The Exercise Renogram. A New Approach Documents Renal Involvement In Systemic Hypertension

John H. Clorius and Peter Schmidlin

German Cancer Research Center, Heidelberg, Germany

Hippurate functional scintiscans were obtained in 51 hypertensive patients and in 15 controls. We investigated the influence that posture and exercise have on hippurate kinetics in patients with hypertension. A posture- or exercise-induced disturbance of renal hippurate transport was sought. All persons were examined in prone and standing positions, as well as during exercise. When prone and upright renograms were compared, 24% of the hypertensives demonstrated bilateral orthostatic renal dysfunction. Exercise caused the hippurate transport disturbance to increase. Fifty-seven percent of all hypertensives developed evidence of marked, bilateral, renal dysfunction during ergometric stress, so that exercise renography was shown to be a more sensitive test of the presence of transient tubular dysfunction in hypertension than the standing renogram. In normotensive controls the hippurate functional scintigram failed to be influenced by posture and exercise. The results suggest presence in hypertension of transient, posture- and exercise-mediated alterations of renal cortical blood flow.

J Nucl Med 24: 104–109, 1983

Hippurate sequential scintigraphy was recently used to identify bilateral orthostatic renal dysfunction (BORD) in patients with hypertension (*1*). The abnormality causes a marked, bilateral disturbance of hippurate transport in the upright position, resulting in parenchymal radionuclide retention, delayed tracer appearance in the bladder, and an elevated third segment of the renogram. The results were interpreted as pointing to the existence of posture-dependent fluctuations of renal cortical blood flow. The present study sought to determine whether exercise may also trigger the vascular reaction responsible for the newly identified perfusion abnormality seen in some patients with hypertension.

METHODS

We report on 76 patients referred for hippurate scintigraphy because of hypertension. For inclusion in the study, patients had to have a minimum systolic blood pressure of 150 mm Hg, or a diastolic value of 105 mm Hg, at the time of presentation for scintigraphy. The initial population included all patients meeting two requirements: referral for evaluation of hypertension, and hypertensive at the time of presentation. Ten patients could not be examined with exercise renography. Eight of these had coronary artery disease. Five of the eight had been treated for infarction, and three had recurring angina pectoris. Two others were physically incapable, following a cerebral stroke. Two more patients refused to participate in the examination series. Thus 64 patients were able to have the series of three examinations. Of these, three had to be excluded from evaluation because the sequence of examinations could not be evaluated. Furthermore, ten patients who had participated in the series of three examinations were excluded when evaluation of results showed that the pulse rate at 10 min after tracer injection was uninfluenced by exercise. These patients had evidently not followed instructions, failing to exercise adequately. Fifty-one hypertensives were thus included in the final evaluation. We also examined 15 normotensive volunteers who served as controls.

All evaluated patients and controls were examined

Received July 12, 1982; revision accepted Sept. 28, 1982.

For reprints contact: John H. Clorius, Inst. of Nucl. Med., German Cancer Res. Ctr., PO Box 10 1949, D-6900 Heidelberg, West Germany.

three times each. Each subject was studied in the prone position, in the standing position, and in an upright posture during ergometric stress. An attempt was made to obtain the sequence of examinations within one week. This was not always possible, but was achieved in most of the patients. To obtain adequate hydration, patients were asked to drink 400 ml of fluid. Fluid intake preceded the radiorenogram by about 30 min.

All patients received careful oral instructions about the series of examinations. The renogram in the prone position was begun within minutes after patient positioning. The renogram in standing position was used to identify BORD. Patients walked up to the camera, and were scintigraphed. We did not examine patients in the standing position by having them get up from the horizontal position immediately before the upright study. The examination in standing position therefore identifies a posture-dependent pattern of hippurate handling. The exercise program was used to observe the influence of exercise on hippurate kinetics. It was stressed that the patient should remain comfortable during the test. The work load was to be considered inadequate if it could be continued indefinitely or too heavy if it resulted in exhaustion. Patients sitting in front of the gamma camera on a bicycle ergometer were asked to sit straight-backed so that the kidney-to-camera distance was kept small. Pulse and BP were noted before the exercise. Ergometric resistance was set at 60 W for women, 80 W for men, after 60 rotations per minute were reached. After 1–2 min of exercise, the pulse-rate change in response to exercise was noted. Renography was begun only after the pulse rate increased at least 20 beats per minute. Following radiotracer injection, the patients continued with exercise, ergometric resistance being adjusted according to the wishes of the patients. Pulse and BP were monitored during interruptions of exercise at 10 min and again at the end of the study. Pulse rate served as an objective parameter of the effectiveness of exercise, and as a test to identify eventual over-exertion. BP measurements were also made to identify potentially dangerous BP elevations in response to exercise.

