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ROUND TABLE CONFERENCE ON CAPTOPRIL

SCIENTIFIC SESSION
OF THE
HUNGARIAN SOCIETY OF CARDIOLOGY
May 7–9, 1986, Balatonfüred, Hungary

(Captopril is marketed in Hungary under the trade name Tensiomin,®
EGIS Pharmaceuticals, Budapest, Hungary)

CONTENTS

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IMPORTANT CLINICOPHARMACOLOGICAL ASPECTS OF CAPTOPRIL

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With a brief description of the physiological role of the renin-angiotensin-aldosterone system in the regulation of blood pressure the most important clinicopharmacological aspects of the converting enzyme inhibitor, captopril, is outlined. Hemodynamic and humoral effects, pharmakoinetics, indications, contraindications, dosage, side effects, drug inractions and usage in diagnostic procedures of captopril is described. The possibility of captopril therapy in children is also discussed.

Keywords: renin-angiotensin-aldosterone system, regulation of blood pressure, converting enzyme inhibitor, captopril, captopril therapy in children

Captopril was the first antihypertensive agent to act through the inhibition of angiotensin converting enzyme (ACE) and proved to be suitable for human use. The role of renin-angiotensin system in the physiological and pathological regulation of blood pressure is more or less known. Renin — a peptidase enzyme — is produced in several tissues (the juxtaglomerular apparatus of kidney, salivary gland, placenta, CNS, etc.) of the organism. In pathomechanism of hypertension renin has distinguished role at two sites; i.e. in the kidney and in the CNS. The polypeptide angiotensinogen, synthetized in the liver (and also in certain cells of CNS) is converted by renin to the decapeptide angiotensin-I which is transformed by ACE to the effective octapeptide angiotensin-II. The main effect of angiotensin-II is vasoconstriction, and hence increase in *total peripheral resistance* (TPR) and blood pressure. Angiotensin-III (a heptapeptide) produced by angiotensinase enzyme from angiotensin-II has some effects similar to those of angiotensin-II since it significantly stimulates *aldosteron* production in the glomerular zone of adrenal gland. The reabsorption of sodium and water in renal tubuli as well as the absorption of sodium in the intestines is increased by aldosteron. As a consequence, *hypervolemia* develops, which, together with the positive inotropic effect of Angiotensin-III., results in an increase of *cardiac output*.

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Angiotensin-II, acting on specific presynaptic receptors at noradrenergic synapses both in the CNS and at the periphery, increases the release of noradrenaline. Thus it significantly elevates the *sympathetic tone* which further augments the cardiac output and peripheral vascular resistance. In addition to these effects, AgII increases also the production of ACTH and vasopressin and water-absorption.

Thus, due to the effect of Angiotensin-II on TPR, cardiac ouput and plasma volume are also increased, consequently, *blood pressure* becomes elevated.

Apart from angiotensin-I, ACE exerts an effect also on the metabolism of *bradykinin*. By destroying bradykinin, it lowers the plasma concentration of this effective vasodilator substance. Bradykinin acts, at least partly, via the increase of the production of vasodilator prostaglandins (PGE_2). In addition, ACE may play a role in the metabolism of certain endogenous opioid peptides, i.e. it may also destroy the vasodepressor beta-endorphin.

Thus, the renin-angiotensin-aldosteron-bradykinin-prostaglandin-beta-endorphin system has a profound influence on the actual level of blood pressure. In this system ACE plays a central role /1, 11, 12, 16, 17, 19, 20, 21, 24, 27, 30, 32/.

1) MECHANISM OF CAPTOPRIL ACTION

Both the hemodynamic and humoral effects of captopril can be explained by the changes brought about by the inhibition of ACE. TPR is significantly decreased while the heart rate is either not changed or decreased by captopril. The decrease of TPR is mainly the consequence of the decrease in the concentration of Angiotensin-II. both in the plasma and the tissue including CNS /6, 7, 8, 14, 25, 27, 29, 32, 33/.

Cardiac output is usually increased due to the decrease of "after-load", however, it may be decreased in patients with hyperkinetic syndrome /47/. The renal blood flow is enhanced /22/; the glomerular filtration rate is either unchanged or decreased. Plasma aldosteron and vasopressin levels are reduced plasma renin activity in enhanced /46, 47/.

Consequently, the urinary excretion of sodium is increased /41/.

Plasma concentration of bradykinin /19, 21, 30/ and that of the vasoactive metabolites PGE_2, /30/ are increased either directly by captopril /12/ or indirectly by the increased bradykinin level. The role of elevated bradykinin and PGE_2 levels in the hypotensive effect of captopril is still under discussion /12, 30/.

The facilitation of noradrenergic transmission by Angiotensin-II. is well-known /20/. Captopril inhibits the pressor response elicited by sym-

pathetic nerve stimulation. The pressor responses elicited by AgII and noradrenaline are inhibited by chronic captopril-administration /1/. Thus, one can assume that pre- and postsynaptic inhibition of vascular sympathetic innervation may also play a role in the hypotensive effect of captopril.

It is well-documented that the effect of captopril on CNS renin-angiotensin system is a part of the antihypertensive effect /7, 17, 32/. The parasympathetic tone, elevated by captopril, may also contribute to the development of antihypertensive effect and, in some instances, to the occurrence of bradycardia /5, 29, 47/.

Since captopril had a favourable effect in migraine and the plasma concentrations of beta-endorphin were elevated by captopril, and the antihypertensive effect of captopril could be inhibited by naloxone in animal experiments it was hypothetical that its effect on endogenous opioid mechanisms may play a role also in the antihypertensive effect /11, 24/. However, the experiments carried out in hypertensive patients do not support this theory /47/.

Summarizing the data one can conclude that captopril potently decreases blood pressure both in high- and normoreninemic hypertension, and in some cases even in low-renin hypertension. Furthermore since its antihypertensive effect does not show a strict correlation with the effect on plasma ACE, it is assumed that other mechanisms may also be involved in its beneficial effect in arterial hypertension. As possible mechanisms the increase of vasodilator bradykinin and PGE_2 levels, decrease of noradrenergic neurotransmission, and activation of depressor endogenous opioid system might be suggested. Further studies are necessary to clarify the exact mechanism of action.

2) PHARMACOKINETICS OF CAPTOPRIL

In case of oral administration captopril is absorbed rapidly and almost completely (75%) from the gastrointestinal tract. Its 30% is bound to plasma proteins. The absorption is decreased after meals therefore it is recommended to take it before meals. The peak value of plasma concentration occurs 30–90 minutes after oral administration.

Unchanged captopril is excreted by urine (30–50%) within 4 hours after the intake. The rest is rapidly metabolized in the liver (Disulfid-dimer, cystein-disulfid-dimer). The half-life of excretion is less than 3 hours in healthy subjects but it correlates well with the endogenous creatinine clearance. In case of reduced renal function higher plasma concentrations have been observed thus the dosage should be decreased accordingly (see Dosage section).

Captopril is rapidly distributed in the various tissues but it does not pass easily the blood-brain barrier. In small amount it is excreted with the breast milk and also passes the placenta-barrier /14, 33/.

3) THE INDICATIONS OF CAPTOPRIL-TREATMENT

Both in *essential hypertension* (WHO grades II–III) and severe, accelerated hypertension the blood pressure can be effectively decreased by combinations containing captopril. In these combinations captopril can be used to supplement the conventional double (beta-blocker plus diuretic, central antihypertensive agent plus diuretic, vasodilator plus diuretic) or triple (beta-blocker plus diuretic plus vasodilator, central antihypertensive agent plus diuretic plus vasodilator) combinations as 3rd-5th step agent. In patients treated previously with diuretics where the renin-angiotensin system is significantly stimulated and volume-depletion exists caution should be exercised due to the probably increased sensitivity to captopril; therefore, smaller dosage (6.25 mg) than the usual is advised with subsequent dose-elevations according to the necessity /41, 43, 44, 45, 46, 47/. Its effectiveness is increased in renovascular hypertension, too; lower dosage (6.25–12.5 mg 3 times daily with dose-increases if necessary) is required also in such cases; the monotherapy is sufficient till the surgical intervention or for treatment of recidive hypertension after the operation /47/. Favourable experiences have also been reported in *renal-transplant recipients with hypertension* /10/.

In hypertensive patients with *bronchial asthma* or *diabetes mellitus* captopril may substitute the beta-blockers thus it can be applied as a first-second choice agent; it does not induce bronchial spasm and does not worsen the metabolic impairment in diabetes. The blood levels of lipids are not influenced. In monotherapy, captopril does not cause orthostatic hypotension; due to lack of this effect it could be administered in monotherapy in *elderly hypertensive patients* with favourable results /9, 41/. Since the antihypertensive effect of captopril appears within 30 minutes, it can be effectively applied in *hypertensive emergency states;* both oral and sublingual administration may be advised in a dose of 20 mg /3, 31/.

Captopril lowers the peripheral vascular resistance and the left ventricular filling pressure in patients with heart failure; it can be recommended in cases of heart failure refractory to digitalis and diuretic combination /40/. It can also be administered in combination with other vasodilators (prazosin, dihydralazine). Due to the higher plasma renin activity, greater hypotensive effect can be expected in these patients; therefore smaller initial dosage (6.25 mg) is advised. The resulting hypotension is well tolerated by the patients probably due to the unimpaired cerebral flow. Heart failure caused

by valvular dysfunction (aortic, mitral), cardiomyopathy, coronary disease and also by hypertension responds well to captopril treatment /36, 37, 38, 40, 45/.

Captopril can be tried for the treatment of primary pulmonary hypertension /25/.

Beside the above diseases, captopril was applied with success in the treatment of *Raynaud' syndrome, scleroderma* (even the renal impairment may improve, /39/, *'s* and *idiopathic edema* /41/.

4) CONTRAINDICATIONS OF CAPTOPRIL-TREATMENT

Since captoptil passes the placenta-barrier and causes embryopathy it is absulutely contraindicated for the treatment of *pregnant* hypertensive patients. It appears also in breast milk therefore it is not indicated for the treatment of *lactating mothers*. When its administration cannot be avoided (e.g. lactating mother with renovascular hypertension refractory to treatment) then the nursing should be stopped /14, 33/. Naturally, it is contraindicated in patients who are hypersensitive to captopril, in severe *leukopenia, thrombopenia*, in *membranous glomerulopathy* induced by captopril.

5) DOSAGE OF CAPTOPRIL

In essential hypertension a daily dose of 75–150 mg divided in 3–4 doses can be initiated. Since the maximum antihypertensive effect appears even after taking the first dose one does not have to wait for days to increase the dose; the requirement should be established by gradual, daily dose-elevations. If high renin hypertension cannot be excluded at the start of treatment or the patients were previously treated with diuretics then the first dose should be quite low (6.25 mg) with close monitoring of blood pressure the subsequent dose can be increased (12.5 or 25 mg).

The maximum daily dose is 300 mg; it is not advised to surpass this level since the hypotensive effect does not increase but the side effects are more frequent and more severe above this dose level.

In case of renal disease the maximum daily dose depends on the creatinine-clearence according to the followings:

Creatinine clearance:	max. daily dose:
2.31–1.18 ml/sec	300 mg
1.15–0.61	150
0.57–0.31	75
less than 0.29	37.5

6) SIDE EFFECTS OF CAPTOPRIL

The following side effects have been reported in the literature: dysgeusia (they appear 2–3 months after the start of treatment and disappear spontaneously,) allergic rashes, flush, loss of appetite, dryness of mouth, aphtous ulceration on the gingiva, vomiting, cholestasis, headache, dizziness, sleep-disturbance, paresthesias, rarely palpitation, chest pain, neutropenia, agranulocytosis, thrombopenia. Although infrequently, the values of liver enzymes may be increased. In patients with bilateral renovascular hypertension, due to the eliminnation of autoregulation an increase of creatinine level may appear which may have diagnostic significance /4/. In renal transplant recipients when the artery of transplanted kidney becomes stenotized an acute status-worsening may occur upon captopril administration which is reversible and may have also diagnostic value (4, 18/. In aldosteron-deficient patients captopril may induce severe hyperkalemia /34, 41/.

It should be emphasized that the side-effects appear very rarely in case of conventional therapeutic doses (75–150 mg a day). Their survey in the literature was based on experiences obtained upon administration of the oversized initial, significantly higher dosages (400–600 mg a day).

7) DRUG INTERACTIONS

Additive interaction was observed between captopril and several other antihypertensive agents (diuretics, adrenergic blockers, vasodilators, central alpha-adrenergic agonists) /41, 47/. It potentiates also the antihypertensive effect of nifedipine. Indomethacin and other cyclooxygenase inhibitors counteract the antihypertensive effect of captopril. Combined treatment with aldosteron antagonists (spironolacton, K-canrenoate) or potassium-sparing diuretics (triamteren, amilorid) may cause severe hyperkalemia and hypadrenic symptoms /41/. Symptoms relating to neurological dysfunction have been observed in two patients taking both captopril and cimetidine /2/. Lethal Stewens–Johnson syndrome has been reported in a patient taking captopril and allopurinol /23/.

8) TREATMENT OF CAPTOPRIL OVERDOSAGE

Hypotension due to the overdosage should be treated with the infusion of physiological NaCl solution. In the most severe cases AgII infusion should be administered with frequent control of blood pressure. Captopril can be dialyzed from the circulation.

9) DIAGNOSTIC POSSIBILITIES WITH CAPTOPRIL

In renovascular hypertension even very low doses elicit significant hypotension due to the increased effectiveness. Following the oral administration of 6.25 mg single dose, blood pressure should be monitored for 3 hours by measuring blood pressure at half-an-hour intervals. If hypotension reaches or surpasses 50/20 mmHg (systolic/diastolic value) then renin-dependence of hypertension is likely, therefore a renovascular pathomechanism can be assumed. Captopril stimulates renin release thus it is supposed that if the ratio of the renin-activities measured in blood samples drawn from the two renal veins 30 minutes after taking 25 mg captopril orally is higher than 3.0 then it enhances the probability of a succesful surgical intervention /15, 16, 26/. The renin-stimulation produced by captopril can be demonstrated also in the peripheral blood /16/ of patients with renovascular hypertension but it cannot be used for the prediction of the success of surgical intervention.

Dynamic renal scintigraphy performed under the influence of captopril indicated higher difference between the sides than without treatment; this finding has also diagnostic significance /42/.

Primary hyperaldosteronism

In contrast to renovascular hypertension these patients have low plasma renin activity and AgII levels. Therefore, the hypotensive effect of captopril is very mild or even it cannot be demonstrated. In patients with aldosteronoma in the adrenal gland captopril usually does not elevate plasma renin activity; it does not decrease the plasma aldosteron level /13/ and does not change the blood pressure, either. Patients with mineralocorticoid hyperplasia react differently to captopril; high dose of captopril (100 mg single dose) can stimulate the plasma renin activity but to a smaller extent than in patients with essential hypertension; the developing hypotensive effect is also weaker.

In most cases the adenoma (Conn's syndrome) and hyperplasia of adrenal gland /13,15) can be differentiated by the administration of high dose of captopril.

10) PEDIATRIC APPLICATION

In case of severe hypertension and heart failure captopril can be administered with extreme caution /36/. The advised daily dose is 1 mg/kg which may be increased to 2 mg/kg. Patients suffering from renovascular hypertension, high renin hypertension or a disease accompanied by sodium and volume depletion are more sensitive to captopril; the occurrence of the so-called

"first dose symptom" (profuse hypotension, collapse) can be expected due to the increased antihypertensive effectiveness thus the first dose (6.25 mg) should be very low /36/.

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A NEW EXAMINATION METHOD FOR DETECTING RENOVASCULAR HYPERTENSION: FUNCTIONAL DTPA RENAL SCINTIGRAPHY SENSITIZED BY CAPTOPRIL

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DTPA functional renal camera scintigraphy (DTPA-FS) was performed in 220 patients with moderately severe and severe hypertension after an initial 7–14-day Captopril+thiazide-type diuretic treatment. If, comparing it with the DTPA-FS prior to treatment, appearance or increase of a side difference were observed and it was also indicated by the clinical picture, nephroangiography was performed. Using this method, 15 cases of unilateral, 3 bilateral renal arterial stenoses were recognized, and in one case restenosis was diagnosed, in all cases of positive DTPA-FS with Captopril. In negative case of DTPA-FS sensitized with Captopril, there was no positive angiographic finding.

The method of DTPA-FS performed under Captopril effect is considered to be a simple, harmless, specific out-patient examination for screening genuine renovascular hypertension. To perform several angiographies likely to be negative can be avoided by this method. The hypotensive effect of Captopril may, at the same time, be a useful guide in differentiating patients with renovascular hypertension being suitable most of all for surgical intervention or angioplasty.

Keywords: Renovascular hypertension, Captopril functional renal scintigraphy.

Since the introduction of Captopril into the treatment of hypertension, several attempts have been made to utilize it for the detection of renovascular hypertension. The trial with the so-called single-dose Captopril has not proved to be specific. Atkinson et al. regard the effect of prolonged Captopril treatment of renovascular hypertension as the best indicator of surgical outcome /1/. In bilateral renal artery stenosis or in artery stenosis of a solitary kidney, administration of Captopril, or particularly its combined administration with a diuretic, may produce reversible renal insufficiency /3, 7/.

It was observed by Wenting et al. that if DTPA functional kidney scintigraphy was performed in patients with renovascular hypertension treated with Captopril, in one part of them the isotope activity over the kidney of a stenotic artery decreased considerably during Captopril treatment /9/.

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After discontinuation of Captopril treatment isotope activity could again be detected also in the kidney of stenotic artery.

It seemed advisable therefore to perform the basic DTPA examination in all patients with moderately severe and severe hypertension and, subsequently, to carry out a repeated DTPA-FS by administering Captopril (Thensiomin ®, EGIS), and a thiazidetype diuretic as an initial therapeutic attempt. The results of the first series of trials, the selection of patients and the method were reported in Orvosi Hetilap (Medical Journal, in Hungarian) /6/.

PATIENTS AND METHODS

Patient were selected from begining of 1985 according to the following criteria: a,moderately severe or severe hypertension b,therapy-resistance c,sudden-onset hypertension or worsening of hypertension d, abdominal vascular bruit over the kindeys in hypertension.

The basic DTPA-FS was made without treatment or continuing the antihypertensive treatment prior to first examination at our outpatient hypertension clinic (considering that these drugs do not influence the glomerular filtration of DTPA). After the basic DTPA examination all antihypertensive drugs were stopped. Captopril were given all patients in a starting dose of three times 6.25 mg or 12.5 mg daily. Besides C diuretics were given to all patients to potentiate the effect of C (Clopamid 10 mg/day or Chlorthalidone 25 mg/day). The next days the dose of C was tailored according to its hypotensive effect. The aim of the treatment was possibly to normalise the blood pressure. The maximal dose of never exceeded three times 50 mg a day.

The second DTPA-FS was done 1.5–2 hours following the last dose of C after 14 days treatment. The DTPA-FS was made with 185 MBq Tc^{99m} DTPA, useing 9100 typ gamma-camera (GAMMA-Hungary) and MB9101/A typ. computer (GAMMA-Hungary). After iv. injection of Tc^{99m}-DTPA analoge serial scintiscans were made in the $0–10^{th}$ seconds (perfusion phase) and in the 3^{rd} and 12^{th} minutes (renographic phase). The first 20 pictures of the time-activity curves were registrated with 0.5 second intervals then the next 50 pictures with 20 seconds intervals. The time activity curves of perfusion and secretion phase were analysed separately with ROI technic. The difference of amplitudes, the change of intrarenal transport of DTPA, the shift of Tmax. and prolongation of half-time was assesed. To eliminate the difference originating from the size-difference of the kidneys we calculated an activity/area time-activity curve too. Increase of side difference (i.e decrease of activity of one side) greater then 50% and shifting of Tmax to the right was considered to be positive. Decrease of activity and shifting to the right on both sides-concomitted with rise of serum-creatinine-was the signs of bilateral renal artery stenosis. In this case the C treatment was stopped.

Şerionephroangiographies were made by the Seldinger-method. The renal function (serum-creatinine) was controlled in all cases of C treatment of the 3^{rd} or 5^{th} day. The patients were admitted to our programme protocol with their informed consent.

RESULTS

DTPA-FS sensitized with Captopril has been performed in 220 patients since September 1984. The results were considered to be positive with an increase of difference in the levels of activity shown in the analogue scintiscans or with the appearance or increase of side difference between the two kidneys in the time activity curves (i.e. decrease of activity of one side).

Table I. summarizes the data of all patients examined and treated with Captopril.

Table II. shows the result of the completed examinations. Positive angiographic findings were obtained in all 19 positive DTPA-FS examinations sensitized with Captopril.

Table I

DTPA functional scintigraphy performed under Captopril effect

No. of patients:	220	(83 males, 137 females)
Mean age:	48.3	(17–76 years)
Mean blood pressure		
Before Captopril:		179.7/113.3 mm Hg
	(S.D. ±	24.4/ 13.4 mm Hg)
After Captopril:		150.8/ 93.4 mm Hg
	(S.D. ±	21.7/ 12.1 mm Hg)

Table II

DTPA functional scintigraphy with Captopril

DTPA-FS with Captopril n=220	Nephroangiography n=87
Positive: 19*	Positive: 19*+

* 15 unilateral, 3 bilateral renal arterial stenosis, 1 restenosis
\+ significant renal artery stenosis

No significant stenosis on angiograms were obtained using a negative DTPA-FS sensitized with Captopril.

It was also notable that the appearance or the mild degree of increase of a side difference sometimes observed in unilateral renal hypoplasia associated with parenchymal damage could be well differentiated from the fairly marked degree of positivity due to stenosis of the renal artery.

Side-effect appeared only in one case out of 220 examinations. The toxic maculopapulous skin change induced by the drug completely disappeared within some days after stopping the drug. Studying the blood pressure response during drug administration, it could be stated that the singificant decrease in blood pressure due to Captopril was not specific for the renovascular hypertensive patients, since a considerable part of patients with essential hypertension showed a similarly markedly reduced blood pressure of the same degree in response to the combined Captopril+thiazide type diuretic treatment. For illustration two cases are presented.

Figure 1. shows the results of DTPA-FS examination of a 35-years-old female patient prior to, and during a 3-day and 14-day Captopril treatment.

In Figure 2. time activity curves were plotted which were naturally made parallel to the analogue scientiscans. It was revealed by both methods that following a 14-day Captopril treatment, the Tc^{99m} DTPA excretion (3 min and 12 min) of the right kidney, decreased fairly markedly, namely it was practically undetectable. The perfusion (blood supply) of the right kidney is maintained (0–10s). The patient's blood pressure decreased from the earlier fairly high level to normal following the first Captopril dose and remained at this level throughout the whole Captopril treatment.

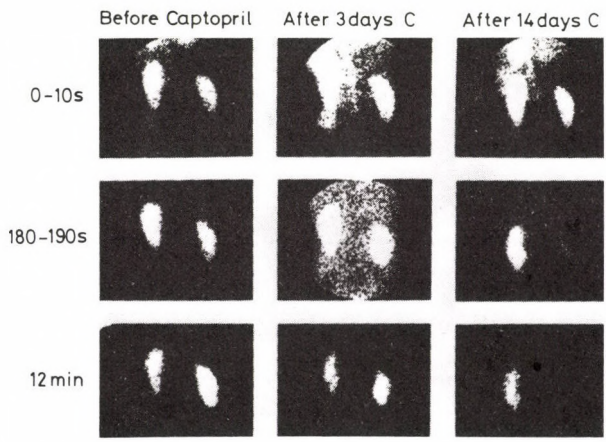

Fig. 1. Mrs. Gy.F. 37 years old woman. Analoge scintiscans. After 14 days C treatment no isotope activity in the right kidney in the glomerular phase

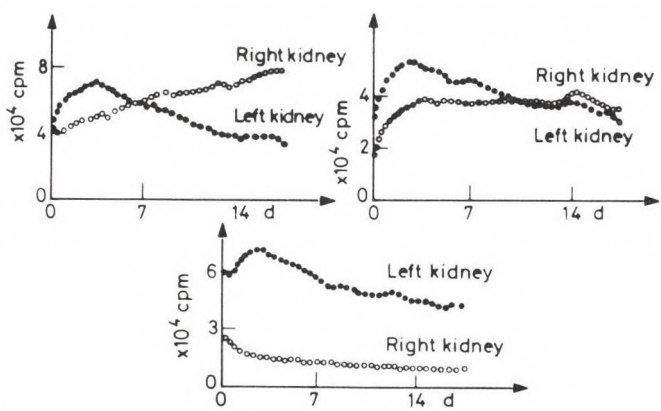

Fig. 2. Mrs. Gy.F. Time-activity curves. After 14 days C treatment the right kidney does not excrete DTPA

Figure 3. shows the nephroangiogram of the same patient having considerable stenosis of the right renal artery.

Figure 4 shows the analogue DTPA-FS scans of a male patient (42 years old), while Figure 5 the time activity curves. It is well discernible that the glomerular function of the right kidney – i.e. its isotope density – decreased significantly. There is no significant side-difference prior to C treatment on the time-activity curves of the two kidney's. The nephroangiogram of the same patient is presented in Figure 6. In the right renal artery there is a marked stenosis. The patient's blood pressure decreased from the earlier very high (190/125 mm Hg) to the normal (125/80 mm Hg) level.

