Term Converting-Enzyme Inhibition in Renal Hypertensive Rats

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The hemodynamic effects of a converting-enzyme inhibitor (CEI) given during 12 consecutive hours were studied in severe chronic renal hypertensive and normotensive Wistar rats. Hemodynamic parameters were obtained by thermodilution method in conscious unrestrained animals twenty-four hours after surgery. A bolus of CEI induced a significant decrease of mean arterial pressure (MAP) (from 192.2 ± 8.2 to 163.3 ± 5.9 mmHg, $p < 0.001$) and total peripheral resistance (TPR) (from 7.69 ± 0.53 to 5.83 ± 0.33 mmHg · min/ml 100 g) in hypertensive animals. Cardiac index (CI) and heart rate increased significantly ($p < 0.05$). Infusion of CEI to hypertensive animals during 12 consecutive hours produced a further progressive decrease in MAP and TPR ($p < 0.05$) and an increase in CI ($p < 0.05$). Heart rate did not change. Acute and prolonged infusions of CEI to normotensive group induced less but similar effect to those observed in hypertensive group. These results suggest that an increase of the renin-angiotensin system activity is the principal mechanism involved in the maintenance of high blood pressure during chronic phase of renal hypertension on the rats.

Key words: Hypertension, Converting-enzyme inhibition, Hemodynamics.

The acute administration of converting-enzyme inhibitors (CEI) to chronic renovascular hypertensive rats induces a decrease of mean arterial pressure (MAP) without reaching normotensive levels (15, 18). The inhibition of converting-enzyme in these animals only produces a decrease of MAP up to normotensive values after prolonged infusion of CEI (15, 18). The mechanisms underlying this response of CEI are unclear. The different effectiveness of CEI could be due to the fact that tissue and vascular converting-enzyme activity, that is stimulated in this experimental model (11, 13) is more inhibited during a continuous infusion than an acute administration (7, 12). However, the hemodynamic changes mediating the hypotensive effect of a prolonged inhibition of converting-enzyme during the chronic and severe experimental two-kidney, one-

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clip hypertension are not well established. The long-term infusion of CEI is more effective decreasing blood pressure in this experimental model (15, 18) than in mild-moderate human hypertension (2-5, 8, 19).

Therefore, the aim of the present study is to examine the hemodynamic changes that mediate the hypotension induced by a bolus (2 mg/kg) and a 12 consecutive hours (1 mg/kg/h) infusion of CEI to chronic and severe renovascular hypertensive rats.

Materials and Methods

Male Wistar rats weighing 200-220 g were used. They were given water and a standard rat diet *ad libitum*. Hypertension was induced by clipping (0.25 mm internal gap: silver clip) the proximal left renal artery under light ether anesthesia. The contralateral kidney was left untouched. Two-kidney, one-clip rats were used at least 16 weeks after surgical induction of severe hypertension (> 180 mmHg of mean arterial pressure). Sham operated rats were used as control.

Surgical procedures. — Cardiac output (CO) was measured by thermodilution; this method has recently showed good correlations between thermodilution and electromagnetic flowmetry measurement of CO (14). In a previous study we found a good reproductibility of thermodilution method for repetitive measurements of CO in rats (6). Twenty-four hours before each experiment, rats were weighed and anesthetized with sodium pentobarbital (40 mg/kg, ip) and then cannulated their left femoral artery and right jugular vein with a PE-50 polyethylene catheter. The right carotid was isolated and a thermocouple (Columbus Instruments) inserted into the aortic root. The three catheters were brought out through the skin at the dorsal side of the neck. The distal ends of catheters were threaded through a lightweight flexible spring connected to a hydraulic swivel. Rats were allowed to recover in plastic cages with the swivels mounted on top allowing complete freedom of movement. The thermodilution curve and the pressure signals were processed in a microcomputer system for CO determination by thermodilution (Cardiomax IIR, Columbus Instruments, OH). Cardiac output was measured by rapid injection of 200 µl of isotonic saline (20-21 °C) into the jugular catheter using a spring-loaded-rate constant-volume syringe (Hamilton, model CR700-200), and the thermodilution curve recorded (MX216 Lectromed). Stroke volume (SV) and CO were digitally obtained by the microcomputer, as well as mean arterial pressure (MAP) and heart rate (HR). Cardiac index (CI) was obtained by the formula CI = CO/weight (g) × 100 and total peripheral resistance (TPR) by the formula TPR = MAP/CI.

Protocol. — The effect of the converting enzyme inhibition with Captopril (SQ14,225) (Squibb) on systemic hemodynamics were studied in conscious unrestrained hypertensive and control rats. Twenty-four hours after surgery arterial catheter was connected to the microcomputer system and, after 60-90 min of stabilization, hemodynamic parameters were measured before and 20 min after acute Captopril administration (2 mg/kg as a bolus), and then a continuous Captopril infusion started (1 mg/kg per hour in saline; flow rate: 0.33 ml/h) throughout the next 12 h. Hemodynamic determinations were made at 4, 8 and 12 hours after starting infusion of Captopril. The dose of Captopril used produced over 80 % inhibition of the pressor response to a test dose of 100 ng of angiotensin I (8.6 ± 1.4 vs 45.3 ± 3.5 mmHg).