Radionuclide renography was carried out after intravenous injection of either 7 μCi I-131 hippurate or 6 μCi I-123 hippurate per kg body weight. A 15-inch gamma camera equipped with a general-purpose medium-energy parallel-hole collimator was used for all studies, with a window setting at 25%, centered over the photopeak of the tracer. One-minute scintiscans were obtained, beginning with the injection, and at 1, 2, 3, 4, 7, 9, 14 and 19 min. To identify initial tracer appearance in the bladder, which was identified on the sequential scans, we extended the uninterrupted one-minute image sequence past the fourth minute when required. The examination was terminated after 20 min. At the end of the study the patients were told to empty the bladder, following which one last scintiscan was obtained. Data

TABLE 1. HYPERTENSIVES WITH POSITIVE AND NEGATIVE EXERCISE RENOGRAMS AS WELL AS NORMOTENSIVE CONTROLS WERE COMPARED WITH RESPECT TO AGE, BP, FREQUENCY OF DISSIMILAR SINGLE KIDNEY FUNCTION, PULSE RATE, PARENCHYMAL TRACER TRANSPORT AND TRACER APPEARANCE IN THE BLADDER

	Patients	Age	Blood pressure			Single kidney function		Pulse			Disturbed parenchymal hippurate transport			Bladder visualized (min)		
	n	Yrs	Prone	Standing	Stress*	Equal	Dissimilar	Prone	Standing	Stress	Prone	Standing	Stress	Prone	Standing	Stress
Positive stress scintigraphy	29	44.5	170/110	156/104	175/107	19	10	74	80	116	0	12	29	3.5	4.6	10.2
Negative stress scintigraphy	22	40.8	158/105	152/109	166/103	14	8	69	71	121	0	0	0	3.1	3.3	3.6
Controls	15	35.9	123/80	117/78	130/79	14	1	76	81	116	0	0	0	3.1	3.0	3.4

* Stress = upright exercise.

were stored on magnetic tape, and were analyzed by minicomputer. Regions of interest (ROI) were placed over each kidney to determine single-kidney function. No attempt was made to exclude the renal pelvic system. Background ROIs were placed around each kidney, using a two-pixel width. Single-kidney hippurate uptake, expressed as a percentage of the total uptake of both kidneys, was determined. Uptake was taken to be proportional to the gradient of the renogram between 24 and 120 sec. The third curve segment of the renogram was analyzed by inspection only. Results of prone, standing, and exercise renography, and serial scintigrams, were compared. The pulse rate was taken and BP measured immediately preceding scintigraphy and after 10 and 20 min. Antihypertensive therapy was noted. We did not document the individual drugs taken by the patients.

RESULTS

Fifty-one hypertensives and 15 normotensive controls had prone, standing, and exercise renography. Twelve (24%) of the 51 hypertensive patients demonstrated bilateral orthostatic renal dysfunction (BORD) (Table 1). Renography in prone position was normal, or at least failed to demonstrate bilaterally disturbed transrenal hippurate transport. The examination in the standing position identified bilateral parenchymal hippurate retension. The bladder appearance time was delayed, with mean tracer appearance at 4.6 min. The same patients demonstrated tracer excretion into the bladder at 3.5 min during the prone examination. All patients who had BORD also had positive exercise renograms. Exercise caused bilateral renal dysfunction in 29 (57%) of the patients with hypertension (Fig. 1). Mean tracer appearance time in the bladder changed from 3.5 min in the prone position, to 10.2 min during ergometric stress (Table 1). Twenty-two (43%) of the 51 hypertensives had no evidence of posture- or exercise-mediated bilateral change of transrenal hippurate transport. Note that eight of these hypertensives did have dissimilar single-kidney function, so that parenchymal or renovascular hypertension must be considered in these patients. Only 14