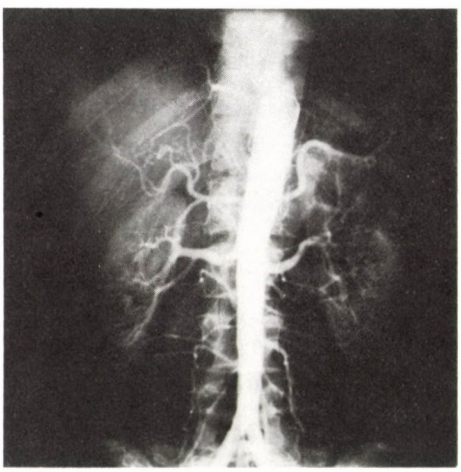

Fig. 3. Mrs. Gy.F. Nephroangiography. Right renal artery stenosis

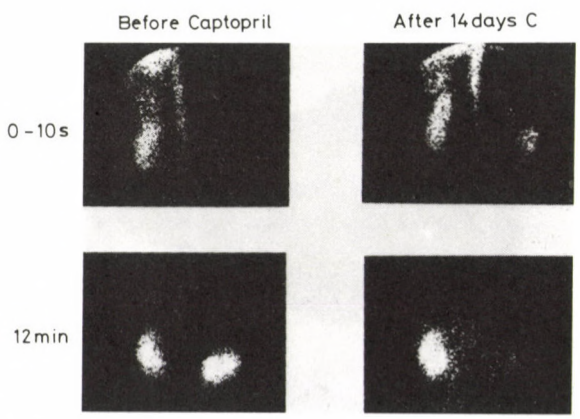

Fig. 4. Mr. M.K. 42 years old man. Analoge scintiscans. After 14 days C treatment there is no activity over the right kidney in the glomerular phase

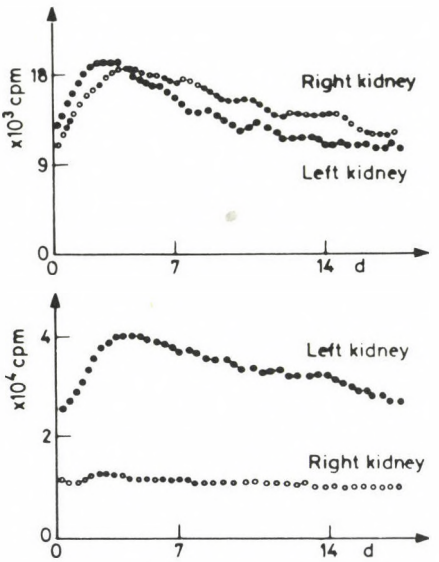

Fig. 5. Mr. M.K. Time-activity curves. Before Captopril there is no significant side-difference. Tmax of the right kidney is only slightly shifted to the right. After C the right kidney does not excrete DTPA

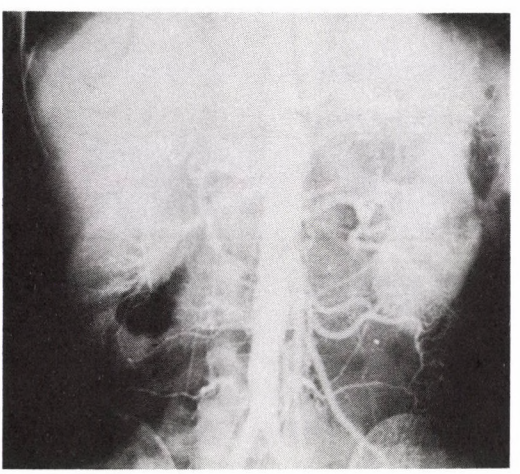

Fig. 6. Mr. M.K. Nephroangiography. Right renal artery stenosis

DISCUSSION

In view of our investigations, it appears that the present examination procedure helps in detecting the haemodynamically significant renal arterial stenosis. That means that genuine renovascular hypertension can possibly be differentiated from renal artery stenosis associated with essential hypertension.

It can be supposed that Captopril stops glomerular function only in haemodynamically significant stenoses. In this case the increased tone of the efferent arteriola is regulated by the intrarenal renin-angiotensin system. It is indispensable for maintaining the effective filtration pressure, compensating the poststenotic decrease of arterial pressure. Inhibition of the intrarenal renin-angiotensin system by Captopril may thus result in a considerable decrease in glomerular filtration in the kidney of stenotic artery. This is primarily not due to the reduced blood pressure but to the inhibition of the intrarenal renin system /2, 4, 8/. Diuretics potentiate this effect of Captopril partly by stimulation the renin system and partly by decreasing the angiotensin-II sensitivity of the mesangial cells.

To our opinion several days of Captopril treatment is needed to the assessment of C induced changes on renogramms, as it is shown on Figure 1 and Figure 2 of our case presentation. The specific effect of C is a cummulative one on the glomerular filtration of a kidney with stenotic artery. It is not in contrast to the observation of Geyskes et al. /3/. The longer use of C makes this diagnostic test more sensitive and specific. In agreement with *Atkinson et al.* the long terms use of C in renovascular hypertension is a better predictor of the surgical outcome than the single dose or short-term treatment /1/.

Renal artery stenosis disclosed with nephroangiography together with negative Captopril DTPA-FS is considered not to be renovascular hypertension, as it was found by some patients of Wenting et al. /9/. In this case essential hypertension and a given degree of renal artery stenosis is coexsisting, or a former renovascular hypertension is transformed to a fixed accelerated hypertension. In this occassions surgical intervention or PTA will esrolve only the stenotic lesion but the hypertension will persist.

DTPA camera nephrography performed under the effect of Captopril is a relatively simple, fairly sepcific, inexpensive and well reproducible method imposing a small radiation load on the patient for the detection of renovascular hypertension. Using this method, the number of expectedly negative nephroangiographies can be considerably reduced in hypertensive patients. The examination can be carried out on an out-patient basis, too. It seems advisable to test and control renal functions (and to eventually reveal a bilateral renal arterial stenosis) before and after Captopril treatment is started.

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MONOTHERAPY AND COMBINED TREATMENT WITH CAPTOPRIL

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The effectiveness of captopril, the dose-response relationships, the influence of diuretics on the effective dose of captopril, the possible combinations of captopril with other antihypertensive agents as well as the clinical value of monotherapy and combined treatment have been investigated in 48 patients with hypertension. This paper summarizes the data obtained in the course of several special clinico-pharmacological studies during a 4 year period (1982–1986). Captopril proved to be an antihypertensive agent with a wide therapeutic spectrum. As a single agent it was used especially in geriatric cases. Of the antihypertensive agents, diuretics have been combined with captopril most frequently but it has been concurrently administered with practically all the other antihypertensive drugs. Captopril appeared to be a safe agent without significant side effects. An increase in serum potassium levels by captopril were seen not infrequently; its advantages, disadvantages, prevention and mechanisms have been dealt with in detail.

Keywords: captopril, antihypertensive treatment, inhibition of converting enzyme

Captopril is a new tool in the treatment of hypertension /1, 3, 13/ and the prospects of its application are getting broader /4–12, 14–32/. Inhibitors of converting enzyme, such as Captopril can be used in the renovascular, malignant and accelerated "high renin" hypertension as well as in the "normal renin" and "low renin," moderate and mild hypertension /1–32/. Beside broad applicability other advantage of Captopril is that it can be combined with almost all the other antihypertensive agents.

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PATIENTS AND METHODS

A total of 48 patients was treated with Captopril (Capoten, Squibb, Tensiomin EGIS) during the 4 year period of acute and chronic studies (1982–86). Special clinico-pharmacological examinations were performed in all cases beside the measurement of blood pressure: endocrine changes and specific renal functions as well as the interaction of posture and the effects of glucose-loading were studied. Blood pressure was measured 10 times daily in supine and standing positions in 10 cases; in the other cases 3 times daily. Captopril was administered first in cases with essential hypertension refractory to the "standard triple therapy" (diuretic plus vasodilator plus beta-blocker); later in moderate and mild hypertension, heart failure, chronic renal failure, geriatric cases, with hypertension or /and edema, idiopathic edema and hepatic cirrhosis with ascites. "Follow up" studies were usually performed, the results of which were reported in our earlier publications /9–26/, The daily dose of Captopril was 12.5–450 mg divided in 3 doses.

In most cases 2.5–3.5 mg/kg/100 ml GFR captopril was administered but this dose could be reduced to one-third by the combined administration of a diuretic /13/. Extreme dosages were applied only exceptionally i.e. 100 mg/16 ml GFR daily /26/. As a diuretic chlorthalidon (Hygroton, Ciba-Geigy-Biogal) clopamide (Brinaldix, Sandoz-EGIS), dihydrochlorothiazide (Hypothiazid, Chinoin), muzolimine (Edrul, Bayer) and piretanide (Arelix, Hoechst) were used. Of the beta-blockers, metoprolol (Betaloc, Astra-EGIS) oxprenolol (Trasicor, Ciba-Geigy-Chinoin), pindolol (Visken, Sandoz-EGIS) and propranolol (Stobetin, Spofa) were administerd. Clonidine (Hemiton, VEB, Arzneimittelwerk), hydralazine (Nepresol injection, Sandoz, Depressan, Intermed) and nifedipine (Corinfar, Intermed) were also administered in the combinations. Considering the various protocols and research purposes of our investigations performed in the last 4 years, in this paper the main directions of our clinico-pharmacological studies are outlined by the presentation of representative cases beside the summarized blood pressure statistics. Methods of blood pressure measurements, classification of hypertension, routine laboratory and RIA hormone examinations as well as of the specific renal and other studies are listed in detail in our previous publications /9–26/.

RESULTS

I. *The effectiveness of Captopril in monotherapy*

First of all, the effective dose of Captopril producing a 10% decrease in blood pressure (BP) was established by gradually increasing the dose at 4–5 days' intervals. In 18 patients, the daily mean value of BP was decreased by 183±28 mg Captopril from 181±5/115±3 mmHg to 159±5/103 mmHg (by 11±1%) (p less than 0.001) (Fig. 1). The heart rate was not changed at the same time (75±2 and 77±2 beats/min).

The BP measured in supine position was decreased from 179±5/116±3 mmHg to 157±5/103±3 mmHg (p less than 0.001) at 8 a.m., from 186±7/119±3 mmHg to 161±5/104±3 mmHg (p less than 0.001) at 4 p.m., from 179±5/114±3 mmHg to 157±5/102±3 mmHg (p less than 0.001) at 10 p.m. The changes in blood pressure in upright position were similar; see. Fig. 2.

In some cases very high doses of Captopril were required for the effective reduction of the BP. In one of the cases, 300 mg daily dose of captopril induced an only small and transient decrease in BP. (Fig. 3). There was a patient whose BP was hardly influenced even by daily 400 mg Captopril;

some effect was observed only for 6 hours out of the 24 (from 4 p.m. till 10 p.m.) Fig. 4).

In another case the effect could be considerably increased only by raising the daily dose from 75 mg to 225 mg (Fig. 5). It was evident from these observations that the patients refractory to beta-blocker+diuretic+vasodilator combination may also be refractory to Captopril. Apparently, in some cases the cessation of resistance was partly dependent on the dose of Captopril.

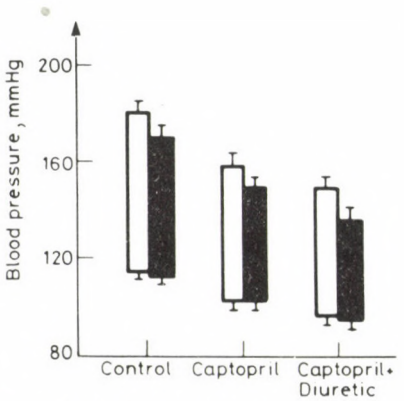

Fig. 1. Captopril elicited statistically significant decrease in systolic and diastolic blood pressure Addition of a diuretic potentiated the antihypertensive effect of Captopril

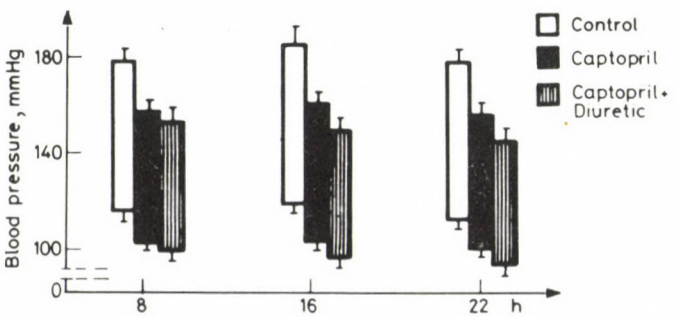

Fig. 2. Diurnal variation of blood pressure in standing position (pretreatment control) and during the administration of Captopril without and with diuretics

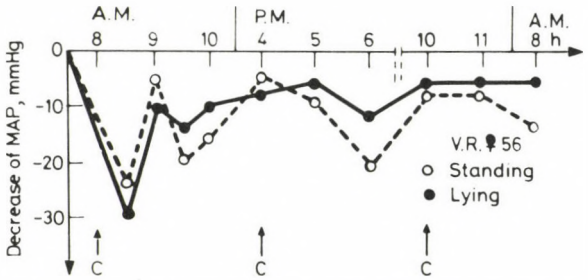

Fig. 3. Transitory small hypotensive effect of Captopril administered in daily 300 mg doses in a patient refractory also to the combination of a diuretic, betablocker and vasodilator. (Not indicated in the Figure: combination of Captopril and a diuretic resulted in a significant decrease in blood pressure

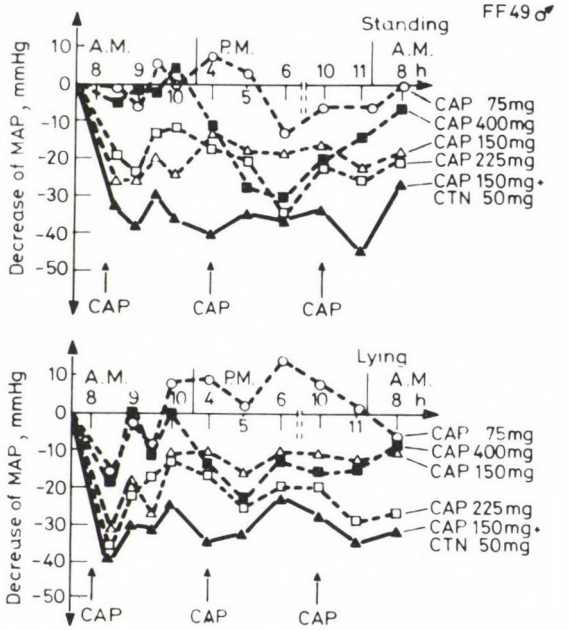

Fig. 4. The effect of Captopril monotherapy (dashed lines) and Captopril plus diuretic combination (drawn line) in a patient refractory to the combination of a diuretic, betablocker and vasodilator. Daily 75 mg Captopril administered alone is ineffective; daily 150—400 mg Captopril have some hypotensive effects. Daily 150 mg Captopril combined with 50 mg chlorthalidon (Hygroton) effectively decreases blood pressure. The effect is slightly more pronounced in the upright position

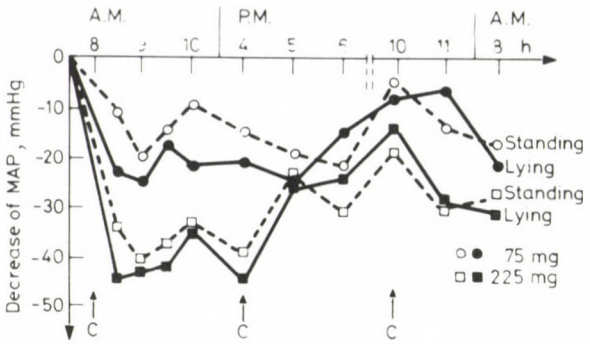

Fig. 5. Treatment of a patient refractory to antihypertensive drugs with gradually increasing Captopril doses. It can be seen that 1. 75 mg daily dose (divided in 3 doses) is less effective than 225 mg; 2. the effect is *not more* pronounced in the standing position (dashed lines) than in recumbency (drawn line); 3. the effect is greater in the first 8 hours than during the rest of the day

II. *Increase of the effectiveness of Captopril by diuretics*

On the basis of our preliminary experiences /13/, we used approximately one-third dose of Captopril in combination with diuretics. In 18 cases, BP measured in upright position was decreased from 150±5/104±3 mmHg to 141±5/96±4 mmHg. at 8 a. m., from 152±5/104±3 mmHg to 136±5/94±3 mmHg at 4 p.m., and from 151±5/101±3 mmHg to 134±6/94±4 mmHg at 10 p.m. (p less than 0.01) (Fig. 2). Although Captopril alone did not enhance the small orthostatic decrease in BP its hypotensive effect in combination with a diuretic was more pronounced in the upright than in supine position (Fig. 2). Diuretics may increase the sensitivity to Captopril and may suspend the resistance to it. In one of the cases where 400 mg Captopril was ineffective and the patient did not react to diuretics either, 150 mg Captopril became effective upon simultaneous administration of a diuretic (Fig. 4).

III. *Combination of Captopril with diuretics and other antihypertensive drugs*

In one of our patients (Fig. 6, upper part) treated with a combination of furosemide, clonidine and hydralazine, hydralazine had to be withdrawn due to side effects. Captopril was chosen for replacement. Very low doses (12.5–37.5 mg daily) proved to be effective (Fig. 6, lower part). The effectiveness of individual doses of Captopril in this case are presented in Fig. 7.

One of our young patients had "high renin" essential hypertension (the stenosis of renal artery had been excluded by angiography) and was refractory to multiple antihypertensive combinations. Although he seemed to be an "uncontrollable" case, a multiple combined therapy including Captopril was

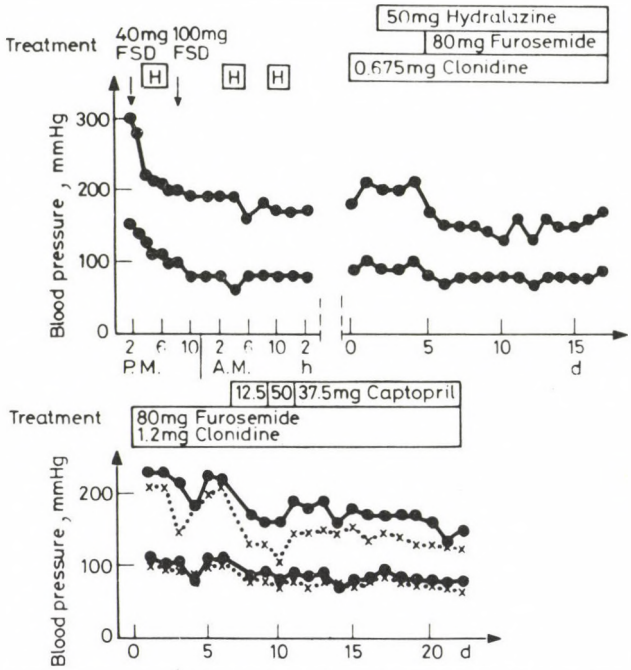

Fig. 6. In the *left upper part* of the Figure: the effect of the treatment of acute hypertensive crisis with the combination of furosemide+hydralazine can be seen. At the *right side:* the effect of triple combination. *Lower part:* the blood pressure was rapidly normalized by changing hydralazine to Captopril

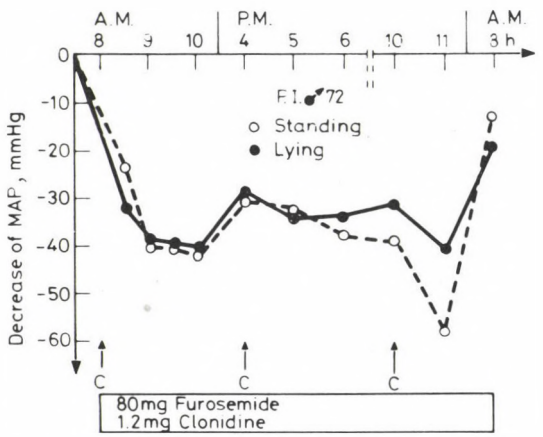

Fig. 7. Effect of 3×12.5 mg Captopril (c=Captopril) in the patient presented in Fig. 6. (drawn line: in the lying position; dashed line: in the upright position)

effective. Combination of 75–150 mg Captopril, 50 mg Hygroton, 60 mg Trasicor and 4 mg Minipress reduced mean BP by 25 mmHg in standing position. BP was decreased twice as much by 1. increasing the dose of Captopril to 250 mg (within the combination) or 2. by doubling the dose of Minipress and Trasicor (with unchanged Captopril dose of 150 mg) (Fig. 8). This is a good example for the utilization of dose-response relationships of antihypertensive drugs to suspend refractoriness.

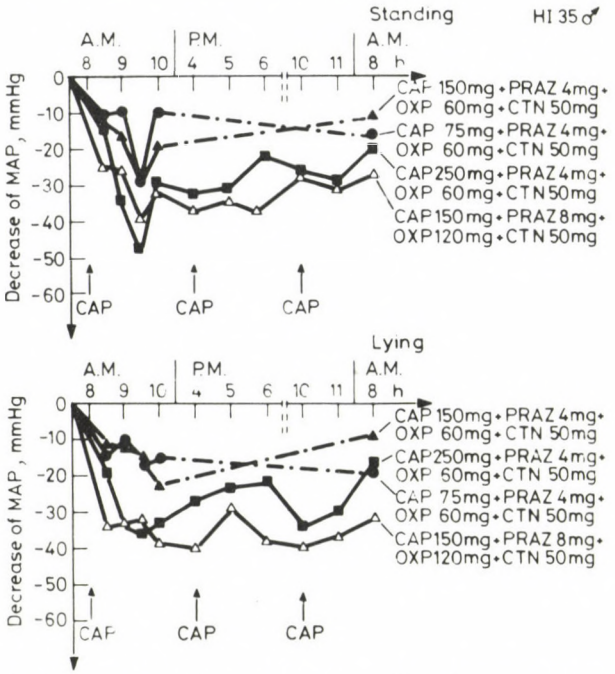

Fig. 8. Effect of the increase of the dose of the drug within the combination on blood pressure in an extremely resistant patient. [Praz=Prazosin (Minipress) CTN=chlorthalidon (Hygroton) OXP=oxprenolol (Trasicor)]

IV. *Captopril in geriatric cases*

The usefulness of Captopril monotherapy in geriatric cases is illustrated by the data of a representative patient in whom the high blood pressure was reduced to normal within a few days of treatment (Fig. 9). Excellent effect of combined therapy with captopril is illustrated by Fig. 10.

V. *Captopril in idiopathic edema*

Captopril was administered in two patients with severe idiopathic edema. Definite diuretic and natriuretic effects were observed in both cases. The edema was drained of and the demand for diuretics decreased. The hyperaldosteronism was ameliorated (Fig. 11).

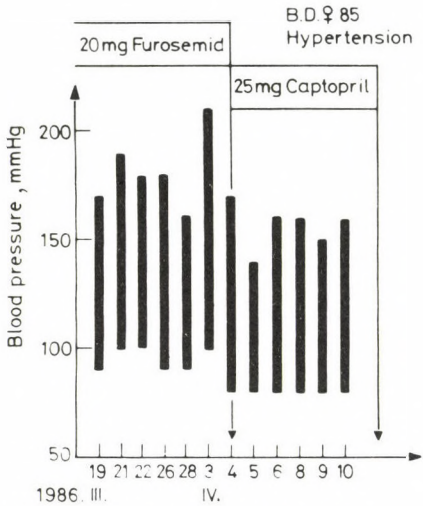

Fig. 9. Immediate effect (rapid clinical improvement) of low doses (2×12.5 mg) of Captopril in a geriatric patient

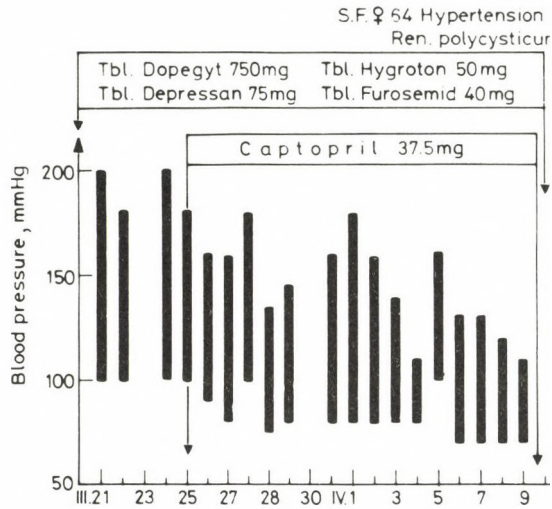

Fig. 10. Excellent effect of combined antihypertensive treatment with Captopril

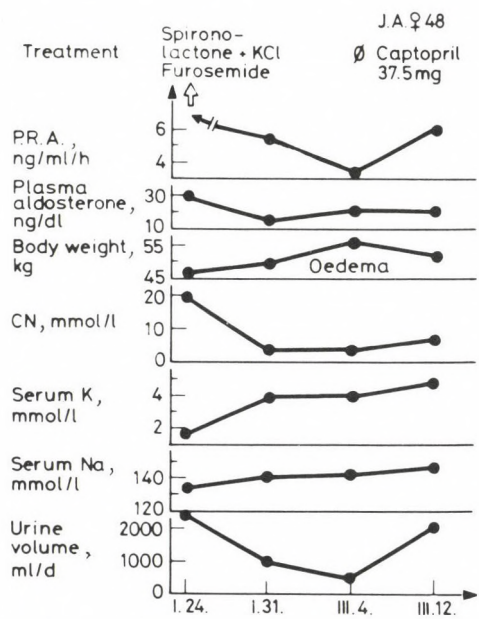

Fig. 11. Diuretic-abuse (furosemid+verospiron) in idiopathic edema, resulted in hypokalemic paresis. The clinical syndrome of pseudo-Bartter syndrome appeared and was characterized by extreme hyperreninemia and hyperaldosteronism. Diuretic withdrawal and extreme dose of KCl infusion restored the "normal" basic state of idiopathic edema; Captopril corrected the basic abnormality

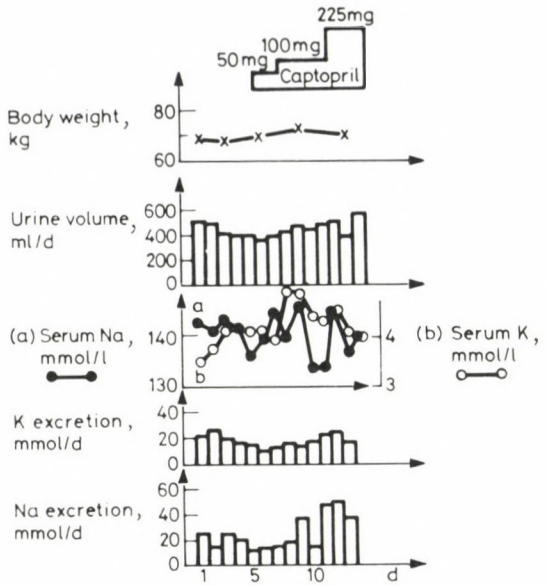

Fig. 12. No significant clinical and laboratory effect of Captopril in decompensated hepatic cirrhosis with ascites

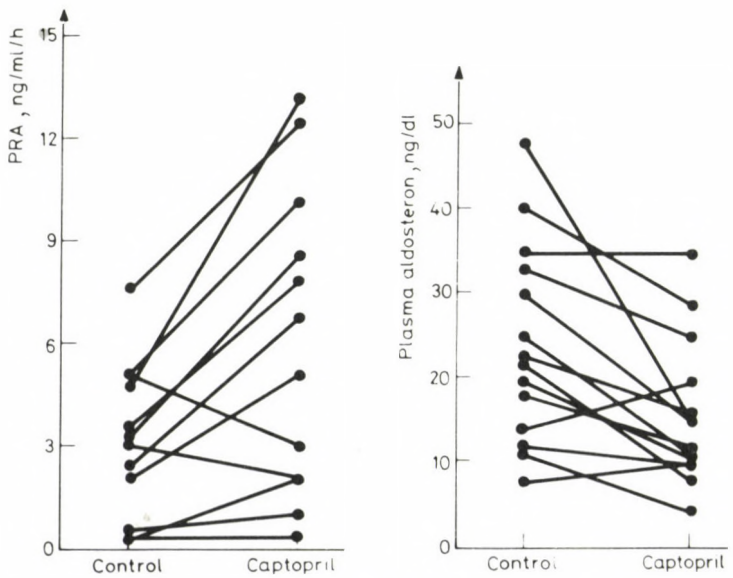

Fig. 13. Endocrine effect of Captopril in hypertensive patients: plasma renin activity was elevated and plasma aldosterone was decreased

VI. *Captopril in hepatic cirrhosis*

This was the only disease where disadvantageous experiences were acquired with Captopril. It was applied to two elderly patients with pulmonary emphysema and alcoholic cirrhosis accompanied by ascites. Although a natriuretic effect could be demonstrated in one of the cases the diuresis was not changed and the ascites was not decreased, either. (Fig. 12) Captopril did not potentiate the effect of furosemide (Table 1.). In spite of the fact that the impaired renal functions were not worsened by Captopril both patients fell worse and the patient's cyanosis of pulmonary origin singificantly increased during Captopril treatment. On the basis of these experiences administration of the drug was stopped.