Statistical methods. — Results presented are the means ± SEM within each

group. Statistical differences between mean values of both groups were evaluated by a modified t-test, using the residual error of two-way ANOVA of each group. Differences were considered statistically significant at $P < 0.05$.

Results

The high blood pressure, in hypertensive group, was maintained by a significant increase in total peripheral resistance (TPR) ($p < 0.001$). Cardiac index (CI) decreased significantly in hypertensive animals as compared with the control group (fig. 1).

A bolus of CEI (fig. 1) induced a significant decrease of mean arterial pressure (MAP) ranging from 192.2 ± 8.2 to 163.3 ± 5.9 mmHg ($p < 0.001$). This hypotension was observed together with a decrease in TPR, a significant increase in CI and also heart rate (HR) (table I) ($p < 0.05$). Minor changes in MAP, TPR and CI ($p < 0.05$) (fig. 1) were observed in normotensive animals when infused with a bolus of Captopril. However, MAP and TPR remain increased and CI decreased in hypertensive animals in comparison with normotensive group.

As shown in figure 1, a 12 hour infusion of Captopril to the hypertensive group induced a continuous and progressive decrease in MAP until 115.7 ± 3.9 mmHg ($p < 0.001$) at the end of infusion period. This fall in MAP was accompanied by a gradual decrease in TPR values up to those observed in control group. These hemodynamic changes were accompanied by a progressive increment of CI ($p < 0.05$) that was induced by a significant increase of stroke volume (31.6 % at the end of infusion period, $p < 0.05$). The changes in CI and TPR were significantly correlated

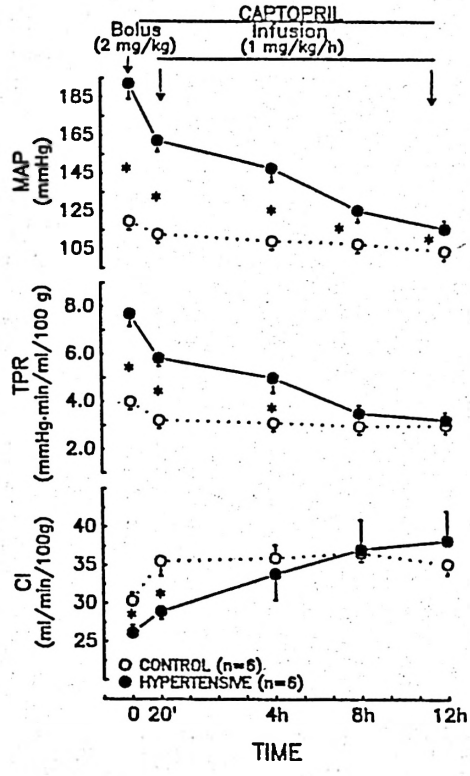

Fig. 1. *Changes in Mean Arterial Pressure (MAP), Total Peripheral Resistance (TPR) and Cardiac Index (CI) after acute and long-term Converting-Enzyme inhibition with Captopril.*
*$p < 0.05$ between groups.

Table I. *Changes in heart rate after acute and chronic converting-enzyme inhibition with Captopril (n = 6).*

Group	Basal	Bolus 20 min	Infusion		
			4 h	8 h	12 h
Control	375 ± 20	392 ± 20	398 ± 17*	387 ± 14	394 ± 12
Hypertensive	352 ± 13	389 ± 22*	412 ± 12*	404 ± 14*	399 ± 10*

* $p < 0.02$ from basal values.

($r = 0.98$, $p < 0.001$). The 12 hours infusion of Captopril to normotensive animals produced a significant and correlative ($r = 0.93$, $p < 0.001$) decrease in MAP and TPR when compared with values observed after acute CE inhibition. After 12 hours of infusion, no differences were observed in TPR, CI and HR between both experimental groups, although MAP remained slight but significantly increased in hypertensive group ($p < 0.05$).

Discussion

The present study shows that a continuous inhibition of converting-enzyme during severe and chronic two-kidney, one clip (2K-1C) renovascular hypertension in rats induces a decrease in total peripheral resistance (TPR) to similar levels to those found in the normotensive group. This change in TPR was accompanied by an increase in cardiac index (CI).

In our study, chronic and severe 2K-1C hypertension was maintained by an increase in TPR. CI was significantly lower than that observed in normotensive group as RUSSELL *et al. reported* (16). It was previously showed that only a continuous inhibition of converting-enzyme to 2K-1C hypertensive rats induced a decrease in blood pressure to normotensive levels (15, 18). However, the hemodynamic changes mediating this fall in blood pressure following the continuous administration of converting-enzyme inhibitor (CEI) in this model of experimental hypertension were unknow. Acute Captopril administration to hypertensive rats produced a significant decrease in blood pressure and TPR, although both parameters still remained higher than in normotensive group. During a 12 hours continuous infusion of Captopril to the hypertensive group, a further progressive drop in blood pressure and TPR was observed.