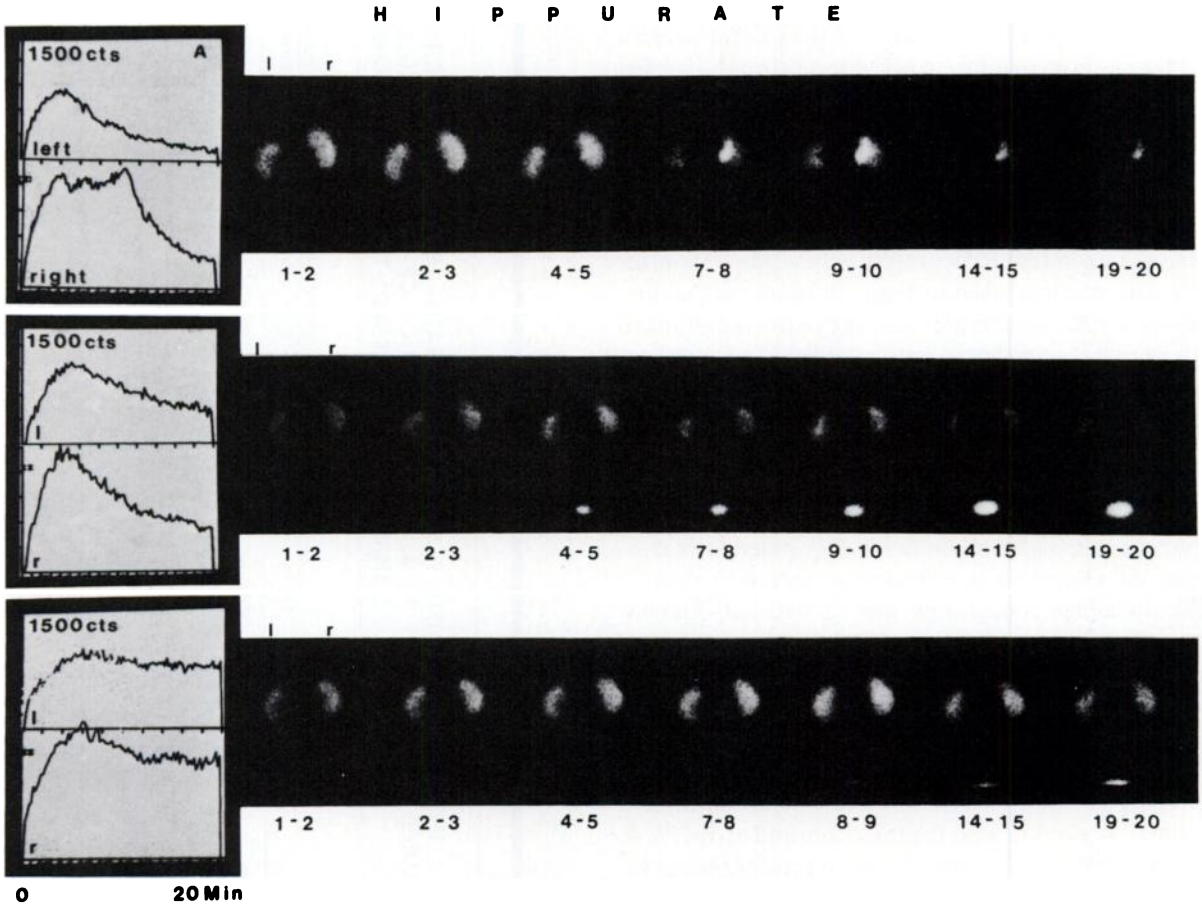

FIG. 1. Renograms and scintiscans from a 40-yr-old hypertensive patient examined in prone and standing positions, as well as during exercise. Prone examination (top row) identified dissimilar single-kidney function: left kidney contributed 37%, right kidney 63% of total function. Parenchymal hippurate transport was normal. Hippurate transit failed to change when patient was examined in standing position (middle row). Exercise renogram (botton row) identified a bilateral disturbance of hippurate transport. Note the renogram's slightly flattened second segment, delayed tracer excretion into bladder, and pronounced tracer retention in renal tissue, causing the renogram's excretory segment to be elevated.