Table I

Comparison of parameters of ion- and fluid balance and renal function in a case during the administration of a diuretic, diuretic + captopril, or diuretic + spironolacton

Therapy	Days	Urine ml/day	GFR ml/min	Cosm ml/min	C_{H_2O} ml/min	Urine Na mmol/day	Urine K mmol/day	Urine $\frac{Na}{K}$
640 mg Furosemid	3	3067±233	46± 8	2.30±0.20	−0.14±0.30	214.4±14.5	70.6±12.7	3.3±0.7
640 mg Furosemid + 37.5 mg captopril	2	2375±275	51±13	2.37±1.45	−0.73±1.25	45.6± 0.6	44.8± 7.7	1.0±0.2
640 mg Furosemid + 550 mg spironolacton	3	3750±260	51±11	3.04±0.15	−0.44±0.14	332.4±58.2	50.0± 3.6	6.6±0.7

DISCUSSION

According to our results and data from the literature Captopril has proved to be a broad-spectrum antihypertensive agent. It decreases the mean arterial blood pressure by approx. 12%; does not cause orthostatic hypotension and does not increase the heart rate. Its great advantage is that the physiological counter-regulatory systems – first of all the angiotensin-aldosteron system – are not stimulated. Hypokalemia, hyperglycemia, disturbance of lipid metabolism and depression are not produced. The general feeling of patients is not impaired by Captopril, in some cases the mood is elevated to such an extent that it may be regarded as euphoria contributing to the improvement of the "quality of life".

Since Captopril does not induce orthostatic hypotension its usage to treat patients having cerebral sclerosis, coronary disease or peripheral vascular

stenosis beside of arterial hypertension seem greatly advantageous. Therefore Captopril monotherapy occupies a distinct place in geriatry (Fig. 9). Although the captopril monotherapy is relatively safe, to predict its effectiveness is difficult and to "titrate" the effective dose requires time. The application of dose-response relationship of Captopril is not so simple in the clinical practice since the development of full effect of a given dose requires a 4–5 days' administration. Therefore the monotherapy is less used apart the aforementioned geriatric cases. On the other hand, diuretics potentiate the effect of Captopril to decrease high arterial blood pressure and may suspend the resistance to Captopril. Accordingly in two series of our nongeriatric patient material, the daily "effective" dose of Captopril by combining it with diuretics could be decreased from 304±38 mg to 119±20 mg and from 210±66 mg to 85±26 mg respectively. The „Captopril-sparing" effect of diuretics makes possible to reduce the occurence of the side-effects and to administer relatively large doses of Captopril relatively safely when necessary, i.e. in the extremely resistent cases.

Captopril may also be used to treat idiopathic edema. As the principle of the disease is a bizarre combination of the extreme orthostatic activation of renin-angiotensin-aldosterone system and the abuse of this system-provoking diuretics (resulting in diuretic-enhancement of the edema) it is understandable that the converting enzym inhibitor treatment of idiopathic odema proved to be effective (Fig. 11).

Hepatic cirrhosis was the only disease in which Captopril had disadvantageous effects. In one case the diuresis was not increased by Captopril, in the other one Captopril seemed even to inhibit the effects of diuretics (Fig. 12).

In our hands Captopril had only few side effects. Dysosmia and dysgeusia were found in 4 cases. Dermatological symptoms occurred in 2 cases. In one case with renovascular hypertension edema and heart failure developed. In 5 cases chronic administration of Captopril was accompanied with cough.

Captopril inhibits the enzyme that converts angiotensin I to angiotensin II. Due to this plasma renin activity is increased (Fig 13). It is certain that the above described mechanism plays a role in the elevation of serum potassium level by Captopril /32/. During long-term Captopril-treatment progressive hyperkalemia has been observed in paralell with the decrease of plasma aldosteron in patients with renal disease while the renal function has improved /26/. However, the increase of serum potassium level is rarely severe /19/; and even in such cases it could be prevented by the use of the ion-exchanger resin (Resonium) /26/. Furthermore, mild increase of serum potassium could be advantageous since simultaneous diuretic treatment frequently induces hypokalemia /14/.

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EXPERIENCE WITH CAPTOPRIL TREATMENT

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Experience with the use of foreign (Capoten Lopirin; Squibb) and Hungarian (Tensiomin; EGIS) captopril preparations is reported. It was found that the first dose of captopril resulted in a larger blood pressure decrease in hypertensive patients with a high blood renin level. A linear correlation was observed between the blood renin level before treatment and the captopril induced blood pressure decrease following the first dose. Captopril monotherapy lowered the blood pressure effectively without significant pulse rate change in patients whose blood pressure was difficult to influence with combined treatment containing no captopril. This paper reports on the area of indications and side-effects of the drug.

Keywords: captopril, hypertension, renin activity

Captopril was the first orally administered angiotensin converting enzyme inhibitor used in clinical practice as a hypotensive agent /2, 4, 6/. Following the favourable experience with foreign drugs (Capoten, Lopirin: Squibb) in the treatment of severely hypertensive patients, the manufacturing of a captopril containing Hungarian drug, Tensiomin was begun (EGIS Pharmaceuticals, Hungary). The present paper reports on comparative studies with Tensiomin and Capoten.

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PATIENTS AND METHODS

In the first study, 12.5 or 25 mg Tensiomin was administered between 8 and 10 a.m. to patients with hypertension of various origins. Five days prior to captopril treatment, the administration hypotensive drugs was stopped. Before treatment, a blood sample was taken determine the plasma renin activity (PRA). After the administration of captopril, patients were allowed to eat and drink. The blood pressure was measured with a sphygmo manometer before 4 hours after captopril treatment.

The next study involved hypertensive patients whose blood pressure could not be adjusted satisfactorily through the use of a combined hypotensive drug regimen. Seven patients received capoten, while 5 patients received Tensiomin, in doses such that the blood pressure did not exceed 150/95 mm Hg. Captopril treatment was begun with a test dose (12.5–25 mg) in the clinic; the administration of diuretic drugs was stopped at least a week previously. After the desired blood pressure had been achieved, the patients were discharged and were subsequently followed up on an outpatient basis. Following adjustment, of the blood pressure the drug was administered in the same dose for 8 weeks, after which the two drug preparations were interchanged.

Blood pressure was measured in a sitting position. Diastolic blood pressure was taken at the Korotkoff phase V. PRA was determined by means of a New England Nuclear (Chicago) kit. Statistical evaluation was performed with the Student two-tailed t-test and regression analysis. Results are given as means±standard error (SE).

RESULTS

The results of the first study are given in Fig. 1. The patients were divided into two groups. Group I (n=8) contained patients with PRA levels below 2 ng/ml/h. The PRA levels in group II (n=8) were higher than this. The patients in group II had slightly higher basal blood pressure values than those in group I. In group I 4 patients, and in group II 5 patients received 25 mg Tensiomin as the first dose. All the others received 12.5 mg. Although

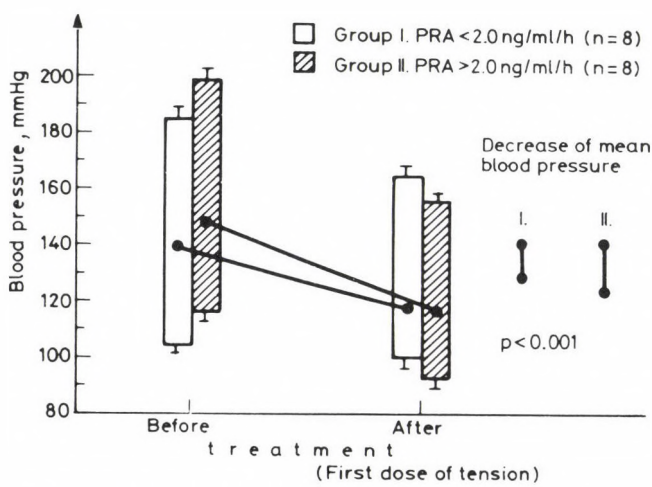

Fig. 1. Blood pressure in patients before and after Captopril treatment

the difference was not statistically significant, it is noteworthy that the blood pressure decrease in responde to the first dose was larger in the group with the higher PRA level.

Comparison was made by giving a mean pressure (mean pressure=diastolic blood pressure+pulse pressure) /3/, and calculating the percentage change relative to this basal value. The difference between the two groups as concerns the latter parameter was statistically significant.

When the correlation between the PRA and the percentage change in the mean pressure was examined, a significant linear correlation was detected both in group I ($n=8$; $r=+0.66$; $p<0.02$) and in group II ($n=8$; $r=+0.63$; $p<0.05$).

The correlation was also studied between the basal blood pressure and the percentage decrease in the mean pressure. A correlation was not found in group I ($n=8$; $r=+0.44$; n.s.), but in group II a significant linear correlation was demonstrated ($n=8$; $r=+0.70$; $p<0.05$).

Data on the patients participating in the second study are given in Table I. In some of the hypertensive patients the treatment was started with Capoten, and in others with Tensiomin. So that the average starting blood pressures for the two groups should be similar, the data on one patient in group I were omitted from the comparison, though they are included in the Table. The results are listed in Table II. When we began to use Tensiomin, we observed that those patients who received earlier Capoten required more Tensiomin for the same blood pressure decrease to be attained.

In the second group the blood pressure adjustment was started with Tensiomin, which was subsequently replaced by Capoten. In this case some of the patients required lower Capoten doses.

At our suggestion, the manufacturer (EGIS) modified the technology, and recently we could find no difference between the efficacies of Tensiomin and Capoten. The pulse rate was not altered by Tensiomin or Capoten.

Table I

Data on patients participating in the comparative study of the hypotensive effects of Tensiomin and Capoten

	No.	Sex	Age (years)	Diagnosis	Previous medication	BP (mm Hg) syst.	diast.
Group I	1.	♂	51	Essential	Minipress, Dopegyt, Hypothiazid	170—200	95—110
	2.	♂	44	Essential Diabetes mellitus	Dopegyt, Minipress	180—190	100—110
	3.	♀	34	Essential	Viskaldix, Sanegyt	165—190	100—115
	4.	♂	41	Malignant	Brinaldix, Dopegyt Minipress	190—215	115—120
	5.	♀	53	Glomerulonephritis (membranoprolif.)	Trasicor, Hypothiazid	180—200	100—110
	6.	♀	44	Chr. pyelonephr.	Brinaldix, Minipress, Betaloc	165—190	100—115
	7.	♂	21	Renovascular Neurofibromatosis	Propranolol, Hypothiazid, Sanotensin	180—205	100—120
Group II	1.	♀	38	Essential	Brinaldix, Minipress, Trasicor	185—200	110—120
	2.	♂	49	Renovascular	Hypothiazid, Trasicor, Dopegyt	175—200	105—125
	3.	♂	27	Essential	Brinaldix, Trasicor, Minipress	170—200	110—120
	4.	♂	44	Malignant	Betaloc, Depressan, Dopegyt	180—210	110—130
	5.	♀	41	Essential	Viskaldix, Minipress	170—190	95—110

Table II

Comparison of hypotensive effects of Tensiomin and Capoten

	No. Initial	Initial BP mm Hg			I. Period BP mm Hg			Dose mg	II. Period BP mm Hg			Dose mg
		Syst.	Diast.	Mean	Syst.	Diast.	Mean	Capoten	Syst.	Diast.	Mean	Tensiomin
Group I.	1. T.M.	183	109	133.6	144	89	107.3	150	153	92	117.3	200
	2. T.J.	185	109	134.3	138	91	106.6	100	150	90	110	150
	3. T.S.	178	104	128	138	84	102	75	131	85	100	100
	4. Cs.Zs.	204	120	148	147	96	113	225	152	94	113.3	300
	5. O.F.	188	119	142	140	94	109.3	187.5	150	92	109.3	200
	6. T.T.	177	109	031.6	132	84	100	150	148	90	109.3	200
	7. K.A.	199	114	143	134	86	102	200	146	93	110.6	250
	Mean	189.3	113.5	138.8	139.2	90.0	106.4	168.8	149.8	91.8.	110.8	216.7
	SD	±10.21	±5.2	±6.5	±5.7	±4.6	±4.8	±44.6	±2.6	±1.6	±1.7	±51.6
								Tensiomin				Capoten
Group II.	1. H.J.	192	114	140	147	96	113	250	145	94	111	200
	2. D.S.	187	109	135	141	92	108.3	200	137	88	104.3	187.5
	3. D.M.	187	116	138.6	148	94	112	200	150	96	114	150
	4. R.J.	208	121	150	152	98	116	300	148	96	113.3	200
	5. N.J.	179	104	129	138	91	106.6	150	135	88	103.6	100
	Mean	190.0	112.8	135.5	145.2	94.2	111.2	220.0	143.0	92.4	109.2	167.5
	SD	±11.1	±6.5	±7.7	±5.6	±2.9	±3.7	±57.0	±6.7	±4.1	±5.0	±42.9

Group I. patients received Capoten, and group II. patients Tensiomin as the initial drug.

DISCUSSION

It was originally believed that captopril might be effective primarily in cases of hypertension dependent on the renin-angiotensin system /2, 7, 8/. It is now known that it can be utilized in a much wider range of diseases /7, 10/. Although the area of indication has still not been clearly defined, there can be no doubt that its primary value is in cases of severe hypertension that do not respond (or only with difficulty to traditional treatment /1, 7, 10/. Since these latter cases pose considerable problems for the practising physician, it is praiseworthy that the Hungarian pharmaceutical industry (EGIS) rapidly elaborated this strong hypotensive agent, Tensiomin.

In our study, the first dose of captopril significantly decreased the blood pressure. It was found that the hypotensive effect of the first 12.5 or 25 mg dose of Tensiomin displayed a linear correlation with the pretreatment PRA level, independently of whether the renin level was normal or elevated. This observation is in accord with other reports /3, 4, 9/. It means that a better hypotensive effect can be expected from the drug in hypertensive patients with higher PRA levels. In hypertensive cases with higher PRA levels, a linear correlation was revealed between the basal blood pressure and the percentage decrease in the mean pressure. This finding is again is agreement with other observations /9/. This means that the higher the basal blood pressure in renindependent hypertension, the greater will be the blood pressure decrease in response to captopril.

As concerns drugs containing captopril as active component, we earlier acquired experience with Capoten and Lopirin, and in the past 7 years with Tensiomin. We have generally regarded the area of indication to be therapy-resistant hypertension accompanied by a high renin level, and malignant hypertension. However, we have also applied the drug in other special indications.

Scleroderma is a rare disease, one of the infrequent (4–10%) complications of which is the scleroderma renal crisis (SRC). This is not to be confused with sclerodermal renal disease, which occurs in 35–50% of the cases. SRC is characterized by a rapid increase in blood pressure, a high blood renin level, fundus changes of grades III and IV in the Keith-Wagener classification, a rapid *degeneration* of the renal function, and death within 4–6 weeks. Of the 32 sclerodermal patients observed in our Department during the past 15 years, renal disease was found in 13 patients (10%), 4 of whom had SRC. Three of the latter were treated with conventional hypotensive therapy, but all died within 6 weeks. A 41-year-old SRC patient has so far survived for 28 months under captopril treatment since the syndrome developed.*

During chronic captopril treatment of several hundred cases, we have observed reversible dysgeusia on two occasions, and leukopenia once. On three occasions, patients complained of a sensation of tachycardiac discomfort. In a 7-year-old boy with primary aortitis, who had severe hypertension because of renal artery occlusion on one side and constriction on the other side /10/. Captopril (Capoten) administration was accompanied by renal glucosuria /11/, which disappeared when captopril treatment was suspended, but reappeared when the treatment was resumed. A similar side-effect has been described only in connection with one other converting enzyme inhibitor, Enalapril /12/.

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COMBINED CAPTOPRIL TREATMENT IN SEVERE AND MODERATELY SEVERE HYPERTENSION RESISTANT TO THERAPY

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Combined Captopril treatment was applied in 61 patients with severe or moderately severe hypertension in patients insufficiently or not reacting to the usual combined antihypertensive therapy (3–7 kinds of drug). The combination included diuretics, beta-blockers, alpha-blockers, vasodilators, Ca-antagonists and centrally acting agents. Diuretics were used in all cases. Average duration of treatment was 8.2 months (i.e. 2–40) months). Mean systolic pressure prior to Captopril treatment was 202.4 mm Hg (S.D. ± 27.6), while the diastolic 122.0 mm Hg (S.D. ± 11.3). During combined Captopril treatment the average values were 154.2 mm Hg (S.D. ± 18.8) and 97.6 mm Hg diastolic pressures (S.D. ± 10.7), the difference being significant ($p<0.001$). Refractory hypertension occured int three middle-aged female patients in response to combined Captopril treatments. Captopril treatment had to be discontinued for the appearance of side-effects (severe skin symptoms) only in a single case. A minor deterioration of renal functions was observed in three patients (in one bilateral renovascular, and in two essential hypertension). Serum creatinine value and renal functions of four patients showed significant improvement as a result of combined Captopril treatment. During combined Captopril treatments (also with a diuretic) two patients had so severe hypokalaemia that they needed potassium substitution or administration of a potessiumsaving diuretic.

Keywords: Captopril, combined treatment, hypertension

The angiotensin-converting enzyme inhibitor Captopril (C) has been available for the treatment of hypertension since the second part of the 1970-s /1, 2/. Experiences on severe refractory hypertension and on long term effects of C were reported at the beginning of the 1980s /3, 5/. In Hungary, Radó et al. were the first to publish their experiences with Captopril /4/. At our department Captopril has been used since 1982. Initially (up to December 1984) the original preparation Capoten ® (SQUIBB), while later, from January 1985, the Hungarian Tensiomin ® (EGIS) were employed. The first 25 patients receiving Capoten treatment were switched over to the Hungarian Tensiomin from one day to the other. During the change, an essential modification of the dosage did not become necessary within the combined treatment either for the Captopril or for other drugs.

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PATIENTS AND METHODS

From 1982 onwards, patients with severe and moderately severe hypertension were selected for receiving combined Captopril treatment, who had been refractory to at least four but rather some more antihypertensive drugs used in maximal doses. The patients underwent a detailed examination for symptomatic hypertension. The following examinations were performed in all cases: urine analysis, serum sodium, potassium, creatinine determination, optic fundus examination and renal functional DTPA scintigraphy with Camera. In almost half of the cases, renin-angiotensin-aldosteron determinations were made and in over half ot them (i.e. 34 patients), serionephroangiography was also performed.

Fourty-eight patients suffered from essential, 9 from renovascular, 3 from renal and one from endocrine (Cushing's disease) hypertension. The data of the patients are summarized in Table I.

The begining dose of C was twice or three times 12.5 mg a day. We tailored always the dose. of Captopril in the light of the hypotensive effect. We employed always diuretic with C in the treatment to reflect the strong additive-synergistic effect of the two drugs.

If no decrease in blood pressure was obtained by the combined administration of 150–200 mg C+diuretic, first a beta-blocker, and when contraindicated, a Ca-antagonist was applied. In lack of an adequate hypotensive effect of the triple combination, for a fouth drug, vasodilator, or alpha-blocker, a Ca-antagonist or a centrally active agent were added separately to, or together with, the combination. The number of the applied drug combinations before and after Captopril treatment is shown in Table II. Patients' blood pressure, renal functions, blood counts, ionograms and urinary findings were controlled according to a previously defined scheme.

Table I

Data of patients

No. of patients:	61	(31 females, 29 males)
Mean age:	45.9	(24—66 years)
Distribution according to the type of hypertension:		
o essential	(EH)	48 patients
o renovascular	(RVH)	9 patients
o renoparenchymal	(RH)	3 patients
o endocrine	(ENH)	1 patient
Renal functions before C treatment:		
serum creatinine < 130 μmol/l		:50 patients
serum creatinine > 130 μmol/l		:11 patients
Mean blood pressure before C treatment:		
202.4/122.0 mm Hg (S.D. ±27.6/±11.3)		

Table II

Number (No.) of drug combinations prior and after Captopril (C) treatment

a. No. of drugs used before introducing C treatment:		**b. No. of drugs given in combination with C:**	
2 kinds of drug	5 patients	2 kinds of drug	20 patients
3 kinds of drug	13 patients	3 kinds of drug	12 patients
4 kinds of drug	19 patients	4 kinds of drug	14 patients
5 kinds of drug	12 patients	5 kinds of drug	10 patients
6 kinds of drug	10 patients	6 kinds of drug	3 patients
7 kinds of drug	2 patients	7 kinds of drug	2 patients

RESULTS

Table III. shows the decrease in blood pressure as well as the changes in renal functions during combined Captopril treatment. Reduction in blood pressure was highly significant. Average dose of Captopril was 145.5 mg, however, a daily dose of 200 mg – except in two cases – had never been exceeded to avoid the increased risk of side-effects.

Table IV. demonstrates the number of drugs combined with Captopril according to how many times they had been used during the treatment of the 61 patients.

In Table V. the combination of antihypertensive drugs according to their mechanisms of action is shown as a function of the number of patients.

DISCUSSION

According to our experiences, in patients with moderately severe and severe hypertension, and in those with one insufficiently or not responding to therapy, combined Captopril treatment can be beneficially applied. Captopril could be favourable combined with antihypertensive drugs used so far. It can be particularly well combined with diuretics, vasodilators and Ca-antagonists. It can be fairly advantageously combined with betablockers and with various types of alpha-blockers too (peripherally and/or centrally acting). Sufficient care should be taken on the combined administration of alpha-sympatolythics and C at increased risk of orthostatic hypotension. We ourselves were compelled by this in one case to omit Minipress during combined Captopril treatment.

Treatment, due to side-effect, had to be interrupted only in one case. The side-effect was a severe maculopapulous rash. Despite earlier experiences, hypokalaemia necessitating potassium substitution or administration of a potassium-saving diuretic was observed in two cases in response to Captopril treatment (i.e. to 150 mg and 75 mg Captopril, and to a thiazide-type diuretic). In the long run normokalaemia could be maintained only in such a way. We believe that Captopril in this case could not prevent hypokalaemic effect of diuretics. Prior to commencing Captopril treatment, both patiens were subjected to a detailed examination for hyperaldosteronism. The results were negative.