The higher decrease of MAP and TPR observed during the continuous infusion in comparison with that observed after the bolus administration of CEI could be due to the fact that vascular and tissue converting-enzyme activity is more inhibited during a continuous infusion (7, 12). It has been recently reported that vascular converting enzyme activity is only stimulated during the chronic phase of renovascular hypertension (11, 13). A higher inhibition of AII potentiating effect of neurotransmitter release (10) could also explain the greater hypotensive effect of prolonged administration of Captopril. An increase of kinins during CEI infusion could also contribute to the hemodynamic changes observed in the present study (9). The decrease of TPR in hypertensive group to values similar to those observed in normotensive animals after infusion of Captopril probably reflects an exaggerated smooth muscle relaxation. This hypothesis is supported by the fact that a vascular hypertrophy has been observed during the chronic phase of 2K-1C hypertension (1). In these conditions, TPR can only decrease to normotensive values if tonic smooth muscle activity is lower than in normotensive animals. In control group, a slight but significant decrease in MAP was observed not only after acute administration but also after prolonged Captopril infusion. The hypotension was due to a decrease in systemic vascular resistance. These results suggest that vascular converting-enzyme could participate in the homeostatic control of blood pressure in normotensive animals.

In our study the acute and prolonged infusion of CEI to hypertensive animals was also accompanied by a progressive increment of CI. These results are not in accordance with previous studies on essential and renovascular human hypertension in which CI did not change during acute and long-term CEI treatment (2-5, 8, 19). However, these studies were undertaken on mild-moderate hypertensive patients and the hypotensive effect of Captopril administration was lower (< 30 mmHg)

than in the present study (> 70 mmHg). The difference between those studies and ours could probably be due to differences in severity of hypertension. However, the possibility that changes observed in CI may be transitory, should not be excluded as it is shown by the fact that these changes were observed accompanied by reflex tachycardia indicating an incomplete downward baroreceptor resetting. The present study does not allow to define the mechanisms responsible for this CI increment. One possibility is that a decrease in afterload secondary to the fall in TPR and a decrease in the venular resistance (5, 19) could contribute to CI increments in hypertensive animals after prolonged CEI treatment.

Acute and chronic blockade of converting enzyme activity did produce hypotension with tachycardia in hypertensive group. This HR increase was slight compared with the large decrease in blood pressure in hypertensive group. It is known that Captopril produces hypotension with minimal changes in HR, probably due to withdrawal of angiotensin II potentiation of sympathetic activity (3) and a downward resetting of baroreflex (17). However, owing to a progressive decrease in blood pressure, resetting of baroreceptor could be incomplete. This incomplete resetting could explain why, in hypertensive group, HR maintained during the continuous infusion of CEI at similar values observed after acute administration.

In summary, the present study shows that TPR of chronic and severe 2K-1C hypertensive rats, decrease to normotensive values during long-term administration of CEI. This effect was significantly higher to that induced by an acute CEI infusion. These results suggest that an increase of the renin-angiotensin system activity is the principal mechanism involved in the maintenance of high blood pressure during chronic phase of 2K-1C hypertension in rats. This hypothesis is supported by the fact that a long-term administration of CEI produced a normalization of the hemodynamic parameters in this chronic phase of 2K-1C hypertension.

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Resumen

Se estudian los efectos hemodinámicos de la administración, durante 12 horas, de un inhibidor del enzima de conversión (IEC) en ratas normotensas y con hipertensión renal crónica. Las determinaciones se obtienen por el método de termodilución en animales conscientes, 24 h después de la intervención quirúrgica. Un bolo de IEC induce en los animales hipertensos, un significativo descenso de la presión arterial media (PAM) (desde 192,2 ± 8,2 a 163,3 ± 5,9 mmHg, $p < 0,001$) y de la resistencia periférica total (RPT) (desde 7,69 ± 0,53 a 5,83 ± 5,33 mmHg·min/ml/100 g). El índice cardíaco (IC) y la frecuencia cardíaca aumentan significativamente ($p < 0,05$). La infusión de IEC, durante 12 horas a los animales hipertensos, produce un ulterior y progresivo descenso de PAM y de RPT y un aumento en el IC ($p < 0,05$). La frecuencia cardíaca no se modifica. La administración aguda y prolongada de IEC, al grupo normotenso, induce cambios menores, aunque similares a los observados en el grupo hipertenso. Estos resultados sugieren que, un aumento de la actividad del sistema renina-angiotensina es el principal mecanismo que mantiene la presión arterial elevada, durante la fase crónica de la hipertensión renal en la rata.

Palabras clave: Hipertensión, Inhibición de enzimas convertidoras, Hemodinámica.

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