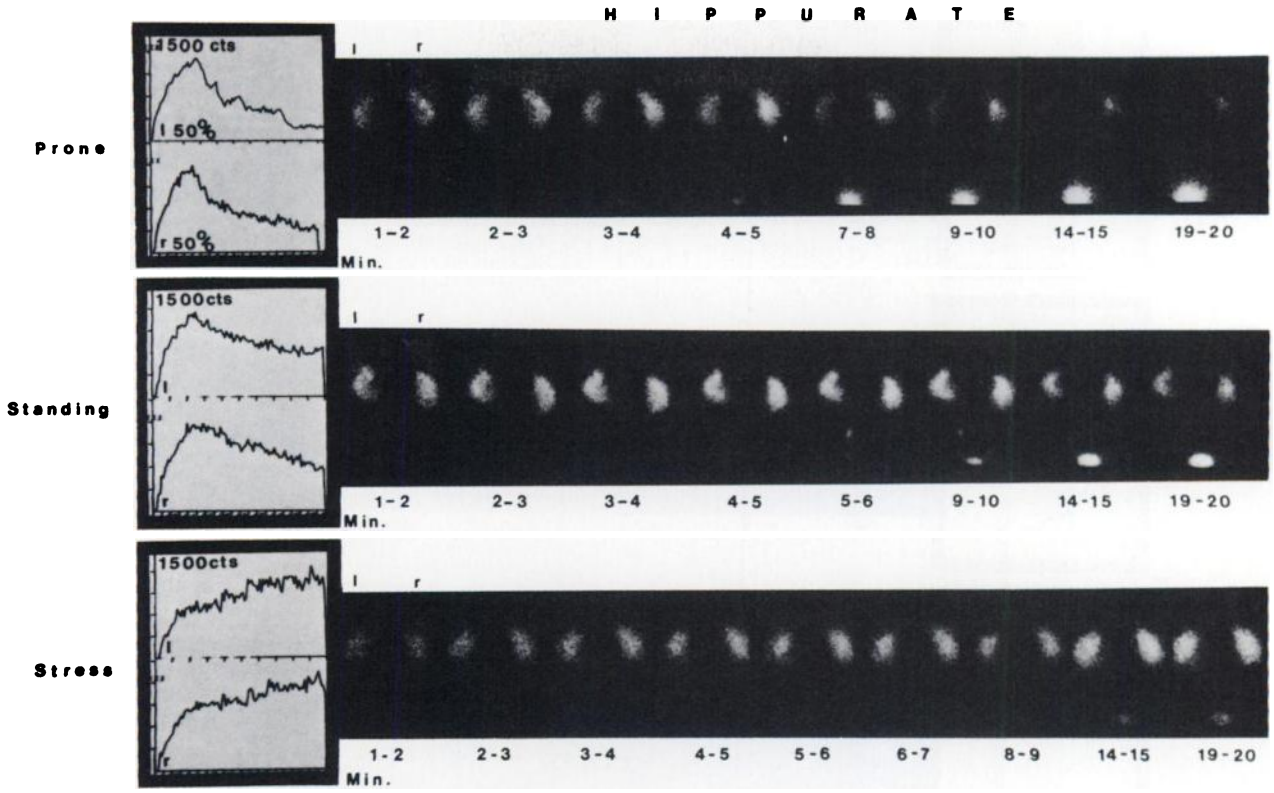

FIG. 2. Renograms and sequential scintiscans of a 45-yr-old patient with hypertension of unknown origin. Examinations were obtained in prone and standing positions, and during ergometric stress. The prone renogram was regular. Note equal distribution of renal function, bladder appearance during third minute, and regular contour of the renogram. Examination in standing position identified BORD. Hippurate appeared in bladder during fifth minute, and renogram's third segment was slightly elevated due to parenchymal tracer retention. Exercise caused a massive disturbance in renal handling of hippurate. Note flattened second segment and elevated third segment of renogram. Sequential scans show tissue retention of tracer, and delayed hippurate excretion into bladder.

(27%) of 51 hypertensives had balanced renal function and lacked evidence of posture- or exercise-induced abnormal hippurate transport. In four patients the transrenal hippurate kinetics were massively altered by exercise, so that radiotracer excretion into the bladder failed to occur during the 20 min of the examination, which was terminated after 20 min. In one patient we documented the first radioactivity in the bladder at three minutes, during the examination in the supine position. Exercise caused a massive functional disturbance, with the first bladder activity visible at 40 min. This was 20 min after the termination of exercise!

We find it remarkable that 19 out of 29 patients having positive exercise renograms had balanced single-kidney function (Fig. 2). This means that the calculated single-kidney function was between 45% and 55% for each kidney (Table 1).

We were unable to document a characteristic blood pressure (BP) pattern in patients with positive exercise renograms. A comparison of systolic BP values showed that stress resulted in a BP elevation in eight, a fall in eight, and no change in 13. Hypertensives with negative exercise scintigrams had an exercise-induced elevation of systolic values in ten cases and a fall in nine, while three remained stable. We considered BP values stable when systolic values were altered less than 10 mm Hg.