A genuine resistance to therapy develops when blood pressure during combined Captopril treatment can not be reduced even not with the maximal doses of 6–7 various kinds of antihypertensive drugs. Thus, in case of our three refractory patients, 300 mg Captopril, 50 mg Chlorthalidone in two cases and 80 mg Furosemide in the other case, 320 mg Propranolol,

Table III

Results of combined Captopril (C) treatment

Captopril dose (mean)	145.5 mg	(50–300 mg)
Duration of treatment (mean)	8.24 months	(2–40 months)
Mean blood pressure:		
before C treatment:	202.4/122.0 mm Hg	
	(S.D. ±27.6/±11.3)	
after C treatment:	154.2/ 96.7 mm Hg	
	(S.D. ±18.8/±10.7)	
	$p < 0.001$	
Successful treatment	58 patient EH:	45
	RVH:	9
	RH:	3
	ENH:	1
Resistant even to C:	3 patients-EH	
Omitted for side-effect:	1 patients-RVH	
Serum creatinine before treatment: 121.75 μmol/l (S.D. ±56.59)		
Serum creatinine after treatment: 126.3 μmol/l (S.D. ±97.12)		

Table IV

Drugs combined with Captopril

Diuretic		Beta-blocker		Vasodilator	Alpha-blocker	Ca-antagonist	Centrally active agents	
Furosemide	9	Propranolol	26	Dihydralazin 25	Prazosin 7	Nifedipine 12	Bromocryptine	2
Chlorthalidone	25	Pindolol	2				Clonidine	2
Clopamide	21	Metoprolol	5				Guanfacin	3
Hydrochloro-thiazide	6	Oxprenolol	4				Methyldopa	2
Triamteren	1							
Total	62*		38	25	7	12		9

* One patient received two kinds of diuretic, Hydrochlorothiazide and Triamteren

Table V

Distribution of patients according to drug combination with Captopril (61 patients)

C	=	Captopril
D	=	diuretic
B	=	beta-blocker
V	=	vasodilator
A	=	alpha-blocker (A=peripherialy acting, Á = centrally acting)
Ca	=	Ca-antagonist
P	=	Parlodel

C+D	20 patients
C+D+B	11 patients
C+D+Ca	1 patient
C+D+B+V	11 patients
C+D+B+A	1 patient
C+D+B+Ca	2 patients
C+D+B+B+A	5 patients
C+D+B+A+Ca	1 patient
C+D+B+V+Ca	4 patients
C+D+B+B+Ca+A	3 patients
C+D+B+V+Ca+A+Á	2 patients (+transitorily P)

200 mg Dihydralazine, 90 mg Nifedipine, 18 mg Prazosin, 900 μg Clonidine in one case and 2 g Alphamethyldopa in the other two cases were used in the antihypertensive treatment. In two cases 7.5 mg Bromocryptine (Parlodel) were given in the antihypertensive combination too.

Moderate deterioration of the renal functions (not exceeding the double of the normal value) was observed in 3 patients, while in four the renal functions significantly improved during combined Captopril treatment parallel to the improvement of hypertension (Table VI.).

As for conclusion introduction of Captopril into antihypertensive therapy improved considerably the treatability of patients with moderately severe and severe hypertension recractory to prior treatment. Giving a dose not exceeding 200 mg, side-effect was only rarely observed.

Table VI

Side-effects during 61 combined Captopril treatment

Maculopapulous rash	1 patient
Transitory itch	1 patient
Hypokalaemia (combined with diuretic)	2 patients
Hyperkalaemia	Ø
Deterioration of renal function (slight increase in serum creatinine)	3 patients
Improvement of renal function (3 malignant EH, 1 malignant RVH)	4 patients

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EFFECTIVENESS AND SAFETY OF CAPTOPRIL (TENSIOMIN) IN PATIENTS WITH HYPERTENSION

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Twenty patients with moderate (4) to severe (16) hypertension, whose blood pressure (BP) could not be controlled on the previous combined antihypertensive therapy, were investigated. In acute studies the first doses of captopril, 25 and 50 mg led to a significant drop in BP 30 min after administration. The maximum fall in BP was recorded at 90–120 min and this effect was maintained throughout the whole observation period (8hours). The fall in BP was similar in supine and standing positions and there was no change in the heart rate. During long-term (14.5 months) therapy only 2 out of the 20 patients exhibited continuing good BP control with captopril monotherapy of a maximum daily dose of 150 mg. A comparison of the acute and chronic BP lowering effects of captopril showed that the first dose of captopril caused a significantly greater decrease in BP than chronic monotherapy. However, combined captopril with a diuretic or with a diuretic and calcium antagonist or beta blocker provided a sustained BP control, significantly better than the previously used antihypertensive combinations ($182\pm27/115\pm11$ mmHg vs $164\pm20/104\pm11$ mmHg $p<0.05$). The Hungarian captopril preparation (Tensiomin), similarly to other captopril products, through its angiotensin converting enzyme inhibition, caused an increase in plasma renin activity and in concentration of plasma angiotensin I and a decrease in plasma angiotensin II. Eight out of the 20 patients developed side effects, which disappeared spontaneously in 4 patients within 2–14 days. Captopril was withdrawn in 3 patients for not achieving satisfactory BP control and/or because of side effects. It is concluded that captopril is safe and effective in the long-term treatment of hypertension, however, majority of the patients with severe forms of hypertension required double or multiple combinations.

Keywords: severe hypertension, captopril, acute and long-term effects

The introduction of angiotensin converting enzyme (ACE) inhibitors represents a new principle in the pharmacological treatment of hypertension.

Captopril is the first orally active competitive inhibitor of converting enzyme (kininase II). This enzyme converts angiotensin I into the vasoconstrictor peptide angiotensin II and inactives the vasodilator peptide bradykinin.

The major hypotensive action of the drug is the inhibition of the formation of angiotensin II. During the past decade captopril has been

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shown to be effective in treating hypertension of all degrees of severity. Also, it might be of value in the management of severe and previosuly unresponsive hypertension mostly in a combination with a diuretic or with a diuretic and a beta-blocker or calcium antagonist for maximal effectiveness.

This study reports on the acute "first dose" and the long-term effects of the Hungarian captopril preparation (Tensiomin) in patients with severe hypertension.

METHODS

Patients

Acute and chronic investigations were carried out in hypertensive patients with captopril (tabl. Tensiomin, containing 25 and 50 mg of captopril). Twenty patients were involved, 14 males and 6 females with a mean age of 46 (38–55) years. Nineteen patients had essential and one patient renovascular hypertension, persisting after dilatation of bilateral renal artery stenosis.

The severity of hypertension was moderate in 4 cases and severe in 16 patients according to the WHO criteria based on diastolic blood pressure (DBP).

The investigations were started in 13 inpatients and 7 outpatients. All but one patient received previous antihypertensive treatment: 2 patients received monotherapy (nifedipin and a beta-blocker respectively), 2 patients double combination of a beta-blocker plus diuretic or prazosin plus diuretic, and the remaining, 15 patients a three- or four-old combination. Eight of the 20 patients had vascular complications: cerebrovascular in 1 and cardiovascular in 7 cases, of which 3 patients had angina pectoris, 1 angina pectoris+mild left ventricular heart failure, 1 angina pectoris and atrial fibrillation, 1 ventricular extrasystole, and 1 patient paroxysmal supraventricular tachycardia. Five patients received concomitant medication, 3 with angina received short and long acting nitrate-preparations and two patients cardiac glycosides which could be stopped in 1 patient after the control of mild left ventricular heart-failure, 1 patient received it continuously for the prevention of paroxysmal supraventricular tachycardia.

Secondary illnesses: obesity in 7, diabetes mellitus in 6 (3 patients on oral antidiabetics), Raynaud syndrome in 1, hypernephroma in 1. Hypernephroma was diagnosed before starting the treatment and removed during the captopril therapy.

DESIGN OF THE STUDY

Antihypertensive medications used previously were discontinued 4 (2–7) days prior to the acute study. Blood pressure and heart rate, 10 min supine and 3 min standing, were measured. A 12-lead ECG was recorded for the measurements of R–R distance, PQ, QRS and QT invervals. These measurements were done before and 30, 60, 90, 120, 150, 180, 240, 360, 480 minutes after the administration of 25 mg captopril. Detailed laboratory investigations (serum Na^+, serum K^+, serum bilirubin, SGOT, SGPT, alkaline phosphatase, blood urea nitrogen, serum creatinine, serum uric acid, blood sugar, serum cholesterol, serum triglycerid, platelet count, urin analysis) were carried out regularly before and during captopril therapy.

Measurement of plasma renin activity (PRA) for the determination of renin activity 200 μl of plasma was incubated at 37°C and pH 7.5 for 1 hour in the presence of disodium EDTA (3 mM), 8-hydroxyquinolin (1.2 mM) and phenylmethylsulfonylfluorid (0.47 mM). The incubation mixture was diluted 1:3 with cold assay buffer and boiled immediately for 15 minutes to stop the enzyme activity. After centrifugation the angiotension I generated during the incubation was measured by RIA. Results are expressed in ng/ml/h (30).

Radioimmunassay of angiotensin I and angiotensin II blood was collected in chilled tubes containing EDTA and plasma samples were separated after subsequent centrifugation and stored at −20° C until tested.

Angiotensin I was separated from 1.0 ml of plasma using a special second antibody method; the residue containing angiotensin I was redissolved in 2.0 ml alcohol containing 0.2M HCl. Angiotensin II was extracted from the supernatant with the elution of 1 ml of alcohol and 1 ml of chloroform. After centrifugation both supernatant were evaporated to dryness at 50° C under warm airstream. The residues were redissolved in 800 μl assay buffer. The incubation volumes were adjusted to 1000 μl with the labelled peptide and the antibody (dilution is 1:20.000 for angiotensin I and 1:5.000 for angiotensin II-RIA). After 24 hours incubation period the bound peptide was separated by polyethyleneglycol and counted (29).

After the evaluation of the acute "first dose" effect of captopril, 25 mg, the patients received 75 mg (25 mg t.i.d.) daily. If after a maximum period of one week this dose was ineffective, the acute effect of captopril 50 mg was tested, and then captopril 150 mg (50 mg t.i.d.) monotherapy, the maximum dose, was administered. When BP could not be controlled with captopril alone first a diuretic, then a diuretic plus a calcium antagonist or a beta-blocker was added.

The patients were seen weekly or biweekly during the dosefinding period of the drug-combination, and then monthly. Before augmenting the dose of captopril, or introducing combined therapy, the laboratory and biochemical tests were repeated.

For statistical evaluation of the results Student "t"-test applied. In the acute studies the mean value of three consecutive blood pressure measurements were used as baseline value. Then captopril (25 and 50 mg) was given. In the chronic study the mean value of blood pressures measured at three different occasions during the previous antihypertenstive herapy served as baseline.

RESULTS

Acute studies

A significant fall of systolic blood pressure (SBP) in supine position could already be observed 30 min after captopril 25 mg ($p<0.001$) and BP reached its minimum at 90–180 min ($p<0.001$).

SBP decreased by 15% (from 178 mmHg to 150 mmHg) after 90 min and remained 11% lower after 480 min. The same significant change in SBP (standing position) was observed after 30 min, and this change was significant at each point of time ($p<0.001$–0.05). The size and time of the maximal effect were similar to those observed in lying position. The lying DBP went down after 30 min ($p<0.001$), the change was most remarkable after 180 min ($p<0.001$) and remained significant after 480 min ($p<0.05$). The magnitude and duration of the effect on standing DBP (–13–14%) did not differ from those seen on lying DBP ($p<0.001$–0.05, Fig. 1.).

Fig. 2 demonstrates the acute antihypertensive effect of captopril, 50 mg.

The changes in SBP were significant after 30 min, and the maximum fall occured after 120 min, 22 mmHg (–13%, $p<0.001$) in supine and 17 mmHg (–11%, $p<0.001$) in standing position. DBP decreased by 11% both in supine and standing positions. These changes in standing position were significant at each point of time, and up to 120 min in supine position ($p<0.001$–0.05).

Heart rate and PQ, QRS, QT intervals, as well as ST segments and T waves on ECG showed no change after the acute administration of 25 and 50 mg captopril.

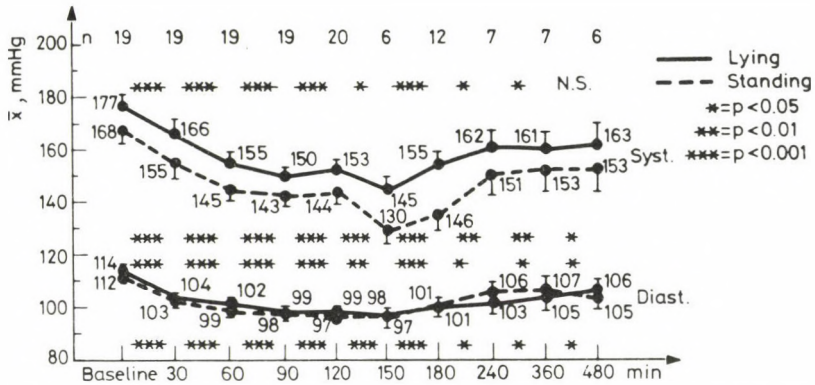

Fig. 1. First dose effect of 25 mg captopril on lying and standing blood pressure

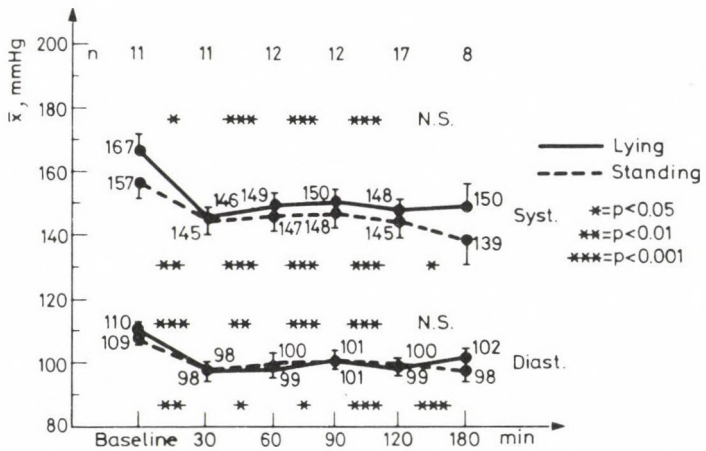

Fig. 2. First dose effect of 50 mg captopril on lying and standing blood pressure

Chronic studies

Average duration of the treatment period in 20 patients was 14.5 months (minimum 6 weeks – maximum 23 months), in 14 cases ≥ 12 months, and in 9 out of these 18 months. Sixteen patients are still on captopril. Captopril therapy was discontinued in 3 patients after 6 weeks (No 6), 2 months (No 15) and 4 months (No 14) because of inadequate control of BP and side effects.

One patient did not attend the outpatient clinic after 6 months on captopril therapy.

In one patient captopril monotherapy, 150 mg daily was effective for 21 months. One patient with Raynaud syndrome remained normotensive on 75 mg captopril daily for 6 months, when guanfacin, 1 mg daily was added

due to palpitation. In 6 other patients captopril monotherapy (75 mg daily in 4, and 150 mg daily in 2) was effective only for 4–8 weeks. In one of the 4 patients increasing the dose of captopril from 75 mg to 150 mg daily resulted in satisfactory reduction of BP for 3 months, but then captopril had to be combined with a diuretic.

In 8 patients captopril was given in a two-fold combination, diuretics in 5, beta-blockers in 2, and centrally acting drug in 1. Ten patients received the captopril therapy in three-fold or multiple combination, 4 with diuretics+ calcium antagonists, 4 with diuretics and beta-blockers, 1 with a diuretic and centrally acting drug, and 1 with a diuretic, beta-blocker, centrally acting drug and calcium antagonist. Potassium supplement or potassium sparing diuretic had to be given in 11 out of 20 patients before the introduction of captopril while in 4 patients during captopril administration.

Individual changes in DBP are shown in Fig. 3. Severe diastolic hypertension ($\geq$115 mmHg) was observed in 10 cases before captopril therapy, and only in 1 case – during the combined therapy with captopril ($p<0.001$). – In 7 cases borderline hypertension or normal blood pressure was seen ($p<0.001$).

Changes in mean BP values during chronic captopril therapy are presented in Fig. 4. As compared to the previous antihypertensive therapy captopril reduced supine SBP from 182±27 to 164±20 mmHg (–10%, $p<0.05$). The fall in standing SBP (–7%) was not significant. DBP decreased by 10% from 115±11 to 104±11 mmHg ($p<0.05$), in lying position, and in standing position by 15 mmHg (–13%, $p<0.05$). No change in supine or standing heart rate was noted.

We compared the first dose effect of captopril, 25 mg to the effect of continuous captopril treatment (75 mg daily) for 3–7 days and again at the end of captopril monotherapy. The data of outpatients and inpatients were analysed together and separately in respect to the possible influence of bedrest on BP. In inpatients supine SBP was 16 mmHg higher ($p<0.005$) on the 3–7 days and 21 mmHg higher at the end of captopril monotherapy, 75 mg daily, than the lowest SBP after the first dose of captopril, 25 mg.

The respective changes in supine DBP were 12 and 10 mmHg ($p<0.01$). The outpatients showed similar rise in BP, so the pooled data of inpatients and outpatients were also analysed. On the 3–7 days of captopril, 75 mg daily supine SBP was higher by 15 mmHg ($p<0.005$) and at the end of monotherapy by 20 mmHg ($p<0.001$). Increment in supine DBP was 9mmHg ($p<0.005$) at both measurements (Fig. 5). The acute antihypertensive effect of captopril, 50 mg was also bigger than that of captopril 150 mg administered continuously (Fig. 6).

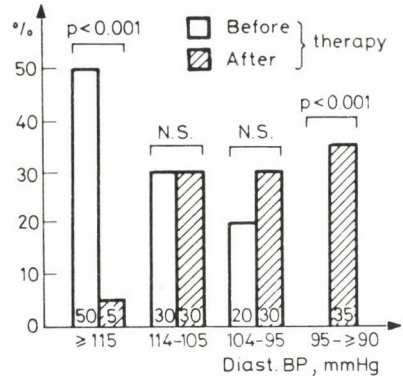

Fig. 3. Changes in individual diastolic blood pressure during captopril therapy (WHO criteria)

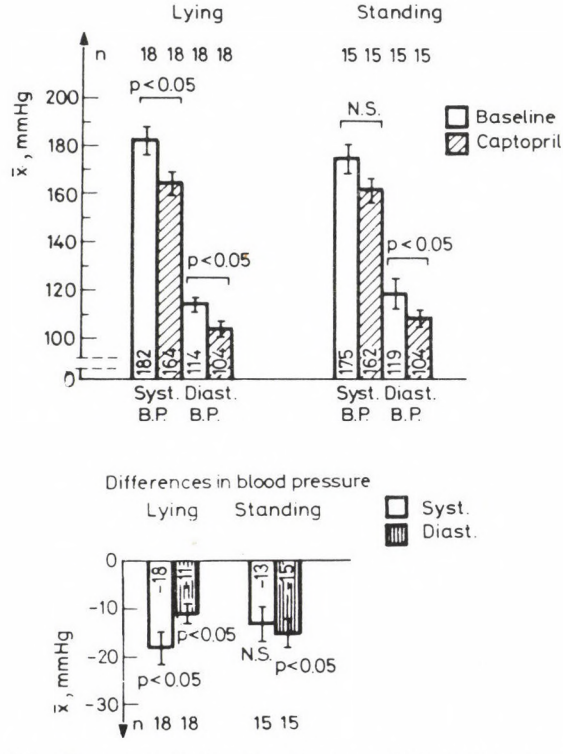

Fig. 4. Changes in mean blood pressure during chronic captopril therapy compared to the previous antihypertensive therapy

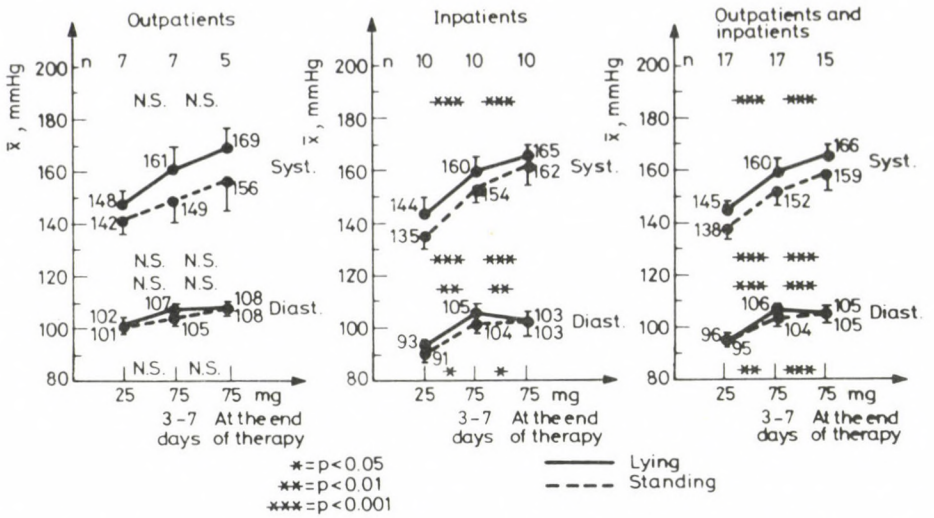

Fig. 5. Comparison of acute effect of captopril 25 mg and subacute effect of captopril monotherapy, 75 mg daily

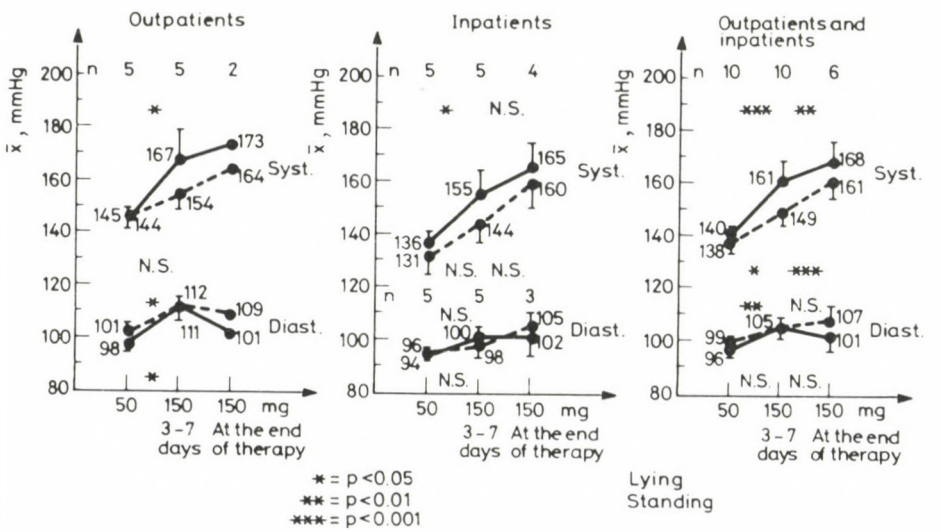

Fig. 6. Comparison of acute effect of captopril 50 mg and subacute effect of captopril monotherapy, 150 mg daily

No significant correlation was found between the acute and chronic BP lowering of captopril. No significant change in biochemical tests or haemogram was observed during captopril administered alone or combined. A small but not significant increase in BUN and serum creatinine was found during captopril therapy combined with diuretics (Fig. 7).

The effect of captopril monotherapy on the plasma renin angiotensin system in 13 patients are summarized in Figure 8. Average value for PRA in this group of patients was 1.63±0.29 ng/ml/h. The average plasma angiotensin I level was 127±18 pg/ml, angiotensin II level was 138±29 pg/ml. Following the captopril monotherapies the plasma concentrations of angiotensin II decreased to 130±49 pg/ml on 75 mg/day and to 117+25 pg/ml on 150 mg/day and according to the reduction of angiotensin II biosynthesis there was an increase in PRA values to 3.03± 1.3 ng/ml/h on 75 mg/day and

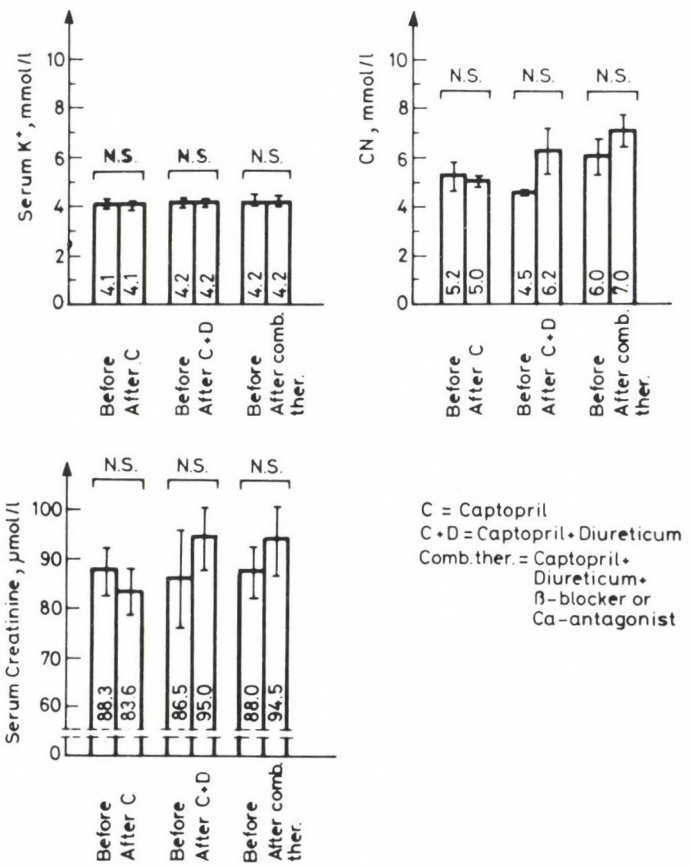

Fig. 7. Laboratory tests during captopril therapy

to 2.16±0.42 ng/ml/h on 150 mg/day and in the concentrations of plasma angiotensin I to 220±70 gp/ml in both groups.

The effect of captopril in combination with diuretics and beta-blockers on the plasma renin angiotensin system in 10 patients are shown in Figure 9. There is a significant increase in the PRA from 1.89±0.36 to 12.00±5 ng/nl/$_h$ ($p<0.05$) and in plasma angiotensin I level from 127±21 to 348±93 pg/ml ($p<0.05$) and a slight increase in plasma angiotensin II level from 144±39 to 162±37 pg/ml in patients treated with captopril plus diuretics. This can be explained by the fact that the release of renin is stimulated by diuretics. The triple treatment with captopril, diuretic and beta-blockers causes a slight decrease in all the three parameters of the renin-angiotensin system (PRA:1.51±0.35 ng/nl/h, angiotensin I:71±16 pg/ml; angiotensin II: 68±16 pg/ml), beta-blockers counteract the renin stimulatory effect of captopril plus diuretics.

SIDE EFFECTS

During the acute study 2 out of 20 patients (No 13, 15) developed side effects. Blood pressure of patient No 13 showed no change after captopril, 25 mg, while captopril 50 mg produced a marked decrease from 160/120 to 110/86 mmHg, in supine position after 120 min dizziness and a feeling of fainting, therefore BP in standing position could not be measured.

After the first dose of captopril, 25 mg one patient (No 15) experienced numbness in tongue, which disappeared within one day. This complaint did not occur during the chronic captopril therapy.

During the chronic sudy 8 out of 20 patients exhibited side effects. Table I. shows the serial number of patients, the type, duration and outcome of side effects. The adverse reactions (nightmares, salty taste, itching without objective signs, periorbital and hand oedema) disappeared spontaneously within 2–14 days in 4 patients (No. 10, 11, 14, 18). In 2 patients (No 4, 13) additional therapy, or change of dose was necessary because of side effects. In one patients (No. 4) palpitation ceased adding guanfacine, 1 mg daily to captopril. Orthostatic hypotension occurred after augmenting the dose of clopamide from 10 to 15 mg in patient No 13. This symptom disappeared on 10 mg clopamide. Captopril therapy was discontinued in 3 paients (No. 6,14, 15) because of side effects or inadequate control of blood pressure. Patient No. 6 developed tachycardia (heart rate, supine, 120 beats/min and standing, 140 beats/min) Metoprolol, 600 mg did not inhibit satisfactorily this symptom. Patient No. 14. felt increased tension and nervousness, and did not want to continue captopril therapy. Patient No. 15. developed palpitation, supraventricular extrasystole and muscle cramps.

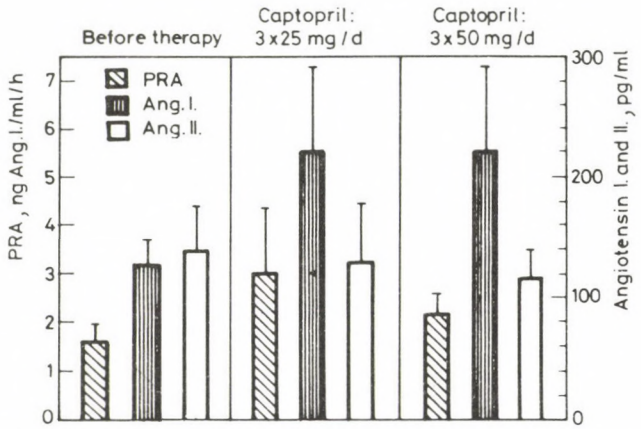

Fig. 8. Effect of captopril monotherapy on plasma renin activity (PRA) angiotensin I and angiotensin II levels

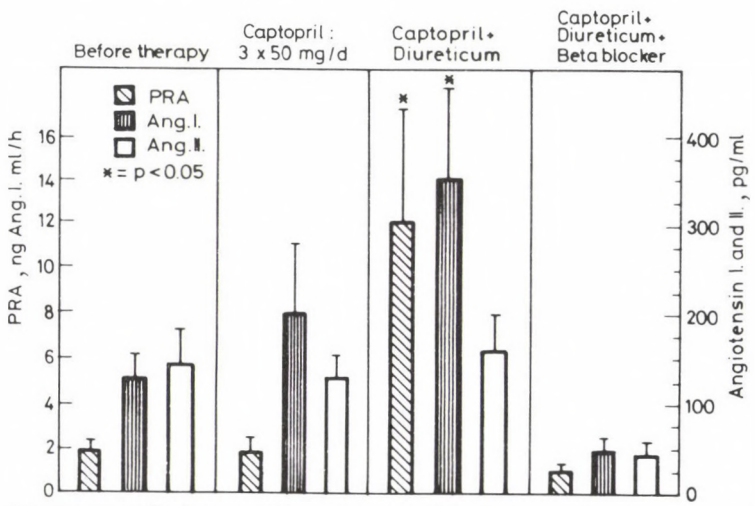

Fig. 9. Combined captopril therapy (diureticum+beta-blocker) on plasma renin activity (PRA) angiotensin I and angiotensin II levels

Table I

Side effects during chronic captopril therapy

Number of patients No	Type of side effects	Captopril mg/die	Drugs combined with captopril mg/die	SIDE EFFECTS				
				Duration (Days)	outcome			
					Ceased spontaneously	Change in dose	Additional therapy mg/die	Cessation of therapy
4.	Palpitation	75	Ø	2	No	Ø	guanfacine	Ø
6.	Tachycardia (120 beats/min)	150	Clopamide 10		No	Ø	metoprolol 600	yes 6 weeks
10.	Nightmares	150	Clopamide 20	14	Yes	Ø	Ø	Ø
11.	Salty taste	75	Ø	3	Yes	Ø	Ø	Ø
13.	Orthostatic hypotension	150	Clopamide 15	1	No	Clopamide 10	Ø	Ø
14.	Itching	150	Clopamide 10	3	Yes	Ø	Ø	Ø
	Nervousness			14	No	Ø	Ø	Yes 4 months
15.	Palpitation, supraventr. ES muscle cramps	150	Ø	14	No	Ø	Ø	Yes 2 months
18.	Oedema (Periorbital, hands)	150	Ø	14	Yes	Ø	Ø	Ø

DISCUSSION

In acute studies the first doses of captopril, 25 and 50 mg caused a significant fall in BP 30 min after administration. Maximum decrease was observed at 90–120/min, and BP remained reduced throughout the whole observation period. The effect of a single dose lasts for minimum 8 hours. Similar fall in BP occurred in supine and standing positions. Heart rate was not affected. Similar decrease in BP and no change in heart rate or cardiac output were reported in most acute haemodynamic studies with captopril. The depressor effect is mediated via a decrease of systemic vascular resistance /1,14, 16/. Following the first dose of captopril, 25 mg the magnitude of the BP fall and the time course to the maximal decrease found by Walker et al. was not different from our data /35/.

A comparison between the acute and chronic BP lowering effects of captopril showed a significantly greater fall in BP after the first dose of captopril, than following continuing administration as monotherapy. No correlation could be demonstrated between the falls in BP following the first doses of captopril, 25 mg or 50 mg and the decreases in BP during

short-term treatment with captopril alone, 75 or 150 mg/day. Our findings are in agreement with those reported by Lijnen et al. /26/ and in contrast to Case et al. /7/, Laragh et al. /25/ who found a close correlation between the initial and sustained BP responses and suggested that the response to the first dose of the drug may have predictive value for its long-term influence on BP.

In our experience captopril monotherapy with a maximum daily dose of 150 mg led to a long-term BP control only in 2 out of 20 patients with severe hypertension. Chronic combined captopril therapy with an average duration of 14.5 months, however, provided a sustained BP control significantly superior to that achieved with the previously used antihypertensive combination. In patients with mild to moderate hypertension the hypotensive effect of captopril alone or combined with a diuretic has been well documented /4, 5, 11, 18, 23, 26, 27, 33, 34/.

In patients with severe hypertension combined treatment with captopril and diuretics may produce about the same BP reduction as can be achieved by standard triple therapy /6, 17, 36/. Also, in patients with severe intractable hypertension the combination of captopril and a diuretic might be effective /3/. Two-third of our patients with severe hypertension received a diuretic and half of them a 3rd drug (calcium antagonists or beta blockers) to achieve and maintain BP control. Captopril accentuates the effects of vasodilators, such as calcium antagonists, direct vasodilators or $alfa_1$ receptor inhibitors /21/. Beta-blockers /28, 31/ or centrally acting drugs, such as guanfacin may be used to supress the tachycardia and to cause additional hypotensive effect. ACE inhibitors block the secondary hyperaldosteronism and resultant deficiencies of body and serum potassium associated with diuretic therapy /23/. In our experience potassium supplements could be stopped in 7 of 11 patients after introduction of captopril therapy. According to its converting enzyme inhibitory effect of captopril, 75 and 150 mg daily increased the plasma renin activity and plasma concentration of angiotensin I and decreased the plasma level of angiotensin II. There was no difference between the effect of the doses of 75 or 150 mg/day. The combination of captopril with diuretics significantly elevated the plasma renin activity and the angiotensin I level in comparison to the captopril monotherapy. After the addition of a betablocker these increases totally disappeared. Beta-blockers counteracted the renin stimulatory effect of captopril and diuretics. Other biochemical tests, haemogram and urinalysis regularly done showed no change in either phase of the chronic study. First dose side effects hypotension has been reported when captopril therapy was initiated in patients who had been previously sodium-depleted by diet or diuretics /15/, and in patients with unilateral renal artery occlusion /2/. Following the first dose of cap-

topril, 50 mg one of our 20 patients who had no renal impairment and had received no diuretics exhibited severe orthostatic hypotension.

Eight of the 20 patients developed side effects from captopril which diappeared spontaneously within 2–14 days in 4 of the 8 patients. Captopril was withdrawn in 3 patients for failure to maintain BP control and/or side effects. All discontinuances occurred within 3 months after starting captopril. No serious side effects were observed during the long-term therapy. In other studies, serious side effects, such as haematological disorders, reversible renal failure with hyperkalemia, nephrotic syndrome were found with high doses of captopril in patients who had impaired renal function, particularly those who have lupus or scleroderma /10, 20, 22, 29/.

Because of dose response in captopril therapy of hypertension, 150 mg captopril/day appears to be the ceiling hypotensive dose /26/ and because of dose related incidence of severe side effect /2/, in our long-term study 150 mg captopril was administered as a maximum daily dose.

It is concluded that captopril has been effective and safe in the long-term treatment of hypertension, the majority of patients with severe forms of hypertension, however, required additional medications.

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CLINICAL STUDIES WITH CAPTOPRIL TREATMENT OF HYPERTENSIVE PATIENTS

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Haemodynamic and humoral effects of captopril were studied in patients with essential and renovascular hypertension. Captopril decreased significantly both systolic and diastolic blood pressure and moderately, it reduced also the heart rate. On the basis of the haemodynamic effects our patients could be divided into two groups: in patients where the total peripheral resistance (TPR) exceeded 2000 dyn × sec × cm^{-5} during rest, captopril exerted its hypotensive effect by decreasing TPR. In patients in whom TPR was lower, the hypotensive action could be attributed to the reduction of cardiac output (CO).

Captopril increased plasma renin activity, and decreased the activity of angiotensin converting enzyme (ACE) in the plasma. In acute study captopril did not influence plasma noradrenaline level but increased it during long-term administration. It did not affect dopamine or adrenaline levels. Captopril had no effect on plasma beta-endorphin concentration, moreover, the opiate antagonist, naloxone, failed to antagonize its antihypertensive effect. Comparing the acute effects of Capoten (Squibb, USA) and Tensiomin (EGIS, HUNGARY) no significant differences were found.

Keywords: captopril–haemodynamic effect–humoral effect

The aim of our study was to test the cardiovascular and hormonal effects of captopril (Tensiomin, EGIS) applied in monotherapy or in combination in patients with essential and renovascular hypertension.

The effects of Capoten (Squibb, USA) and Tensiomin (EGIS, HUNGARY) on blood pressure and heart rate were compared.

Detailed haemodynamic, humoral and laboratory examinations were performed following acute and long-term captopril administration.

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PATIENTS AND METHODS

A total of 59 patients participated in the study (mean age: 48.1 ± 2.7 years, mean weight: 74.9 ± 4.9 kg). Not all of examinations listed below were performed in every patients-the actual number of tests in the individual study groups are presented in the following section. Patients had been diagnosed as having essential and renovascular hypertension of WHO grades I through III.

An open study was performed. Exclusion criteria were pregnancy, lactation, severe hepatic or renal insufficiency, disturbances of electrolyte, fluid and acid base regulation, haematological diseases and the lack of adequate collaboration.

A 10-day drug-free period preceeded the study when the "baseline" examinations were performed. Then the patients were given captopril and acute or chronic haemodynamic, humoral and laboratory examinations were performed according to the protocol.

Blood pressure was measured by mercury sphygmomanometer with the auscultation method. The diastolic value indicated by Korotkov's phase V. The pulse rate was simultaneously determined from the radial pulse.

Cardiac output was determined by radiocirculography (I^{113}-indium) as described in details previously /5/. The plasma volume was calculated from the dilution of isotope, by determining the haematocrit the blood volume could also be calculated. The total peripheral resistance (TPR) was calculated from the values for cardiac output and blood pressure.

Plasma renin activity (PRA) and *plasma beta-endorphin concentration* (bE) were determined by radioimmunoassay. *Plasma dopamine, adrenaline* and *noradrenaline* levels were assessed by radioenzymatic assay /5/. *Plasma ACE activity* was determined by a spectrophotometric method, by detecting the degradation of a synthetic substrate /2/. Since there are data indicating that upon storage captopril dissociates from the ACE in the plasma and it may cause false increase in ACE activity the analysis of blood, drawn from the patients, was started within 2 hours. Our previous results and data in the literature indicated that within 2 hours the ACE activity is not modified by storage in plasma samples of patients treated with captopril. The naloxone (an opiate antagonist) test was performed in the following way: 1.6 mg naloxone (NARCAN, Endo Labs., USA) was administered as an intravenous bolus and blood pressure and heart rate were measured 1, 2, 3, 5, 7, 10, 20, 40 and 60 minutes after the intravenous injection. The test was considered positive if the mean blood pressure increased by at least 12 mmHg.

ECG examinations (12 leads) were also carried out. The following parameters were studied: PQ, QRS, QT Intervals, P, R. T amplitudes, ST segment, wave-form deviations.

Laboratory examinations: blood cell counts (RBC, Hb, Ht, platelet), urine analysis (protein, sugar, ubg, sediment), serum levels of bilirubin, SGOT, SGPT, alkaline phosphatase, gamma GT, urea, creatinine, sodium, potassium, sugar, uric acid, cholesterol and triglyceride determined.

The side effect were reported by the patients and recorded.

For statistical analysis of the data Scheffé's method, paired "t" test and linear regression analysis were used.

RESULTS

1. *Acute effects* (12 patients)

Captopril, in the single dose of 25 mg, decreased blood pressure, from 181 ± 9/116 ± 3 mmHg to 138 ± 5/93 ± 4 mmHg (mean ± SEM). The effect became statistically significant even 15 min after the administration of the drug. The maximal effect appeared 2–3 hours later. The heart rate was decreased from 86 to 73 beats/min ($p<0.05$) Side effects were not observed.

2. *Long-term effects* (12 patients)

If the initial dose of 25 mg captopril decreased systolic blood pressure at least by 40 mmHg, the treatment was continued with the daily dose of 12.5 mg t.i.d. If the blood pressure reduction was smaller, the patients were given 25 mg t.i.d. The dose was adjusted according to the blood pressure and the highest dose was 150 mg/day. The data are summarized in the (Table I.) Both systolic and diastolic blood pressure were significantly decreased by captopril treatment. The hypotensive effect somewhat sub – sided around the 14th day: in most of the cases the dose had to be increased at this time.

By the end of the first week normotension could be achieved in all patients but one (in this patients blood pressure could not be decreased below 160/90 mmHg even by increasing the dose to 150 mg daily).

Considering the data of the 2nd and 3rd week, captopril significantly decreased the heart rate. This bradycardiac effect seemed to be clinically significant on the 2nd week.

Table I

Laboratory examinations during captopril (Tensiomin) treatment

	Baseline	1	2	3
Blood pressure (mmHg)				
systolic	187±6	141±3*	154±5*	144±3*
diastolic	112±5	87±2*	96±3*	86±2*
Heart rate	80±2	75±2	68±3	72±2
Blood picture				
RBC (M)	4.71±0.19	4.83±0.14	4.68±0.19	4.82±0.21
Hb (mM)	8.34±0.38	9.18±0.27	8.71±0.34	8.79±0.36
Ht	0.42±0.02	0.41±0.01	0.42±0.01	0.42±0.01
WBC (10^3)	6.5 ±0.4	6.8 ±0.5	6.9 ±0.5	7.05±0.53
Thr (G)	185±16	171±12	163±9	168±10
Liver function				
SeBi	17.1±2.0	14.4±1.2	14.0±1.1	12.7±0.8*
SGOT	11.6±0.9	11.6±1.4	13.1±1.9	13.2±1.6
SGPT	12.6	15.0	—	—
seAP	110±11	115±17	105±23	141±31
gamma GT	19.1±4.4	16.5±2.4	19.5±3.9	16.3±4.0
Renal function				
urea	5.75±0.45	5.75±0.43	5.64±0.60	5.35±0.51
creatinine	78.2±5.0	77.8±2.7	77.2±5.0	75.7±4.6
Other				
Na	140±0.5	140±0.5	139±0.5	140±0.6
K	4.2 ±0.1	4.5 ±0.1	4.6 ±0.1*	4.6 ±0.1*
blood sugar (mM)	5.30±0.21	5.16±0.16	5.25±0.24	5.12±0.21
uric acid	332±24	326±24	301±25	330±24
cholesterin	6.65±0.21	6.45±0.32	7.0 ±0.33	6.03±0.41
triglyceride	1.55±0.31	2.01±0.25	1.62±0.32	1.69±0.18

1, 2, 3: duration of captopril treatment (in weeks)

* significant change ($p<0.05$)

3. ECG examinations (12 patients)

Captopril had no effect on ECG parameters either during the acute or during the long-term administration. The only change was the increase in the R-R interval due to the bradycardiac effect. The PQ interval was not affected either.

4. Laboratory investigations (12 patients)

Data are presented in the Table I. in details. Captopril elicited no significant changes in laboratory parameters studied with the only exeption of the serum potassium level which was slightly increased within the normal range.

Table II

Changes in ECG characteristics during captopril (Tensiomin) treatment

	Baseline	1	2	3
PQ interval	0.14±0.03	0.16±0.03	0.15±0.04	0.15±0.03
QRS	0.08±0.001	0.08±0.001	0.08±0.001	0.08±0.001
QT	0.36±0.03	0.38±0.03	0.38±0.03	0.37±0.02

5. Comparison of the acute effects of Tensiomin (EGIS) and Capoten (SQUIBB, USA) (12 patients)

The acute effects of single doses of Tensiomin (25 mg orally) and Capoten (25 mg orally) were compared in a single-blind, cross-over study. After a 30 min recumbent rest (during this period the blood pressure and the heart rate were measured at every 5th min) patients were randomly given either Tensiomin or Capoten. On the following day the alternative order of drugs was repeated. After the administration of the drug the blood pressure and the heart rate was measured at every 15th min for 2 hours and at every 20th min for further 2 hours.

Tensiomin: The blood pressure was decreased from 181±9/116±3 to 138±5/93±4 mmHg, by 43±8/23±4 mmHg. The rate decreased from 86±3 to 73±3 beats/min.

Capoten: The blood pressure was decreased from 176±8/116±4 to 146±7/94±4 mmHg, by 31±5/22±3 mmHg. The heart rate decreased from 83±3 to 75±2 beats/min (Fig. 1.)

The effects of Tensiomin and Capoten were not significantly different as far as the maximal effects are concerned. When the time course of the hypotensive action was compared a more rapid onset of the effect of Capoten was found: the hypotensive action was statistically significant 15 min after

taking the drug, and the effedt started to subside as early as after 3 hours. In contrast to this, the effects of Tensiomin was significant only after 30 min but it was still significant in the 4th hour of examination.

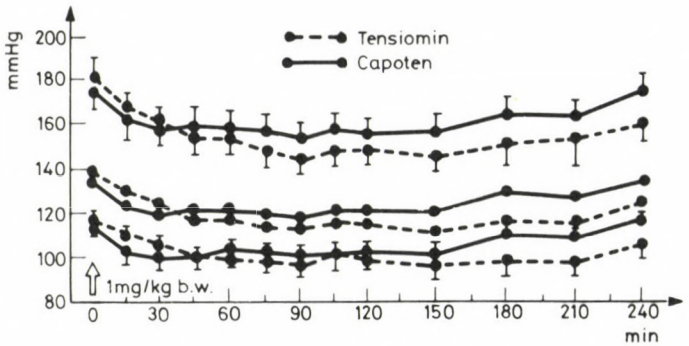

Fig. 1. The time course of the hypotensive effect of Tensiomin and Capoten

6. Hemodynamic effects (20 patients).

Both systolic and diastolic blood pressure were significantly reduced by acute administration of 25 mg captopril in this study. The heart rate was also decreased but this reducation seemed not to be clinically significant. Since it became evident from the evaluation of the hemodynamic parameters that captopril decreased total peripheral resistance (TPR) in some patients and cardiac output (CO) in others, the parameters of these two groups are presented separately.

In 12 patients, in which the CO was low at baseline, captopril increased the CO from 3.82±0.24 to 4.47±0.27 liter/min and it increased the cardiac index from 2.32±0.13 to 2.72±0.16 liter/min/m^2. Systolic volume in these patients was increased from 46.9±3.0 to 58.4±2.5 ml and TPR was decreased from 3052±268 to 2283±283 dyn. sec. cm^{-5}. The blood pressure decreased from 180±3/118±5 to 160±7/104±5 mm Hg and the heart rate from 82±2 to 76±2 beats/min.

In 8 patients, in which the cardiac output was high, captopril decreased CO from 6.19±0.24 to 4.75±0.45 liter/min and the cardiac index from 3.52±0.17 to 2.71±0.28 liter/min/m^2. The systolic volume in these patients was also decreased by captopril from 80.2±3.6 to 67.±7.4 but this change was not statistically significant. On the other hand the TPR increased from 1630±63 to 2245±292 dyn. sec. cm^{-5}. The blood pressure of these patients decreased from 163±5/106±3 to 154±5/106±5 mmHg and the heart rate from 77.5±2 to 72±2 beats/min.

Thus our study has shown that in hypertensive patients characterized by high TPR captopril decreases TPR while the fall in blood pressure in patients with high CO is associated by the decrease in CO. The cut-off point between these two groups (high TPR and high CO) was found at the value TPR of 2000 dyn. sec. cm^{-5}.

The hypotensive effect of captopril was more pronounced in the group characterized by the high TPR (Table III).

Table III

The acute haemodynamic effect of captopril (Tensiomin)

	TPR (dyn. sec . cm^{-5})		Cardiac output (l/min)	
	before captopril	after captopril	before captopril	after captopril
High baseline TPR (n: 12)	3052±268	2286±285	3.82±0.24	4.47±0.22
High baseline cardiac output n: 8	1630±63	2245±282	6.19±0.34	4.75±0.46

7. *Humoral effects* (20 patients)

The acute effects of 25 mg oral dose of captopril were investigated in this group of patients.

The plasma renin activity was increased by captopril from 1.43±0.32 to 2.06±0.53 ng Agt I/ml/hr. The converting enzyme activity (ACE) was decreased from 22.62±2.22 to 8.89±1.36 nM/ml/min, two hours after the administration of captopril.

There was no correlation between the baseline blood pressure and the baseline PRA or baseline ACE activity ($r=0.1748$ and 0.2667, resp., NS). At the same time there was a significant linear correlation between the changes in mean blood pressure and PRA as well as between the changes in blood pressure and ACE activity ($r=-0.5991$, $p<0.05$ and $r=0.6607$, $p<0.01$). There was no significant correlation between the baseline PRA and ACE levels or between their changes in response to captopril.

The baseline plasma dopamine level and the level after captopril were 2.51±0.44 ng/ml and 2.39±0.43 ng/ml respectively. The changes were not significant ($n=5$).

The baseline noradrenaline concentration and the level two hours after captopril were 0.106±0.034 ng/ml and 0.130±0.041 ng/ml, resp. These changes were not significant either ($n=5$).

The plasma adrenaline level was not affected by captopril. The values before and after the treatment were 0.130±0.044 ng/ml and 0.120±0.023 ng/ml, resp. (n=5). (Table IV.)

Table IV

The acute and subacute humoral effects of captopril (Tensiomin)

	Baseline	2nd hour	7th day
Plasma renin activity (ng) Agt/ml/h)	0.65±0.15	1.05±0.18	2.32±0.73*
ACE activity (nM/ml/h)	22.62±0.15	8.87±1.36*	13.62±2.07*
Plasma dopamine concentration (ng/ml)	2.51±0.44	2.39±0.43	3.13±0.36
Plasma adrenaline concentration (ng/ml)	0.130±0.044	0.120±0.025	0.140±0.018
Plasma noradrenaline concentration (ng/ml)	0.160±0.034	0.130±0.041	0.280±0.082*
Plasma beta-endorphin concentration (pM)	6.61±0.77	7.37±0.62	7.16±0.86

* Significant change ($p<0.05$)

8. Haemodynamic and humoral effects of treatment for one week (5 patients)

The above mentioned haemodynamic and humoral parameters were determined again following a one-week course of captopril monotherapy (25 mg oral captopril 4 times daily) two hours after taking the last dose. The blood pressure of these 5 patients was decreased from the pretreatment value of 161±5/108±4 mmHg (in the 2nd hour: 148±4/104±7) to 144±7/104±7 mmHg by captopril treatment. Heart rate was decreased from 82±3 (in the 2nd hour: 74±4) to 78±4 beats/min. The latter change was not significant. Cardiac output values were 5.16±0.7 l/min before (in the 2nd hour:5.15±0.42) and 5.46±0.61 l/min after treatment for one week (NS). Cardiac index values remained also unchanged, the values being 3.08±0.42 l/min/m^2 before (in the 2nd hour: 3.09±0.24) and 3.34±0.26 l/min/m^2 after the treatment (NS), resp. TPR was gradually decreased from 2125±330 (in the 2nd hour:1906±214) to 1755±839 dyn. sec. cm^{-5} (Table V.). Plasma

renin activity was increased from 0.85±0.15 (in the 2nd hour: 1.05±0.19±) to 2.32±0.73 ngAg-I/ml/h. ACE activity was 13.62±2.07 nM/min/ml. Plasma dopamine level was not changed by captopril monotherapy for one week:

Table V

Acute and subacute haemodynamic effects of captopril (Tensiomin)

	Baseline	2nd hour	7th day
Blood pressure (mmHg)			
systolic	161±5	148±4*	144±7*
diastolic	108±4	104±7	104±7
Cardiac output (l/min)	5.16±	5.15±0.4	5.64±0.6*
Cardiac index ($l/min/m^2$)	3.08±0.4	3.09±0.2	3.34±0.3*
TPR ($dyn \cdot sec \cdot cm^{-5}$)	2125±330	1906±214	1755±839*

* Significant change ($p<0.05$)

3.13±0.36 ng/ml. Plasma adrenaline level was not changed either attaining 0.140±0.018 ng/ml at the end of the treatment. However, plasma noradrenaline concentration was significantly altered. It was increased to 0.280±0.62 ng/ml (Table IV.).