Fifteen normotensives participated as controls. None demonstrated bilateral renal dysfunction as a result of exercise (Fig. 3). BORD also failed to occur in this group (Table 1).

DISCUSSION

Exercise renography appears to us to be a most exciting approach for the evaluation of patients with hypertension, since exercise was shown to be a potent trigger of transient renal dysfunction. We believe the procedure to be of interest for the following three reasons.

1. Exercise renography appears to be a powerful new tool to study transient tubular dysfunction in the kidney, a function response that has escaped previous detection. Bilateral orthostatic renal dysfunction (BORD) was described recently (*1*), and its identification resulted in a search for other physiologic stimuli capable of revealing the tubular disturbance. The present study shows that exercise is a powerful trigger of transient tubular dysfunction. Note that we identified BORD in 24% of

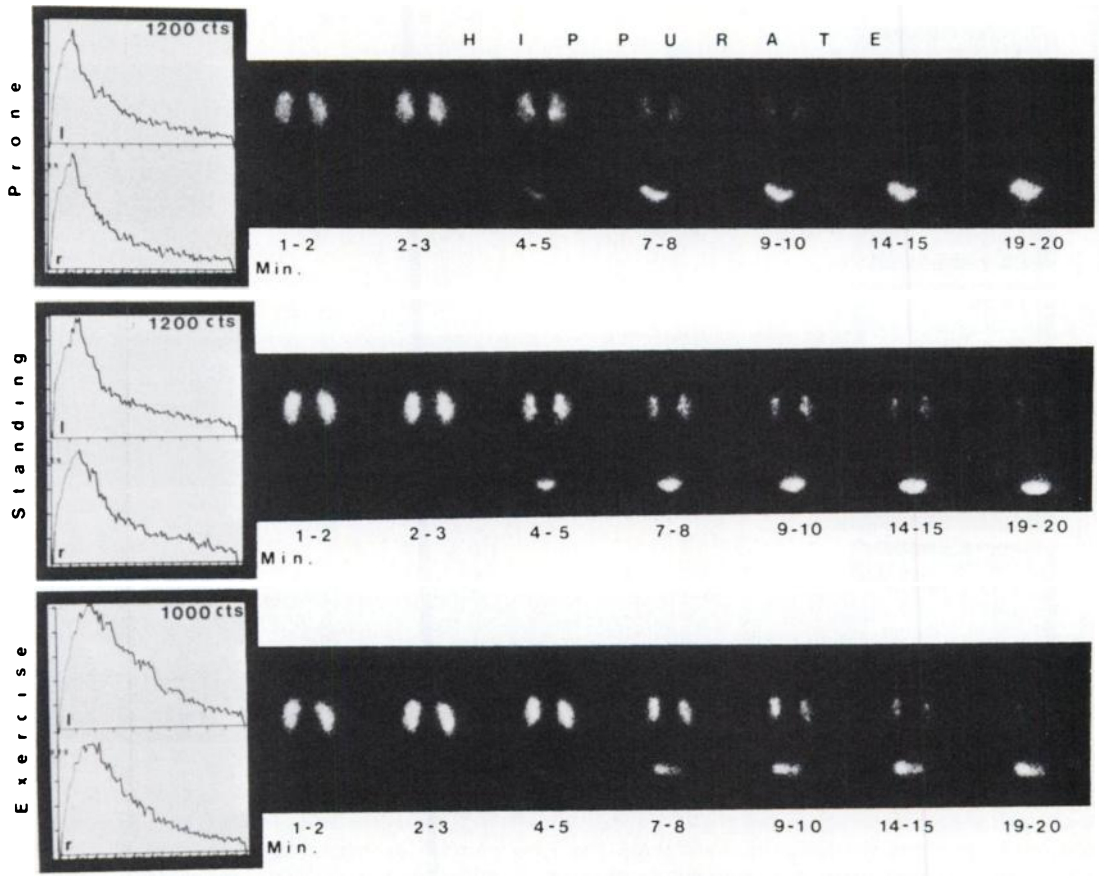

FIG. 3. Renograms and scintiscans of a normotensive 29-yr-old volunteer. Renography was not influenced by posture or exercise.

the patients, and were able to document exercise-induced bilateral tubular dysfunction in 57% of the hypertensives examined.