9. *The effect of captopril on endogenous opioidergic mechanisms*

Following a one-week drug-free period 11 patients were given 1 mg/kg b. w. captopril orally, and blood pressure was measured every 10 min., for 2 hours. Blood was drawn for beta-endorphin determination in the 60th and 120th minutes. Naloxone-test was performed 120 min after the oral administration of captopril. Subsequently the patients were given 1 mg/kg b. w. captopril daily in three divided doses and blood was again drawn for plasma beta-endorphin determination and the naloxone-test was repeated on the 4th day (2hours after taking the first daily dose of captopril).

The baseline blood pressure was decreased by captopril from 161±5/90±3 to 143±4/90±3 mmHg (2nd hour). Blood pressure on the 4th day did not differ from the value of the 2nd hour: 145±4/91±3 mmHg. Intravenous naloxone did not affect the blood pressure of these patients, thus the naloxone-test was proved to be negative.

The plasma beta-endorphin levels were 6.61±0.77 pM : 7.27±0.90 pM : 7.37±0.62 pM and 7.16±0.86 pM, prior to the treatment, 1 and 2 hours after taking captopril and on the 4th day, resp. These differences were not statistically significant (Fig. 2).

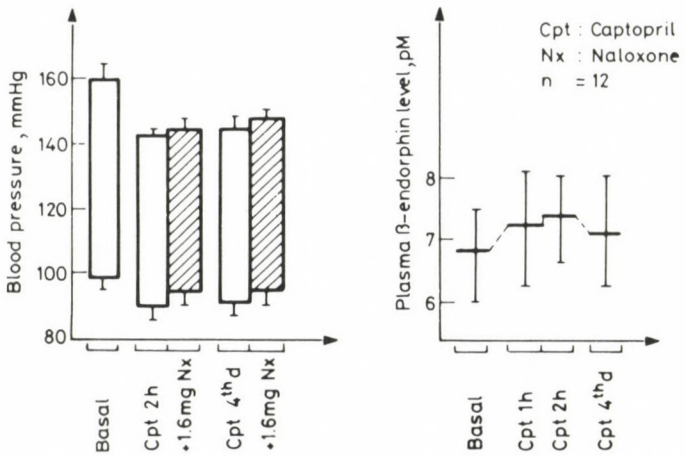

Fig. 2. The hypotension induced by captopril could not be influenced by the opiate antagonist naloxone. Plasma beta-endorphin level was not changed either

10. Captopril in combination (15 patients)

Favourable results were obtained with captopril also in combination treatment. Fifteen patients were treated with captopril by supplementing the double or triple combinations (beta-blocker+diuretic, occasionally vasodilatator) for several months. As an initial dose 25 mg was given to those patients then the daily dose was increased according to requirements at intervals of 2–3 days to a daily dose of 150 mg. Eleven patients suffered from accelerated essential hypertension and 4 from renovascular hypertension. Of the latter patients blood pressure was normalised in 1 case after surgical intervention. Three patients – because of inoperablitiy – have been treated continuously. In 9 out of 15 patients normotension could be attained in such a way that the dose of vasodilatator (dihydralazine) could be significantly reduced, and it could de even withdrawn in 3 patients. In 6 patients the blood pressure could not be normalised. Captopril elicited a significant reduction in blood pressure even in these patients: blood pressure became stabilized at an „acceptable" level (systolic value: 160–180 mmHg, diastolic value: 95–105 mmHg. (Table VI.)

Table VI

Changes of blood pressure after captopril (Tensiomin) treatment

	Blood pressure			
	systolic		diastolic	
	BC	AC	BC	AC
Accelerated hypertension	218±8	172±9*	124±5	103±4*
Renovascular hypertension	205±6	143±3*	128±4	93±2*

BC = before captopril treatment
AC = after captopril treatment
* significant change ($p<0.05$)

SIDE EFFECTS

Renal or haematological side effects were not observed during the study. Transient dysgeusia appeared in 1 patients which disappeared during therapy approximately in 2 weeks.

DISCUSSION

It was demonstrated in this study that blood pressure was significantly lowered by captopril treatment. Heart rate, although moderately, was also decreased. In patients characterized by high TPR the decrease in blood pressure could be explained by TPR-lowering effect. Our results were in good agreement with the data of others /1, 6, 10, 11/. This effect was accompanied by an increase in cardiac output, cardiac index and systolic volume, indicating a favourable haemodynamic action. According to our studies in patients characterized by low TPR, cardiac output and index were decreased by captopril, resulting in a smaller hypotensive effect. The calculated TPR was increased in these patients. Similarly an increase in TPR (above the baseline value) following a transient decrease had already been reported during chronic captopril treatment /11/. At the same time, we also reported the decrease of cardiac output. The mechanism of this phenomenon is unknown. To identify its cause further examinations are needed. As it is evident from this study it is not associated with the acute changes of plasma catecholamines. The plasma renin activity was increased both in response to acute and

one-week captopril treatment. This phenomenon is well-known and can be explained by the decrease of the feed-back mechanism through the juxtaglomerular apparatus. The reduction of plasma ACE activity was also a good indicator of the effect of captopril in our studies. The effect of captopril on PRA and ACE activities may be taken as an indication of the absorption of the compound. We could not find any data in the literature which would help explaining the increase in the plasma noradrenaline concentration following one-week captopril treatment. A change in the noradrenaline concentration of the opposite direction could be expected because of the reduction of presynaptic facilitation by AgII of noradrenaline release. This finding may be relevant in context with the change in the TPR but these relationships need further studies. As it was demonstrated in the present observations plasma beta-endorphin level was not altered by captopril and the hypotensive effect of captopril could not be influenced by the opiate antagonist naloxone. It was reported that captopril increased the plasma beta-endorphin level of patients suffering from migraine /3/. In animal experiments naloxone blocked the hypotensive effect of captopril /8/ although negative findings have also reported /7/. Our results have lent support to the latter observation and argued rather strongly against the assumption that captopril would activate the endogenous opioidergic mechanisms in essential hypertension.

Comparing the effects of Tensiomin and Capoten no significant differences were found between them.

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CAPTOPRIL IN HEART FAILURE

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The renin production, angiotensin II and aldosterone plasma levels have been proved to occur in heart failure. This pathological abnormalities can be stopped by the inhibition of ACE. This action of captopril is accompanied by a favourable clinical effects, the improvement of the symptoms of heart failure and the increase of sodium and water excretion and the increase of serum potassium level.

Keywords: ACE-inhibition, captopril, heart failure

In heart failure the pump function of the heart is altered in such a way that the myocardium which has genetically determined properties and is influenced by various factors, e.g. ischemia, degenerative processes during the course of life, is not further able to perform its function without compensatory mechanisms because of the impairment of contraction and relaxation.

The compensation may took place by two possible mechanims:

1. The first one originates from the venous side where the raised venous tone increases the flow into the heart and the diastolic volume of the ventricles. According to the Starling's principle an increase of performance (systolic volume, cardiac output) is possible by passive lengthening of the fibers of the myocardium. The volume overload usually increases the left ventricular filling pressure and the end-diastolic pressure (increased preload).

2. The arterial system represents the other possibility of compensation since the low cardiac output, weak ejection force can be partly substituted through the increase of vascular resistance, thus the local tissue perfusion, the perfusion pressure should remain adequate. However peripheral vasoconstriction increases the resistance to the blood flow out of heart (increased afterload), which might be dangerous: from a haemodynamic point of view it is a pressure-load; it may increase the myocardial oxigen demand through the increase of myocardial wall-tension and endocardial pressure. /1, 7/

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A. THE MECHANISMS INITIATING THE COMPENSATORY PROCESSES

Two important factors should be mentioned. One is the activation of the *sympathenic nervous system;* The other is the stimulation of the *renin-angiotensin-aldosterone system.* As a part of the general protective mechanism, renin production is increased mainly due to the decrease in renal blood flow; the result is high plasma renin level. One of the main effects of angiotensin II is peripheral vasoconstriction which increases systemic vascular resistance; it also stimulates aldosterone secretoin thereby causing sodium an fluid retention.

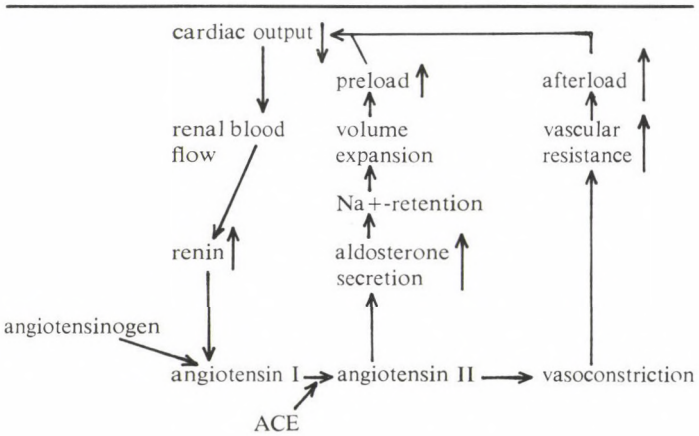
High plasma renin, angiotensin II and aldosterone levels have been proved to occur in heart failure; an increase of plasma noradrenaline concentration as an indicator of increased sympathetic activity has been verified as well.

On the basis of the above-mentioned data it is evident, that high filling pressure of the left ventricle, increased vascular resistance, sodium retention and tachycardia occuring as a part of sympathetic predominance, when reaching a certain level, can cause further deterioration of the primary process, thus the perpetuation of heart failure (Table I). /7/

It seemed appropriate to stop this process at one of essential links (renin-angiotensine-aldosterone) by the inhibition of ACE. It has been proved also in heart failure that captopril decreases the plasma level of angiotensin II and aldosterone. This action is accompanied by a favourable clinical effect, the improvement of the symptoms of heart failure and the increase of sodium and water excretion. The inhibition of aldosterone stimulation increases serum potassium level, which is of practical importance in the pharmacological treatment of heart failure.

Table I

Perpetuation of heart failure



B. THE HAEMODYNAMIC EFFECTS OF CAPTOPRIL

After taking a single dose (25 mg) the haemodynamic effects of captopril appear in approximately 30 min. attaining the maximum response in 1–1.5 hours and lasting 6–8 hours. Raising the dose mainly prolongs the duration of action.

a) The *mean blood pressure* is decreased by 7–20% in the majority of cases. In patients with low cardiac output systolic hypotension may cause symptoms forcing the physician to decrease the dose.This phenomenon should be considered with special attention in patients treated also with diuretics.

b) The effect on *heart rate* deserves particular attention since tachycardia accompanying vasodilatation does not appear as opposed to other vasodilatators; moreover, there is a significant decrease (10–14% on the average) in the heart rate in most cases. The increase in the sympathetic tone mediated by angiotensin II also fails to occur, which is also favourable effect it is an important factor from the point of view of myocardial oxygen demand, especially in ischemic heart disease.

c) *Total, systemic* and *pulmonary vascular resistance* are decreased, on the average by 25–30%, 20–30% and 35–45%, respectively by the drug. The systemic and pulmonary vascular effects of captopril are almost identical.

d.) Captopril decreases *pulmonary capillary wedge pressure,* the pressure in the *pulmonary artery* and in the *right atrium* by 35–50%, 15–30% and 25–40%, respectively.

e) The favourable effect on heart performance is characterised by an increase of *cardiac output* and *cardiac index,* by 25–30% and 14–40%, respectively.

f) The non-significant decrease in coronary blood flow and the significant decrease in *myocardial oxygen demand* have been verified by invasive studies.

g) Although only cautious administration of captopril is advised in the case of impaired renal function, nevertheless in heart failure the renal blood flow may be increased in parallel with the general improvement of circulation. The increase of sodium excretion and potassium retention should be mentioned, too. /1, 2, 3, 6, 7/

C. THE FAVOURABLE CLINICAL EFFECT OF CAPTOPRIL IN HEART FAILURE

The preload and afterload reducing effect of captopril results in a decrease of the filling pressure and an increase of the cardiac output without any significant changes in the heart rate, or even sometimes at lower heart rates. These are especially favourable in heart failure accompanying ischaemic heart disease since myocardial oxygen demand is decreased to a significant extent.

In recent years many papers have been published on the favourable effect of captopril and the first hungarian experiences are now known, too. It is interesting that, according to the studies, the effect of captopril is more favourable in the more severe cases with very high pulmonary venous pressure values, although it can be applied in all grades of heart failure. Most authors have administered the drug to patients of grade III and IV severity according to the NYHA functional classification, who were refractory to the conventionally applied diuretics or the customary vasodilatators. /4, 7, 8/

The clinical condition has improved in 80–85% of the patients treated with captopril:

a) General health (clinical condition) of patients improved, the *severity of symptoms of heart failure decreased* or the symptoms disappeared; the patients usually improved by two NYHA classes.

b) *Exercise tolerance* improved by 30–80%; this favourable effect was observed already 1–2 weeks after the administration of the drug.

c) There was a decrease of the *filling pressure* in the left ventricle, a decrease of the ventricular dimensions and an improvement of the *ejection function.*

The immediate, rapid effect of captopril has been sufficiently proved; the effect is sustained and tolerance does not develop. There are no satisfactory data, however about the further prospects of captopril therapy (prognosis), i.e. the survival of patients suffering from heart failure. /5, 7/

D. DOSAGE IN HEART FAILURE

Captopril administration can be initiated in heart failure when properly applied digitalis and/or diuretic treatment has no adequate clinical effect; these drugs should be continued during captopril treatment.

The *initial dose* of captopril is 25 mg *three times a day,* but the *dosage should be individualised.* It means that good results may be achieved by 12.5 mg or even 6.25 mg doses of captopril 3 time daily. The *daily maximum dose* is *350–400 mg* but this requires close monitoring of the patient. In the practice doses higher than 50 mg 3 times daily (a daily total of 150 mg) are required only very rarely. Most patients respond favourably to treatment within a week.

The *hypotension* occuring at the beginning of treatment may be a problem for the patient and may require cautions dose reduction but not drug withdrawal. Also, the dose should be increased very slowly, at intervals of 2–3 days.

During captopril administration potassiumsparing drugs (e.g. spironolactone) should not be administered and potassium substitution in patients receiving diuretics should be performed with continuous blood level monitoring

since the increasing effect of captopril on serum potassium level is well-known. Even the previously existing hypokalaemia may be normalised by captopril treatment. /6/

E. CASES REQUIRING CAPTOPRIL TREATMENT

1. *Primary disease*

a) all kind and forms of ischemic heart disease resulting in heart failure
b) congestive cardiomyopathy
c) myocarditis resulting in heart failure
d) valvular dysfunction accompanied regurgitation (especially in mitral insufficiency and aortic insufficiency)
e) prosthetic dysfunction with regurgitation after mitral or aortic valves replacement

2. *Haemodynamic state*

a) high ventricular filling pressure
b) increased ventricular end-diastolic pressure
c) volume overload
d) low cardiac output

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STUDY OF THE EFFECT OF TENSIOMIN (CAPTOPRIL) IN CHRONIC HEART FAILURE

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Tensiomin (captopril) was tested in 23 patients with chronic heart failure for 7.5 months on the average. In 9 outpatients suffering from congestive cardiomyopathy the effect of Tensiomin as an adjuvant to digitalis, diuretic, vasodilator etc. was evaluated by non-invasive methods. During the 3-month follow-up period the heart rate was decreased and the PEP/LVET ratio was improved. The parameters calculated from the X-ray examination (cardiothoracic index, cardiac volume index) indicated the regression of cardiomegaly. Radioisotopic circulatory examinations (systolic volume index, cardiac output index) indicated an increase in cardiac performance. In addition to the significant changes of these parameters the patients' clinical state was also improved in all cases as assessed according to the NYHA classification. Significant side effects were not observed during the treatment.

Keywords: heart failure, congestive cardiomyopathy, Tensiomin treatment, systolic intervals, X-ray examination, radioisotopic circulatory examination

The favourable clinical effect of long-term oral Tensiomin (captopril) treatment in congestive heart failure as well as the improvement of cardiac haemodynamics and functional capacity during such treatment have been regarded at least comparable to that of other vasodilators. According to the results obtained during prolonged follow-up, the improvement seems to be long-lasting /1, 2, 9, 10, 14/

In the present study 23 patients were given Tensiomin at the Hungarian Institute of Cardiology. At the Department of Cardiology the drug was administered to 14 patients suffering from heart failure of various origin refractory to other treatment and its clinical effects were evaluated. Beside this, at the special out-patient department for patients with cardiomyopathy prospective examinations with oral Tensiomin treatment were started and carried out in 9 patients with congestive cardiomyopathy as the most severe and progressive form of chronic heart failure /3,5/.

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PATIENTS AND METHODS

Of the hospitalized patients treated at the Department of Cardiology (14 patients, mean age: 58 years, range 32–78 years) the severe heart failure was due to previous myocardial infarction in 6 cases, systemic and pulmonary hypertension, postoperative state after the implantation of mitral valve prosthesis, each in one patient and in 4 patients cardiac failure was of unknown origin (COCM). Six patients fell into NYHA class III and 8 patients into class IV.

Tensiomin treatment was applied as a supplementary therapy; the evaluation of the effect was based mostly on the changes in the clinical state and the functional class of patients. Renal function and serum electrolytes were regularly checked; attention was also paid to the possible occurence of side effects.

In *congestive cardiomyopathy* (COCM), the prospective studies were carried out in 9 outpatients under the care of the special outpatient department (1 female, 8 males; mean age: 38 years range: 17–46 years. The diagnosis was established by the case history, physical symptoms as well as by non-invasive examinations (ECG, phono-mechanocardiography, X-ray, echocardiography). Heart catheterization was performed in 4 cases together with myocardial biopsy and coronarography.

The duration of illness of the outpatients suffering from COCM was 3.8 years (range: 0.8–7 years); they were under the supervision of the special outpatient department of the Hungarian Institute of Cardiology for 3.7 years on the average (range: 0.6–6 years).

The possibility of viral carditis as an etiological factor arose in 3 cases.

The treatment was indicated in the outpatients with COCM who belonged to NYHA classes III and IV and in whom the disease showed rapid deterioration as judged by the clinical symptoms and non-invasive examinations. Of the 9 patients 5 and 4 patients were in NYHA classes III and IV, resp.

Prior to treatment the following studies were performed: recording of the patients' physical state and heart rate, blood pressure determination of NYHA class, ECG, phono-mechanocardiography, chest X-ray examination. Of the laboratory parameters serum potassium, sodium, creatinine, BUN and blood picture were determined. The PEP/LVET ratio was calculated from the systolic time intervals according to Weissler's method /4, 7, 13/.

On the basis of the chest X-ray, the cardiothoracic index (CTI) (normal value: $\leq$0.50) and the cardiac volume index, calculated according to Jefferson's method were evaluated; the latter was calculated by the following equation:

$$V = \frac{L \times B \times D \times K \times M}{A}$$

L = the longitudinal heart diameter
B = the transverse heart diameter
D = the maximum diameter in depth (cm)
K = ellipsoid constant
M = factor of magnification
A = body surface area according to DuBois (m^2)

550 ± 79 ml/m^2 and 500 ± 79 ml/m^2 values of cardiac volume index were regarded as normal in males and females, resp.

Of the data yielded by isotopic circulatory examinations, the resting systolic volume index (SVI) and the cardiac output index (COI) were evaluated, the latter being calculated by the radiographic method with precordial detection following the administration of 99 m Tc-HSA as an intravenous bolus of 0.37 mBq dose. Follow-up examinations included all the above mentioned studies after the 1st week and in the 1st, 2nd and 3rd month. Control examinations were performed every other months thereafter.

Tensiomin (captopril) treatment lasted 1–27 months (mean: 7.5 months) in the 23 patients. The maximum and minimum daily *doses of Tensiomin* were 200 mg and 37.5 mg, resp. (75–100 mg on the average). The hospitalized patients received digitalis, diuretic and vasodilatator treatment according to their clinical state. Of the diuretics, all patients were given furosemid; the mean daily dose was 210 mg. Five subjects received daily 100–800 mg intravenously while the others took oral daily doses of 80–160 mg:

The 9 outpatients suffering from COCM were given regularly digitalis and diuretics (8 patients

spironolactone) while 5 patients were given also vasodilator treatment. Two patients received antiarrhythmic and 1 anticoagulant treatment, too.

In the 3 cases where an inflammatory process could be assumed, prednisolon (40 mg daily) was also given. The medication was not changed during Tensiomin treatment. When the adjuvant therapy was given to patients with COCM at the outpatients department, the unchanged doses of the previously taken drugs were supplemented by a daily dose of 3×25–3×50 mg of Tensiomin.

RESULTS

The adjuvant Tensiomin treatment of inpatients allowed the starting of oral treatment in all cases. Digitalis and vasodilator were continued in all patients; apironolactone treatment was discontinued in 3 patients while potassium supplements were withdrawn in 1 patient. Intravenous furosemid could be replaced by oral administration in all cases; the mean daily dose of furosemid could be reduced from 210 to 110 mg, while the dose had to be increased in 1 patient.

The changes in the NYHA functional classes were as follows: before the treatment, 8 patients fell into class IV and 6 into class III according to the NYHA functional classification, whereas after the treatment 4 patients fell into class III and 10 into class II.

The results of outpatient investigations undertaken in the patients with COCM were as follows:

Heart rate: at the beginning of treatment the mean heart rate was 101.09 ± 25.1 beats/min. After oneweek treatment it was decreased to 86.2 ± 8.9 beats/min; the difference is significant ($p<0.05$). The mean values in the 1st, 2nd and 3rd months were 79.9 ± 16.3 ($p<0.05$), 78.0 ± 11.26 ($p<0.05$) and 80.5 ± 11.1 ($p<0.05$); they are all lower than the baseline value.

Blood pressure: The mean systolic and diastolic values of baseline blood pressure were 130.67 ± 41.22 and 87.22 ± 17.16 mmHg, resp. Moderate decrease

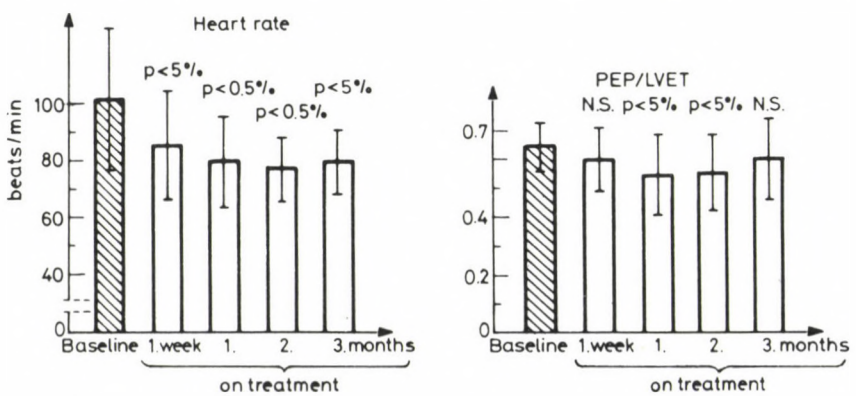

Fig. 1. Changes in the heart rate and PEP/LVET ratio during the control examinations ate th outpatient clinic

was observed during the study; only the mean diastolic value in the lst week decreased significantly ($p<0.05$).

Out of the *systolic intervals,* the PEP/LVET ratio was calculated.

The mean baseline value was 0.652 ± 0.86. Significant change did not occur in the first week while the mean values in the 1st (0.555 ± 0.138) and 2nd ($0,565\pm0.26$) months were significantly lower than the baseline value ($p<0.05$). The change in the 3rd month (0.601 ± 0.143 was not significant.

On X-ray examination, the *cardiothoracic index* (0.5777 ± 0.066) showed cardiomegaly, characteristic to the disease. The cardiac volume index can be considered as a more sensitive parameter; the baseline value (1044.6 ± 299.0 ml/m^2) of the patients was approximately twice the normal value.

The decrease in the CTI was not significant in the first week; however, it proved to be significant in the first (0.546 ± 0.053), 2nd (0.561 ± 0.551) and 3rd (0.543 ± 0.055) months ($p<0.05$).

The decrease of the *cardiac volume index* was close to statistical significance (931.3 ± 111.6) and in the 3rd month (826.6 ± 193.7 ml/m^2) ($p<0.05$) it was already significant.

The *SVI value* (16.78 ± 8.41 ml/m^2) measured by isotopic circulatory method showed a marked decrease of cardiac performance in our patients as compared to the normal value in our laboratory (45.3 ± 5 ml/m^2). The increase was significant as early at the end of the 1st week (1st week: 20.54 ± 7.95; 1st month: 21.19 ± 7.03; 2nd month: 22.34 ± 10.73; 3rd month: 23.12 ± 7.26, $p<0.05$).

The *value of COI* was 1.55 ± 0.63 ml/m^2 at the beginning of treatment. It was very low as compared to the normal value (3.5 ± 0.3) but it also showed a significant improvement already from the first week on (1st week: 1.80 ± 0.55; 1st month: 1.76 ± 0.37; 2nd month: 1.87 ± 0.56; 3rd month: 1.93 ± 0.62 ml/m^2; $p<0.05$).

The clinical state of the patients was evaluated according to the NYHA classification.

The changes observed in the inpatients were as follows: 8 patients belonged to NYHA class IV and 6 to class III. After the treatment 9 patients were transferred to NYHA class II and 4 to class III; 1 patient remained in NYHA class IV and died later.

Of the outpatients with COCM belonging to NYHA class IV, 2 patients were transferred to NYHA class III and 2 to class II. The clinical state of 5 patients in NYHA class III was also improved; they moved to NYHA class II.

Considering the very favourable effect of the drug the *side effects* were not significant. In the inpatients, a moderate impairment of renal function was observed in 6 subjects which was only transient in 3 cases; it was accompanied by significant hyperkalaemia in 2 cases. In the same patients significant hypotension was also observed; and in one of these, Tensiomin had to be withdrawn for a short period. Of the above 6 patients 5 took also spironolactone.

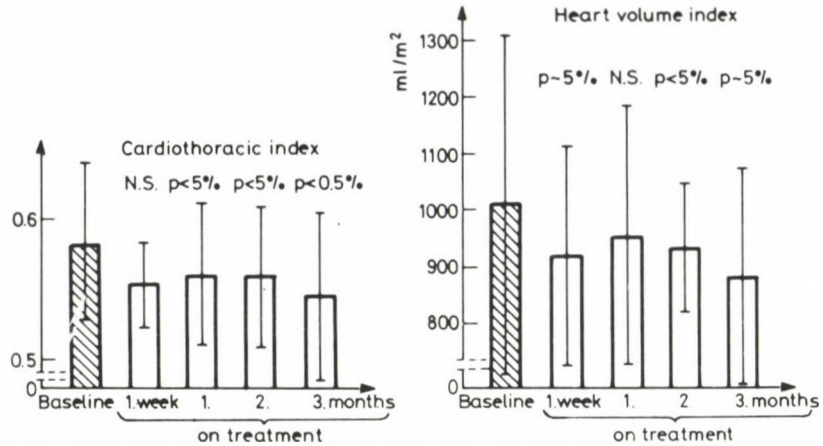

Fig. 2. Changes in the cardiothoracic index (CTI) and cardiac volume index (CVI) calculated on the basis of the chest radiogram during Tensiomin treatment

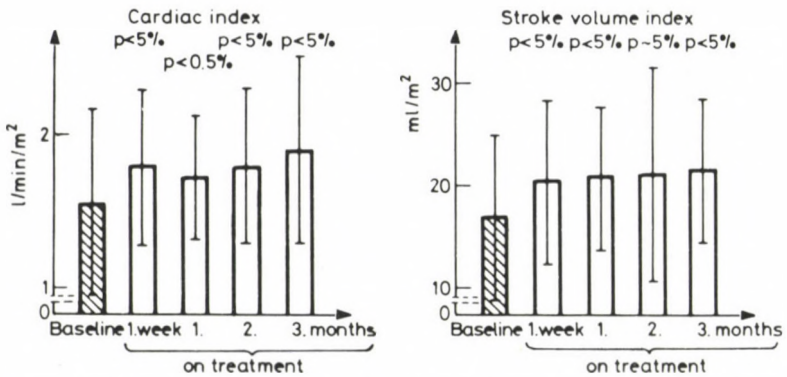

Fig. 3. Changes of cardiac output index (COI) and systolic volume index (SVI) calculated from radioisotopic circulatory studies

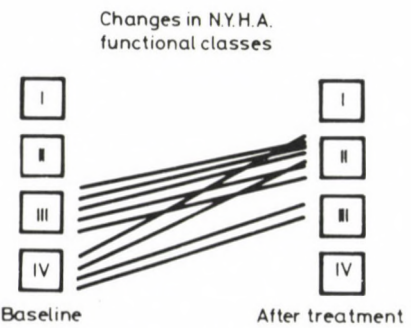

Fig. 4. Changes in NYHA classes at the end of the 3rd month

One of the inpatients with non-operated heart defect died after temporary improvement.

In the outpatients with COCM side effects necessitating the adjusment of previously established therapy were not observed. The decrease of oral potassium supplementation was necessary in one patient because of the moderate increase of serum potassium level.

Of the COCM patients 1 patient died 4 months after the beginning of treatment due to complications associated with the primary disease.

DISCUSSION

In Hungary experiences with long-term administration of Tensiomin in heart failure are rather scanty. The chronic heart failure accompanying congestive cardiomyopathy would be an attractive field of indication for this promising drug.

In this disease surgical treatment, except for cardiac transplantation performed at the final state, is out of the question. Thus, improvement of the patients' clinical condition and delayment of the unavoidable progression can be attained only by pharmacological treatment. Recently, supplementation of digitalis and diuretic treatment with vasodilators has been advocated but failed to yield really satisfactory results /6, 15/. As shown in the present study, the haemodynamic effects of Tensiomin exerted through the neuroendocrine system seems to provide a promising novel pharmacological tool in the treatment of patients duffering from COCM.

Due to progressive nature of the disease, the previously administered drugs were not withdrawn; Tensiomin was applied in combination with these agents as an adjuvant. According to our experiences in the outpatient clinic supported by the data of complex non-invasive examinations, a rapid improvement of the patients' state could be achieved in the first week after the introduction of Tensiomin. Cardiac dilatation due to myocardial damage and the cardiomegaly characteristic of the disease were markedly decreased. The heart rate was decreased during treatment; Tensiomin had a favourable effect on the compensatory tachycardia. Cardiac performance as characterized by the cardiac output was increased first of all as a result of increased systolic volume. Irrespective of the baseline blood pressure value, hypotension necessitating withdrawal of the drug occurred in one patient.

Our experiences indicated that the improvement of the patients's clinical condition was associated by favourable changes in the NYHA functional classification and this could be verified also by objective haemodynamic examinations.

It is an open question whether these favourable initial results would bring about a delay in the deterioration of the disease.

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COMPARATIVE STUDY ON THE SHORT-TERM EFFECTS OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS (LOPIRIN, SQUIBB AND TENSIOMIN), AND DIHYDRALAZINE IN CHRONIC CARDIAC FAIULRE

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The aouthors have compared the short-term effect of two captopril (ACE inhibitor) preparations namely the Lopirin (SQUIBB) and Tensiomin (EGIS) and dihydralazine as well as placebo in 15 patients with severe heart failure (NYHA III–IV. class). In case of 8 patients with NYHA IV. functional class the short-term effect of the combined therapy of dihydralazine and Lopirin and dihydralazine and Tensiomin as well dihydralazine and placebo have been compared. The underlying disease was dilated cardiomyopathy (DCM) and ischaemic heart disease (IHD).

At the end of the treatment with different drugs and placebo the clinical signs of heart failure (complaints and physical status) and the echo and mechanocardiographic parameters of left ventricular function were assessed. The parameters, apart from the clinical signs, have been evaluated in double blind fashion.

Compared to placebo all the three drugs i.e. dihydralazine, Lopirin as well as Tensiomin have decreased significantly the NYHA classes, influenced favorably the non-invasive parameters of left ventricular function and decreased blood pressure. As to the dihydralazine, it improved the left ventricular ejection function and the clinical state of the patients with DCM in a higher degree than the two ACE inhibitors did. The effect of Tensiomin and Lopirin was the same in every respect. Both have influenced more favourable the complaints and physical state of patients with IHD than dihydralazine has. The left ventricular filling pressure, the double product (heart rate x wall tension) indicating the myocardial oxygen demand were more reduced in their effect than in that of dihydralazine. Unlike dihydralazine both decreased the heart rate. Administering one of the two ACE inhibitors to the dihydralazine benefical additive effects have been experienced; the NYHA classes, the heart rate, the left ventricular wall tension and the double product diminished.

The authors, on the bases of the results, consider Tensiomin and Lopirin as equivalent in their effect. In their opinion the administration of these drugs mean a new, efficient way of therapy, first of all in cases of heart failure caused by IHD. In the most severe cases they suggest a trial with the combined dihydralazine–ACE inhibitor therapy.

Keywords: dilatative cardiomyopathy, ischaemic heart disease, heart failure, vasodilator treatment, ACE inhibitor treatment, non-invasive examination.

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For decades the treatment of heart failure has been an issue of prominent importance in clinical cardiology /6/. The disease is progressive, has a high mortality rate and, as a consequence, the treatment of the patients bears severely on the financial and organizational resources of health care /35, 36/. The application of vasodilator agents should be regarded as the most important therapeutic achievement of the last decade. Their combination with traditional agents (digitalis and/or diuretics) may be effective even in otherwise drug-resistant cases; starting therapy at an early stage of the disease usually means that a sustained stabilization of the patients' clinical condition can be achieved. Their favourable effect is apparent not only acutely but also in long-term studies; the state of the patients and the haemodynamic parameters being considerably improved. These results can be achieved both with preparations acting dominantly at the „arterial" or „venous" side as well as with the so-called balanced preparations /3, 8, 22, 13, 19/. However, the results of the recently performed double-blind placebo-controlled studies put a halo to the initial optimisme: contrary to expectations, the sustained favourable effect and the significantly higher survival rate could not be demonstrated /18, 24, 25, 32/.

Based on the observation that the renin-angiotensin-aldosterone system has a key role in the pathomechanism of chronic heart failure a novel, indirectly acting vasodilator therapy with multiple mechanismes of action has been introduced for 8 years based on the application of an inhibitor of the enzyme generating angiotensin II from angiotensin I (ACE); this enzyme inhibitor was captopril /10, 16/. Captopril, in addition to reducing angiotensin levels, decreases the levels of aldosterone, catecholamines and vasopressin and has an inhibitory effect on bradykinin breakdown /28/. The extensively documented therapeutic effect suggests that captopril is an important tool in the treatment of heart failure; thus, the attractive theoretical considerations appear to be supported also by clinical experience /28/.

At our department, vasodilator agents, initially dihydralazine and nitrates /2, 11/ have been applied in the therapy of congestive heart failure since 1976. The first experiences with the therapeutic application of captopril were obtained in 1984 when we started administering Lopirin (SQUIBB). Tensiomin (EGIS) was first given at the beginning of 1985. The studies to be presented below were aimed at comparing the effectiveness of the two ACEI preparations with each other as well as with that of dihydralazine which is known to reduce primarily the arteriolar resistance. The side effects as well as the development of tolerance to these preparations were also compared.

SUBJECTS

Consecutively admitted 21 patients (18 males and 3 females) with heart failure of NYHA classes III and IV were enlisted. Of them 13 had DCM and 8 IHD. The age of patients varied from 30 to 73 years; the mean age was as high as 53 years. In 12 patients significant mitral insufficiency was revealed; one had also functional tricuspidal insufficiency. All patients had sinus rhythm. Ventricular extrasystoles were seen in 7 cases; their incidence did not interfere with the evaluation. None of the patients with IHD had unstable angina or had any history of myocardial infarction within six months prior to the study. None of the patients had hypertension or chronic renal disease. The severity of heart failure as assessed according to the NYHA criteria was approximately identical in the patients with DCM and IHD. At the same time, however, similarly to our earlier observations /12/, IHD patients had more markedly elevated left ventricular filling pressure and a slighter impairment of the ejection function as compared to the DCM group. The treatment of the patients, save for the compounds to be evaluated and only minor adjustment in the dose of diuretics according to the demands, remained unchanged throughout the trial.

The course of the trial

Patients were informed about the aims and the course of trials; after having given their consent they were enlisted.

The first phase of the trial consisted of a 7-day stabilization period. In this phase the previously given vasodilator agents (nitrates and, in 12 patients dihydralazine) were omitted, the digitalis and/or diuretic (Henle-loop diuretics, ethacrinic acid or furosemid) therapy was optimized and the abnormalities in electrolyte levels were also normalized. In 7 cases, mexiletine was administered to control ventricular extrasystolia. At the end of this period the parameters to be detailed below were assessed.

In the second phase the short-term effects of the drugs and placebo were evaluated and compared. The patients, in different order, received Tensiomin, placebo, dihydralazine, placebo and Lopirin. The drugs or placebo were administered orally in 3–4 divided daily doses for 12–16 days (the captopril preparations were given for at least 14 days). The starting daily dose of dihydralazine was 4 times 12.5 mg which was gradually increased to daily 4×25–4×50 mg. The mean daily dose was as high as 150 mg.

The initial daily dose of Lopirin and Tensiomin was 3×25 mg; the dose of the diuretics was for a few days reduced prior to this treatment. If the systolic blood pressure was low (100 mmHg or below) the starting dose was 12.5 mg 3 times. The dose was increased daily or every other day until a daily total of 100–150 mg (mean; 143 mg) was reached.

The dose of Lopirin and Tensiomin was identical in the same patient. The clinical symptoms of heart failure and the parameters of left ventricular function were evaluated at the end of each treatment period. The application of the drug and the evaluation of the clinical picture was performed in an open fashion. When making this choice we considered that we were treating patients with severe heart failure whose state, according to our previous experience, could be affected favourably by vasodilator administration. At the same time, however, with the exception of the patients' complaints, the data of the physical examination and blood pressure measurements, all other parameters were evaluated in a blind manner; moreover, the patients were unaware which preparation they were actually receiving.

The comparison of the short-term drug effects could be completed in 15 (10 with DCM and 5 with IHD) out of the 21 patients. These 15 subjects constituted *Group 1*. In 6 out of the 21 patients (3 with IHD and 3 with DCM of NYHA class IV) there was a worsening of the clinical condition in the course of the placebo period and their response to dihydralazine treatment (the 3 IHD patients) or to the administration of one of the captopril preparations (the 3 DCM patients) proved to be unsatisfactory. In these cases theoretical considerations, data from the literature /21/ and our previous, favourable experience prompted us to decide a combined treatment with dihydralazine and Lopirin or Tensiomin. To assess the potential advantage, the effectiveness of the dihydralazine-Lopirin and dihydralazine-Tensiomin combinations was compared not only to each other but also to that of the dihydralazine-placebo combination: thus, the combined drug treatment periods of varying order were spaced by a dihydralazine-placebo treatment period. In addition to the 6 patients mentioned above a treatment schedule of similar design was applied in 2 further patients with DCM, whose heart failure had worsened during a previous phase of sustained therapy when one of them was receiving dihydralazine and the other Tensiomin. These 8 patients (5 with DCM and 3 with IHD in NYHA functional class IV) constituted *Group 2*. In this group the different treatment periods lasted 8–12 days; at the end of these periods, with the exception of the assessment of the clinical picture and the measurement of blood pressure, the evaluation was performed in blind fashion, as well.

Upon completion of the short-term studies the treatment that had been found as most favourable was given for a longer period; the results of this treatment will be presented in a separate report.

METHODS

The following parameters were recorded: 1., *heart rate* (HR) which was determined from the ECG and phono-mechanochanocardiographic records, 2., *mean arterial BP* (MABP), for the assessement of *left ventricular ejection function* 3., the *PEP/EP* values calculated from the intervals measured by ECG and phono-mechanocardiography and 4., the *linear ejection fraction* (dD%) determined by M-mode echocardiography, to characterize left atrial and left ventricular *filling pressure* 5., the *preisovolumetric contraction period/isovolumetric relaxation period (PIVCP/IVRP)* quotient obtained by phono-mechanocardiographic method, 6., *end-systolic was tension (ESWT)*, an M-mode echocardiographic parameter to assess the afterload obtained by multiplying systolic blood pressure with the end-systolic left ventricular cavity diameter /wall diameter ratio. Its calculation was as follows:

$$\frac{\text{systolic arterial pressure x/end-systolic left-ventricular cavity diameter} \times 2^{-1}}{(\text{end-systolic left ventricular septum} + \text{posterior wall diameter}) \times 2^{-1}}$$

7., *double product*. the product of heart rate and the above wall-tension parameter (ESWT) to characterize *myocardial oxygen demand*, the *clinical signs of heart failure* and the patients' complaints which were evaluated by determining, 8., the *NYHA class*. The changes in the latter parameter during a given period was determined mostly on the basis of the reports given by the patients themselves.

The echocardiographic measurements were carried out by a one-dimensional device (Picker Echoview 80 C type). The measurements were carried out on records making correct evaluation possible. The records were taken at the level of the mitral valve, at 25 or 50 mm/sec chart speed. The polycardiographic recordings were made on a 6-channel direct recorder (Hellige EK-21 type); the records were evaluated at 100 mm/sec paper speed. Both the echo- and polycardiographic parameters represent the mean values resulting from at least 3 consecutive cardiac cycles. The differences between placebo and drug effects were evaluated by group comparisons. At the end of the respective treatment periods the mean and SD values were calculated; the differences between groups were evaluated by analysis of variance. The data obtained in the two placebo (P_1 and P_2) and ACEI periods (Lopirin and Tensiomin) were pooled: for further comparisons they were considered as single homogenous groups. The pooling of data was statistically justified because the values of variables obtained in the two placebo or ACEI periods were similar and no significant differences were found between the groups to be pooled. The statistical calculations were performed on a "ZX Spectrum" personal computer, using the relevant statistical program.

RESULTS

The mean and SD values of various parameters obtained in the different drug and placebo periods, as well as the results of statistical comparisons are presented in tabulated form. Table 1 contains the data for the Group 1. of patients, whereas the statistical comparisons are given in Table II.

The *mean arterial blood pressure* was reduced significantly by dihydralazine and the two captopril preparations; the reduction produced by the ACEIs tended to be slightly greater although the difference did not attain statistical significance. Tensiomin and Lopirin decreased significantly the *heart rate* as compared to the values obtained in the placebo period whereas during dihydralazine treatment it did not change.

As demonstrated by the results of the echo- and polycardiographic measurements, the most prominent improvement in *left ventricular ejection function* was produced by dihydralazine as compared to the placebo period; the two

Table I

Parameters of non-invasive measurements at the end of the various treatment periods
(Group 1, 15 patients)

PERIOD	Dihydralazine	Placebo 1.	Lopirin	Placebo 2.	Tensiomin
PARAMETER					
MBP, mmHg	86±8	95±10	84±9	96±10	85±8
HR, beats/min	94±9	95±8	82±7	96±9	83±8
PEP/EP	0.58±0.092	0.77±0.123	0.67±0.103	0.77±0.124	0.67±0.112
PEP/EPI	0.36±0.043	0.48±0.062	0.41±0.041	0.46±0.054	0.42±0.052
△D %	16.1±4.01	10.3±3.20	13.2±3.51	11.1±3.43	13.4±3.21
PIVCP/IVRP	0.67±0.103	0.79±0.124	0.58±0.081	0.80±0.133	0.54±0.082
end-systolic wall tension, mmHg	294±27.3	369±44.4	268±27.1	358±47.1	274±28.9
Double product, mmHg/min	27874±2038	36104±4098	22408±1841	34810±3872	23579±2208
NYHA class	2.47±0.516	3.60±0.507	2.53±0.516	3.53±0.516	2.57±0.507

Table II

Comparison of parameters measured and calculated during the virus treatment periods
(Group 1, 15 patients)

PARAMETER	MBP mmHg	HR beats/min	PEP/EP PEP/EPI	⊿D%	PIVCP/IVRP	End-systolic wall tension mmHg	Double product mmHg/min	NYHA class
Difference between D and P	P<0.02	NS	P<0.01 P<0.01	P<0.01	P<0.05	P<0.01	P<0.01	P<0.001
Difference between D and C	NS	P<0.01	P<0.05 P<0 05	P<0.05	P<0.05	NS	P<0.02	NS
Difference between T and L	NS	NS	NS	NS	NS	NS	NS	NS
Difference between C and P	P<0.01	P<0.001	P<0.02 P<0.05	P<0.05	P<0.001	P<0.01	P<0.001	P<0.001
Difference between P_1 and P_2	NS	NS	NS	NS	NS	NS	NS	NS

Abbreviations: D = dihydralazine; L = Lopirin; T = Tensiomin;
C = Tensiomin and Lopirin drawn together;
P = Placebo 1 and placebo 2 drawn together

ACEIs caused a slighter although statistically still significant amelioration of this parameter. In Figure 1 a characteristic captopril effect is demonstrated as evaluated by M-mode echocardiographic method: the significant shortening of end-diastolic diameter is accompanied by a moderate (from 9 to 11%) improvement in the linear ejection fraction (Figure 1). The *left ventricular* filling *pressure* as characterized by the PIVCP/IVRP quotient was reduced most markedly by the two AGEIs whereas the effect of dihydralazine was weaker (Fig. 2).

The reduction in the *end-systolic tension* i.e. in the left ventricular afterload was of similar extent during Lopirin, Tensiomin and dihydralazine treatment.

The indicator of myocardial oxygen demand, the *double product* was decreased most prominently by Tensiomin and Lopirin; the effect of dihydralazine was less (Fig. 3).

The *clinical signs of heart failure,* the complaints, i.e. the *NYHA class* was affected to a similar extent by all three drugs, as compared to the placebo: the improvement was approximately one NYHA class. Dramatic improvement by two NYHA classes was produced by both ACEIs in two patients with IHD. In 4 out of 5 IHD patients of the group the improvement was more marked upon ACEI treatment; one patient responded similarly to both dihydralazine and the captopril preparations. Dihydralazine ameliorated more effectively the clinical signs in 6 DCM patients characterized by severe impairment of the pump function and significant mitral regurgitation whereas in one patient the ACEIs proved to be more effective; 3 patients with DCM responded similarly to ACEIs and dihydralazine. As to the response to Lopirin and Tensiomin it was found to be identical in all but one patients. Death did not occur during these treatment phases.

Table III contains the data and statistical comparisons for Group 2 of the patients who have received combined treatment (Table III).

As compared to the dihydralazine-placevo period, the *heart rate* was significantly reduced by dihydralazine-Lopirin and dihydralazine-Tensiomin combination. The *mean arterial pressure* tended to be lower upon the addition of ACEIs to dihydralazine although this fall attained statistical significance only in the case of the Lopirin-dihydralazine combination. The *ejection function,* as it was demonstrated by both parameters used for its characterization, was not affected by the addition of captopril preparations to dihydralazine treatment. The *left ventricular filling pressure* as characterized by the PIVCP/IVRP quotient was significantly decreased by combined treatment with ACEIs and dihydralazine.

The values for *end-systolic* tension and the *double product* during drug combinations are presented in Figure 4.

It is apparent that there was a favourable identical change in both parameters when either Tensiomin or Lopirin was added to dihydralazine therapy.