The presented renographic pattern must be interpreted as pointing to variations of renal cortical blood flow. We believe that a cortical vasomotor disturbance is the mechanism responsible for transient tubular dysfunction in hypertension. The sympathetic nervous system and the renal system of autoregulation must be considered as capable of initiating the vasomotor disturbance. Numerous reports have implicated an elevated sympathetic nervous tone in the genesis of hypertension (*2–8*). We are inclined, however, to emphasize the renal system of autoregulation in explaining the observed abnormality. Case et al. felt that constriction of renal arterioles may result when these are hyperresponsive to vasoconstrictor stimuli, or when endogenous vasodilator mechanisms are deficient (*7*). The observation of posture-dependent tubular dysfunction in renal transplants with vascular stenosis and hypertension (*9*) indicates that transient vascular spasm is not dependent upon the sympathetic nervous sytem. Consider that the transplant's vascular system is not under direct sympathetic control. Britton recently presented a most convincing theoretical model in which he postulated the existence of overcontraction of cortical nephron afferent arterioles in essential hypertension (*10*). Britton's hypothesis lends considerable suport to the interpretation of our findings.

2. We feel that initial results with exercise renography suggest renal involvement in essential hypertension, and our guess is that this condition is probably a form of nephrogenic hypertension. This hypothesis is based on the following: (a) We have a theoretical model, independently formulated by Britton, that helps explain the results of our study (*10*). Our work was guided by a working hypothesis similar to the one offered by Britton (*1*). The identification of frequent bilateral tubular dysfunction, triggered by work, appears to meet the expectations of the formulated models. (b) A large number of hypertensives show abnormal renograms. Note that 29 (57%) of our hypertensive patients had abnormal exercise renograms, while another 8 (16%) without bilateral abnormality, had unilateral reduction of hippurate uptake. Only 14 (27%) hypertensives had no renographic evidence of tubular dysfunction. Renal hypertension, as currently defined, could not account for this very high frequency of abnormal renograms in this patient population. (c) We find many hypertensives with balanced renal function. This too suggests that our

population of exercise-positives includes hypertensives traditionally not classified as being nephrogenic in origin.

3. Results of exercise renography may help to explain the contradictory reports relating to the value of renography in the evaluation of hypertension. It now appears that the physiological model used in the past was inadequate for renogram interpretation in patients with hypertension. We have noted that renogram normalization may lag far behind the exercise stimulus. Note that posture, as well as unintended exercise (stairs, haste to be punctual for the renal-function study) may influence the outcome of renography in hypertension.

ACKNOWLEDGMENTS

We thank Ms. Doris Weber for her expert technical assistance and Mrs. Ellen Bender for her help in preparing the manuscript.

REFERENCES

1. CLORIUS JH, SCHMIDLIN P, RAPTOU E, et al: Hypertension associated with massive, bilateral, posture-dependent renal dysfunction. *Radiology* 140:231-235, 1981
2. DE CHAMPLAIN J, FARLEY L, COUSINEAU D, et al: Circulating catecholamine levels in human and experimental hypertension. *Circ Res* 38:109-114, 1976
3. ANDREJAK M, SIMON A, HARDIN JM, et al: Hypertension artérielle systémique: Rôle pathogénique due système nerveux sympathique. *Nouv Presse Med* 6:3963-3967, 1977
4. ESLER M, JULIUS S, ZWEIFLER A, et al: Mild high-renin essential hypertension. Neurogenic human hypertension? *N Engl J Med* 296:405-411, 1977
5. LÖRELIUS LE, LÖFROTH PO, MÖRLIN C, et al: Renal haemodynamics before and after splanchnic block in patients with hypertension. *Scan J Clin Lab Invest* 38:233-240, 1978
6. LÖRELIUS LE, MÖRLIN C, WIDE L, et al: The effect of splanchnic block on renin production and renal haemodynamics in hypertensive patients. *Scan J Clin Lab Invest* 39: 241-246, 1979
7. CASE DB, CASARELLA WJ, LARAGH JH, et al: Renal cortical blood flow and angiography in low- and normal-renin essential hypertension. *Kidney Int* 13:236-244, 1978
8. HOLLENBERG NK, BORUCKI LJ, ADAMS DE: The renal vasculature in early essential hypertension: Evidence for a pathogenic role. *Medicine* 57:167-178, 1978
9. CLORIUS JH, DREIKORN K, ZELT J, et al: Posture-induced disturbance of pertechnetate flow and I-123 iodohippurate transport in some renal graft recipients with hypertension. *J Nucl Med* 21:829-834, 1980
10. BRITTON KE: Essential hypertension: A disorder of cortical nephron control? *Lancet* II:900-902, 1981