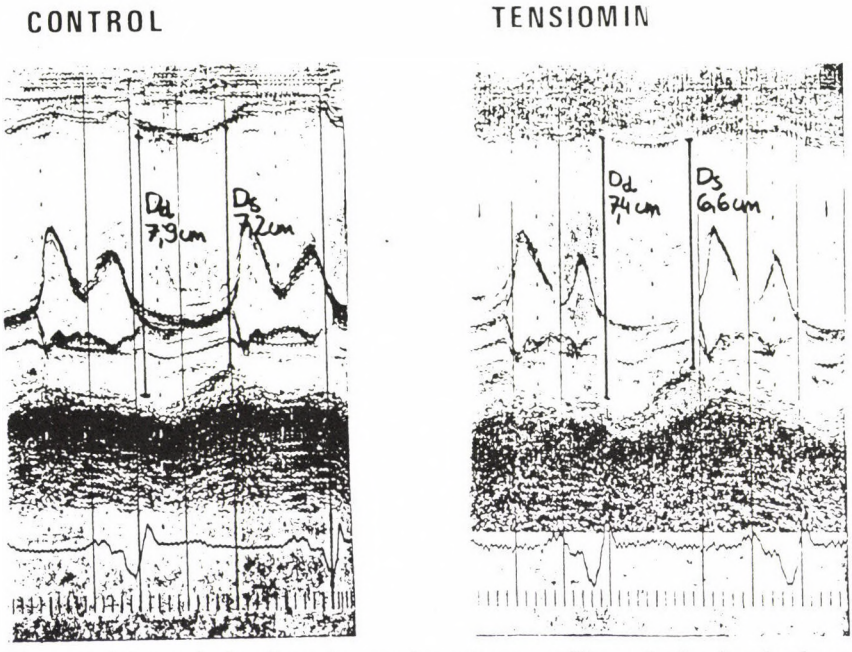

Fig. 1. Changes in left ventricular dimension; moderate increase of linear ejection fraction in response to Tensiomin. Left side: before Tensiomin administration Right side: during Tensiomin administration
D_d = end-diastolic diameter of left ventricle
D_s = end-systolic diameter of left ventricle

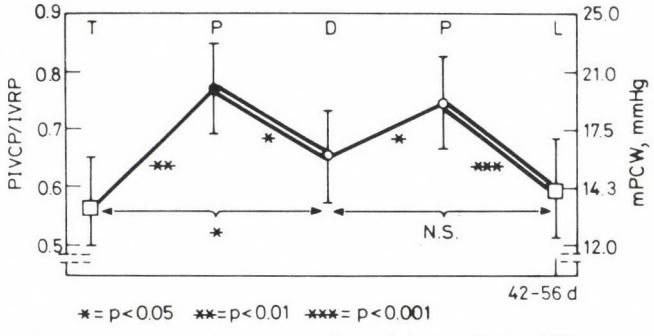

Fig. 2. The effect of drugs and placebo on calculated left ventricular filling pressure in Group 1. On the vertical axis the PIVCP/IVRP values, and the corresponding mean pulmonary wedge pressure values are presented. The level of significance of differences are shown too. Abbreviations: T = Tensiomin, P = placebo; D = dihydralazine; L = Lopirin; mPCW = mean pulmonary wedge pressure

Table III

Parameters of non-invasive measurements at the end of treatment periods
(Group 2, 8 patients)

PERIOD	Dihydralazine + Lopirin	Dihydralazine + Placebo	Dihydralazine + Tensiomin
PARAMETER			
MBP, mmHg	80±7	89±9	82±8
HR, beats/min	86±9	96±10	88±9
PEP/EP	0.84±0.091	0.89±0.101	0.82±0.084
△D%	14±3.4	13±2.6	15±3.3
PIVCP/IVRP	0.70±0.10	0.93±0.13	0.66±0.09
End-systolic wall tension, mmHg	385±41.6	478±48.3	367±36.1
Double product, mmHg/min	34320±3123.8	46752±4306.3	32608±3208.8
NYHA class	3.25±0.463	3.87±0.353	3.25±0.463

Table IV

Comparison of parameters calculated during the various treatment periods
(Group 2, 8 patients)

PARAMETER	MBP mmHg	HR	PEP/EP PEP/EPI	.1D%	PIVCP/IVRP	End-systolic wall tension mmHg	Double product mmHg/min	NYHA class
PERIOD								
Difference between D+L and D+P	P<0.05	P<0.02	NS	NS	P<0.02	P<0.01	P<0.001	P<0.01
Difference between D+T and D+P	NS	P<0.05	NS	NS	P<0.02	P<0.001	P<0.001	P<0.01
Difference between D+T and D+L	NS	NS	NS	NS	NS	NS	NS	NS

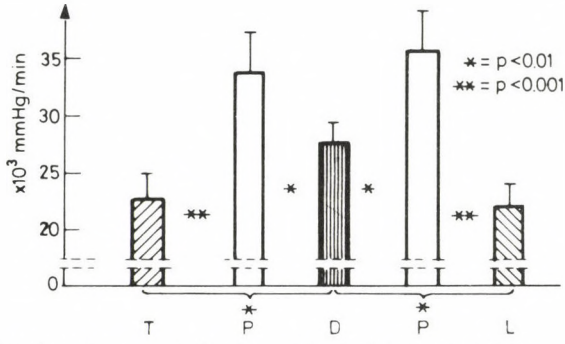

Fig. 3. The effects of various drugs and placebo on the double product (heart rate × end-systolic wall tension) in patients of Group 1.
The crosses between the columns indicate the level of significance of differences
Abbreviations: T = Tensiomin; L = Lopirin; P = placebo; D = dihydralazine

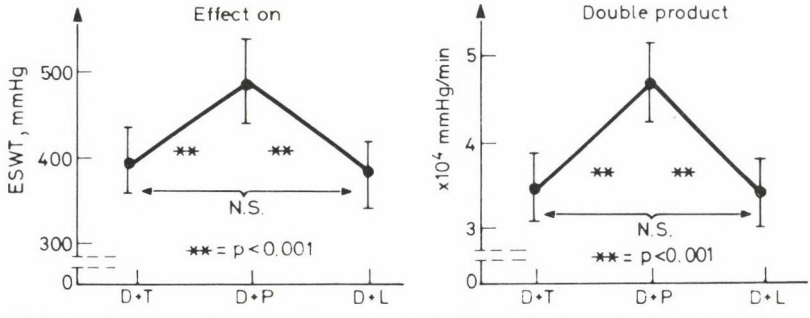

Fig. 4. Effects of various drug combinations and dihydralazine+placebo on end-systolic wall-tension (left side) and on the double product (right side) in patients of Group 2.
The level of significance of differences is also presented
Abbreviations: ESWT = end-systolic wall-tension;
D+T = dihydralazine+Tensiomin
D+P = dihydralazine+placebo
D+L = dihydralazine+Lopirin

The clinical symptoms of heart failure were improved in 6 patients; the NYHA class became lower by one unit upon the addition of either Tensiomin or Lopirin to dihydralazine therapy. Out of the 5 patients with DCM and 3 with IHD the clinical condition of only 2 patients (one with DCM and one with IHD) showed no improvement. No death occurred in these phases of trial.

When comparing the effects of the dihydralazine-Lopirin and dihydralazine-Tensiomin combinations, there was no significant difference in any of the observed parameters.

LABORATORY TESTS

The BUN, serum creatinine, K and Na levels, the white blood cell count, urine sediment and protein content were determined before and once a week during the treatment with ACEIs. No significant alterations were found. The decrease in the white blood cell count was only moderate: in the case of Lopirin, from an initial mean of 6800/mm^3 to a mean of 5900/mm^3 by the end of treatment; for Tensiomin, the value fell from 7100/mm^3 to 6300/mm^3 The BUN and serum creatinine levels became moderately elevated usually by the end of the first week of the treatment; at the end of the second week the values approached the initial figures and in 6 well-responding cases the values fell below the initial level. The favourable responses to dihydralazine treatment were characterized also by a fall in the BUN values.

SIDE EFFECTS

Transient fall of blood pressure occured in 5 patients; it was accompained by dizziness and, in one case, collapse. Of these patients, one received Lopirin, one Tensiomin, two the dihydralazine-Tensiomin and one the dihydralazine-Lopirin combination. Of the 3 patients who were receiving combined treatment 2 responded with rapid normalization of blood pressure upon an elevation of the legs in the supine position and both drugs were discontinued for a brief period, whereas in the rest transient dose reduction proved to be sufficient.

At the beginning of dihydralazine treatment or upon increasing the dose of the drug 2 patients developed significant tachycardia; this tachycardia, which became subsequently reduced, provoked angina pectoris in one patient with IHD. Headache was apparent in 6 patients in the first few days of dihydralazine administration; in one case it persisted throughout the treatment period.

None of the side effects necessitated the permanent discontinuation of treatment.

DISCUSSION

The effect of vasodilators and ACEIs could be assessed by evaluating the changes in left ventricular function during the treatment. Other parameters such as the levels of hormones and endogenous vasoactive substances correlate rather weakly or ambiguously with the therapeutically relevant drug effect; sonsequently, their value in assessing and comparing the effectiveness of drugs is rather doubtful /28/.

In this study left ventricular function was evaluated by non-invasive techniques, mostly by echo- and mechanocardiographic methods. In addition

to the well-known advantages of the non-invasive techniques, there were some other, special factors which prompted us to choose these methods for the present study. Some data in the literature /20, 29, 34/ and, in certain aspects our previous findings /14/ and clinical experience demonstrated convincingly that these methods are suitable for assessing both the systolic and diastolic functions of the left ventricle, and also for the reliable evaluation of their changes, these are suitable for assessing and comparing pharmacological effects. Moreover, recent findings have cast some doubt as to the value of the invasive methods in the evaluation of vasodilator treatment /27, 28/.

When analyzing the effects exerted on the different parameters it should be pointed out that the reduction of the *heart rate* by ACEIs and the absence of its change on the effect of dihydralazine is a known reaction in patients with severe heart failure /21, 26/. Lowering of the heart rate and, consequently, prolongation of the diastole, by all probabilities result in a reduction of myocardial oxygen demand and an improved myocardial blood supply. At the same time, the heart rate lowering effect partly abolishes the favourable effect exerted on cardiac output.

When analysing the almost identical decreases of *mean arterial pressure* in response to the two ACEIs and dihydralazine it is important to note that the identical values mean higher systolic and lower diastolic blood pressure i.e. greater pulse amplitude under the effect of dihydralazine. This can be explained by the more pronounced decrease in arteriolar resistance and the higher cardiac output caused by dihydralazine /26/.

For the assessment of the effects of the drugs *on left ventricular ejection function,* two methods, the echocardiographic linear ejection fraction and the polycardiographic PEP/EP quotient were used. To exclude the effects of any significant changes of heart rate in Group 1 the PEP/EPI value was also evaluated. Both methods are extensively applied for the assessment of pump function /20, 23, 30, 37/. The disturbing phenomenon that both parameters correlate only moderately with the ejection fraction determined by ventriculography in the case of segmental wall movement abnormalities is partly compensated by the fact that most patients had dilated cardiomyopathy characterized by diffuse hypokinesis of the ventricular wall. Another important point is that our main object was not to assess the absolute values but rather to observe the changes of the ejection function. In agreement with data in the literature /26/ we found that the greatest improvement in the ejection function was induced by dihydralazine while the effect of ACEIs was more moderate in this respect. Our observation that the subjective wellbeing of the patients with DCM related to heart failure were ameliorated more frequently and to a greater extent by dihydralazine may be partly explained by this favourable effect on the ejection function. It is well known that the dominant pathophysiological abnormality in this disease is the failure of the pump function. This insuffi-

ciency is correlated not only with the degree of reduction of contractility, but according to recent data, also with the disproportionally high afterload in some cases (so-called afterload mismatch) /17/. Further explanation for a more favourable effect of dihydralazine in patients with DCM may be the better ejection function of patients with IHD belonging to the same NYHA class /12/.

However the opposite is true in case of the diastolic function, the increase of filling pressure dominating in IHD while being less prominent in DCM /12, 17/. In our patients the mean pulmonary capillary wedge pressure was in fact found to be higher in patients with IHD than in patients with DCM belonging to the same NYHA class.

The decrease of the *filling pressure* to a certain level is one of the main aims of treatment in patients with heart failure. In accordance with the results of other investigators /26/ in the present study both Tensiomin and Lopirin lowered the assessed value of this parameter to a greater extent than dihydralazine. This difference can partly explain the more favourable effect of ACEIs on the subjective symptoms in patients with IHD. The more marked lowering effect of ACEIs on the filling pressure in cases where it was only moderately-increased, that was characteristic for patients with DCM, may result in normal or nearly normal end-diastolic pressures that may be unfavourably low from the point of view of an optimal ejection function. As in Group 1 the filling pressure was lowered by ACEIs by 14 mmHg it is evident that such an unfavourable situation might have developed in several patients with DCM of this group. In this disease any substantial decreases of filling pressure are often unnecessary, moreover, unfavourable, and the less favourable effect of ACEIs on DCM may be explained by this effect. In our study the left ventricular filling pressure was measured by a polycardiographic method which proved to be reliable to the estimation of the mean pulmonary wedge pressure /14/. The value of its echo-phonocardiographic equivalent has been reported by several research teams and has been considered suitable for monitoring drug-effects /1, 29/.

The main determinant of myocardial oxygen demand, in addition to contractility and heart rate, is *left ventricular wall-tension*. Its high level is one of the factors contributing to the progression of heart failure /17, 33/. To decrease it without deteriorating left ventricular function, moreover, even to improve the function is an important, longterm aim of the treatment of heart failure that may delay or even stop progression /13, 33/. Benjamin et al. /5/ based on pathological examinations, introduced a quotient by dividing the diameter of the left ventricular wall by that of the ventricular cavity, the decrease of which correlated significantly with the severity, progression and mortality of heart failure.

The left ventricular wall tension can be measured by several non-invasive methods. We applied the M-mode echocardiographic method recommended by Quinones et al. /31/; the values and changes of the end-systolic wall tension characterizing the afterload were evaluated. This parameter considers, in addition to the size of the left ventricular cavity and the wall diameters, the other important component of tension, the systolic blood pressure too. The values correlate well with left ventricular peak tension measured by invasive methods. The parameter is complex indicates the ejection function of the left ventricle too, containing end-systolic diameters. This complexity can explain that its correlation with the patients' complaints and the progression of the disease is possibly closer than any of the partial parameters. In line with their favourable effect on the afterload both ACEIs and dihydralazine significantly decreased the degree of end-systolic tension. The similarity of the effects of ACEIs, though decreasing less markedly the arteriolar peripheral resistance, to that of dihydralazine may be explained by their more favourable effect on end-diastolic diameters.

The other possible explanation is that ACEIs decrease the systolic blood pressure more markedly.

When considering the heart rate, the other main determinant of myocardial oxygen demand, and calculating a version of the *double product that involves* the wall tension instead of blood pressure, mirroring the afterload in a more reliable way, the more favourable effect of ACEIs becomes unequivocal. This finding is in agreement with the results of direct measurements made by Chatterjee et al. /9/, which have shown that captopril significantly decreases myocardial oxygen consumption and demand while dihydralazine has no significant effect on it. On the basis of these observations it can be concluded that the effect of ACEIs is especially favourable in heart failure caused by IHD. In such cases it is essential that a drug improve left ventricular function and at the same time decrease myocardial oxygen consumption. Indirectly the latter effect can further ameliorate the left ventricular function. The lowering of catecholamine level is also likely to be favourable first of all in IHD.

What is more important than the effect on any of the haemodynamic parameters is how the treatment influences the patients' subjective well-being. It is all the more important to emphasize this circumstance since there is only a weak correlation between the effects on various parameters of left ventricular function and the patients' complaints. Frequently, the significant favourable change in the haemodynamic data is followed by the improvement of the patients' well-being and capacity to work only with a delay of several days or even weeks. The subjective component of the clinical picture thus is not directly correlated with the changes of the left ventricular functional parameters but is the result of complex processes, i.e., the improvement of peripheral perfusion and peripheral oxygen consumption too.

In our study, by determining the *NYHA classes,* the complaints characteristic of heart failure were evaluated numerically. Their decreases were almost identical in response to the two ACEIs and dihydralazine, however a more pronounced improvement of less patients with IHD during the administration of ACEIs, merits attention.

It is important to note that, due to the short observation period, the favourable effect of captopril preparations might have been underestimated in some cases, since there are data indicating a delayed increase of their effect /7/. The response observed during short-term treatment should not be considered to be unambigously valid for the results of a long-term treatment.

The experiences obtained during *combined treatment* indicate that in cases refractory to one or the other drug their combination may have favourable effect. In our study we examined the response to captopril being supplemented to dihydralazine. Changes in case of dihydralazine supplementation to captopril are expected to be different. *Massie* and his co-workers examined the latter form of combination in 8 patients with heart failure /21/: the most important result was the further significant improvement in the ejection function when dihydralazine too was added. In our study by supplementing dihydralazine with ACEIs the ejection function was not significantly improved, however there were important favourable effects, i.e. the decrease of the heart rate, left ventricular filling pressure, end-systolic wall tension, double product and NYHA class. These changes, particularly those of the tension and the double product raise the possibility of long-term effects delaying the progression of the disease, at least in cases where treatment is initiated well before the final stage of the disease. In this respect we should like to stress that it seems to be unambigously reasonable to start the treatment soon, in NYHA class II, as opposed to the conventional indication when the disease is advanced, frequently intractable. This is true first of all for captopril or dihydralazine monotherapy. At the same time, the advantage of combined treatment is emphasized by the circumstance that the late tolerance to dihydralazine can be explained, at least partly, by the activation of the renin-angiotensin-aldosterone system /22/. Thus, simultaneous administration of captopril may be expected to prevent this tolerance.

Considering the *results of the chemical and laboratory examinations* they support the opinion that side effects rarely occur if the daily dose of captopril is not higher than 150 mg /28/. A rise in serum potassium level was not observed during the study, nevertheless aldosteron antagonists were withdrawn when administration of the ACEIs was started and potassium supplements were also discontinued or reduced to 1–2 g daily in cases where high doses of diuretics were used.

The most important *side effect* of ACEIs, especially in combination with dihydralazine, was the marked hypotension causing transient dizziness

in some patients. This observation emphasizes that lower initial doses should be applied, the dose of diuretics should be reduced on the preceeding day and patients should be closely monitored for 0.5–1.5 hour after taking the first dose. These precautions are especially important in the treatment of patients with severe heart failure. When emphasizing the potential danger of hypotension we also report that most patients tolerated fairly well the fall in blood pressure to a systolic value between 80–90 mmHg induced mostly by ACEIs. This can be explained by the favourable effect of captopril on brain blood flow, as a consequence of which the cerebral perfusion is not decreased in spite of the significant fall of blood pressure /4/.

Similar mechanism ensures renal function to be unchanged despite the reduction in blood pressure apart from the cases with renal artery stenosis and renal insufficiency. Dihydralazine induced more side effects than the captopril products; the importance of individual treatment based on the diagnosis is indicated also by the observation that even angina pectoris was provoked by dihydralazine in IHD.

In our study we aimed at comparing the effects of the drugs and the conclusions we can draw are as follows: Lopirin and Tensiomin have identical effects, i.e. the treatment with either of them, compared to dihydralazine, results in a decreased heart rate, a more marked decrease of left ventricular filling pressure, a decrease of myocardial oxygen demand (double product), a less pronounced increase in ejection function. On the other hand similar effects could be recorded on mean arterial blood pressure and end-systolic wall tension. A favourable additive effect was found in several cases betwene dihydralazine and ACEIs.

Our results suggest an individual pharmacologic treatment of heart failure according to the underlying disease often characterized by special haemodynamic fault. However, because of the low number of patients, first of all with IHD, we are not authorized to draw definite conclusions. Nevertheless, we think that the data presented are worth giving an impulse to further examination.

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TREATMENT OF HEART FAILURE ASSOCIATED WITH ACUTE AND CHRONIC OF ISCHAEMIC HEART DISEASE BY CAPTOPRIL (TENSIOMIN, EGIS)

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The effect of oral Tensiomin treatment, 53.4 mg daily in 29 patients suffering from congestive heart failure associated with acute of chronic forms of ischaemic heart disease, e.g., recent and/or advanced myocardial infarction, aneurysm etc. was studied.

The acute and long-term beneficial haemodynamic effects were verified in 4 patients by thermodilution Swan-Ganz catheterization as well. The parameters of ejection function improved moderately, while left ventricular filling pressure (PCW) decreased significantly.

The balanced vasodilator effect was not accompanied by an increased myocardial oxygen demand. The "double product" was lowered in response to Tensiomin.

During the clinical follow-up (from 6 days to 2 years) there was an improvement in the NYHA functional class by an average of 1.2 however 4 patients died in spite of combined vasodilator and dobutamine treatment.

Owing to the improvement of regional blood flow to the brain and the kidney Tensiomin seems to be well-tolerated in patients with low arterial blood pressure. In pts with acute myocardial infarction and angina the critical fall of blood pressure and that of the coronary blood flow should be avoided by giving the drug in appropriately titrated.

Side effects were observed only with higher doses of Tensiomin in a small number of patients, i.e., transient worsening of renal function in 3 patients and dysgeusia in 2.

Our data indicate that Tensiomin treatment is effective and safe in patients suffering from all kinds of congestive heart failure complicating ischaemic heart disease.

Keywords: vasodilator treatment, – effect on regional circulation, myocardial oxygen demand, acute myocardial infarction, ischaemic cardiomyopathy

It is general belief that heart failure refractory to conventional treatment is prognostically as bad as acute leukaemia /27/.

The use of vasodilators in the treatment of heart failure has in recent years provided significant results: it has improved the quality of life and the exercise tolerance of the patients. However, survival could not be so definitely influenced /25/. While treatment is effective it is palliative of nature. The

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importance of primary and secondary prevention, the necessity of avoiding the development of congestive heart failure can not be sufficiently emphasized, especially, in the case of heart failure developing as a result of ischaemic heart disease. Fibrinolytic treatment and other pharmacological manipulations, by decreasing the size of the infarction, and also surgical interventions (revascularisation, coronary angioplasty) may contribute to better results in this field.

In addition to the conventional vasodilator drugs, e.g., nitroprusside, prazosin or nitrates, Ca-antagonist, hydralazine, phentolamine, applied in the treatment of heart failure associated with ischaemic heart disease (IHD) the angiotensin converting enzyme inhibitor captopril (Tensiomin, EGIS) has been administered at our Department since September, 1984.

Our aim was to establish whether it is useful in the treatment of heart failure accompanying acute and subacute myocardial infarction. To test whether there was an acute haemodynamic improvement, in some patients a right-side heart catheterization was performed at the bedside.

METHODS

Twenty-nine patients (23 males, 6 females; mean age: 65.3 years; range: 49–83 years) with heart failure accompanying IHD have been treated with captopril at our Department since September 29, 1984. The study was performed in the acute phase of IHD in more than half of the patients (acute myocardial infarction (first occurence) in 10 cases and recurrent transmural myocardial infarction in 6 cases) In the rest of the patients (previous infarction in 9 and ischaemic cardiomyopathy in 4 cases) no actual ischaemic abnormality could be demonstrated.

Acute or protracted left ventricular failure was indicated also by malignant, severe arrhythmias refractory to therapy (ventricular ectopy in 7 and supraventricular arrhythmia in 4 cases) and by the findings of the physical examination (rales on both bases audible at least up to the apex of the scapula) and the chest X-ray examination. Clinically significant hypertension was associated with IHD in 7 patients; the other patients were normotensive.

The average daily dose of captopril was 54.3 mg.

Table I

The applied doses of captopril (Tensiomin, EGIS)

Dose of captopril				No of PTS
2 × 12.5	=	25	mg/die	3
3 × 12.5	=	37.5	mg/die	10
2 × 25	=	50	mg/die	7
3 × 25	=	75	mg/die	7
4 × 25	=	100	mg/die	1
3 × 50	=	150	mg/die	1
mean	=	54.3	mg/die	29

$\bar{x}$ = mean daily dose

In patients with clinical signs of left ventricular insufficiency the treatment was started even during an acute ischaemic event. Doses of 6.25–12.5 mg were given initially. When the desired decrease in systolic pressure failed to ensue the dose was repeated within 2–3 hours. The changes in blood pressure (systolic, diastolic, as well as mean arterial pressure=MAP), heart rate and the so called "double product" (=heart rate x MAP) were measured in 20 patients at the peak effect of captopril (usually 3–5 hours after taking the first dose).

Thermodilution by Swan-Ganz catheterization was performed (using Edwards Fr. 7 catheter, Gould apparatus for the determination of cardiac output and Siemens Sirecust electromanometer). The filling pressure of the left ventricle and the ejection function were characterised by the pulmonary wedge pressure (PCW) and the so-called "stroke volume index" (SVI=cardiac index/heart rate, in ml/min) resp. The values determined at rest during the drug-free period 2 hours after the placement of the catheter were considered as baseline values. The measurement was repeated 3 hours after taking 12.5 mg captopril orally. The determinations of cardiac output were repeated at least three times for each measurement; the values obtained were averaged when the difference of the individual determinations did not exceed±15%.

In 29 cases the clinical condition of the patients was followed according to the NYHA (New York Heart Association) classification /11/ for 6 days to 2 years.

RESULTS

In Fig. 1. the changes in the heart rate (HR), systolic (BP_s) and diastolic (BP_d) blood pressure, mean arterial pressure (MAP) as well as the "double product" 2–4 hours after taking 12.5–25 mg Tensiomin are presented (acute

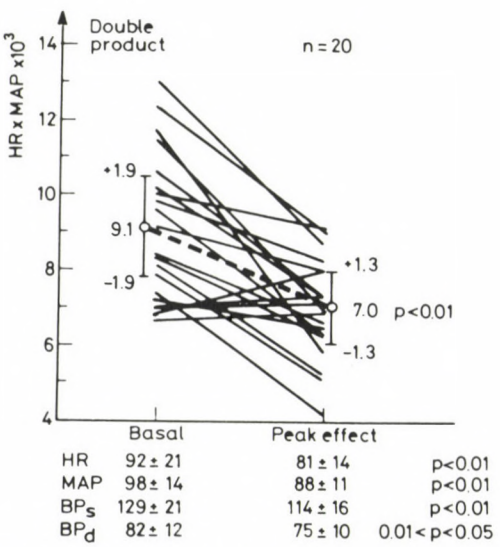

Fig. 1. The acute effects of captopril on basic circulatory parameters
Abbreviation: MAP = mean arterial pressure
BP_s = systolic, BP_d = diastolic blood pressure
HR = heart rate
Double product = HR × MAP

response). The mean heart rate and MAP were decreased from 92 to 81 beats/min and from 98 to 88 mmHg, resp. ($p<0.01$). Accordingly, the double product (heart rate × MAP) wich has been shown to be correlated with myocardial oxygen demand /20/ was decreased from 9.1×10^3 to 7×10^3 ($p<0.01$). More significant decreases in systolic blood pressure (to 80–90 mmHg) occured in 4 patients; the heart rate was decreased even in these cases. These patients reported on the worsening of anginal symptoms; the cerebral perfusion remained at a satisfactory level in 3 out of 4 patients in spite of the low systolic blood pressure whereas the drug had to be temporarily withdrawn in one case because of confusion and cerebral hypoperfusion. Occurence of new arrhythmia or the aggravation of the existing one was not observed.

The well-balanced vasodilator effect i.e. the decrease of both the preload and afterload which is well-documented in the literature /1, 5, 6, 7, 8, 10, 13, 16, 17, 19, 24, 25, 26, 28/ were proved by thermodilution Swan-Ganz catherization in 4 cases.

After taking 12.5 mg Tensiomin orally the right and left-side filling pressure (central venous pressure or diastolic pressure in pulmonary artery and the PCW pressure) decreased. The cardiac index and SVI were increased; systemic vascular resistance (SVR) was decreased considerably while pulmonary vascular resistance remained essentially unchanged.

The changes in the filling pressure (left ventricular end-diastolic pressure = LVEDP) and "stroke volume index" (SVI) of four patients are presented in Fig. 4. The left ventricular filling pressure was decreased from 29.8 to 19.2 mmHg (−34.2%) on the average while the SVI was increased from 21.7 to 31.2 ml/min (+43.8%). The decrease in the filling pressure and the improvement of ejection fraction dominated in 3 cases and 1 case, resp.

The NYHA functional state was improved by 1.2 classes on the average during the clinical follow up (5 days to two years) (Figure 5.) 8 out of the 9 patients in functional state II at the start of the study were transferred to state II while one remained unchanged. Of the patients in class IV 7 were transferred to class II and 9 to class III, resp. Of these patients with severe condition 4 died in spite of the combined parenteral inotropic therapy applied, due to the persistent circulatory insufficiency refractory to therapy on the 6^{th}–21^{st} days of observation.

Of the side effects transient deterioration of renal function was observed in three cases, wich improved on dose-reduction. All the three were above 75 years of age and had hypertension. The significantly decreased systemic blood pressure, not sufficient to sustain the renal perfusion, could provoke the symptoms. Dysgeusia occured in 2 patients treated with higher doses (100 or 150 mg daily) permanently (at least for 6 months): in the first case the symptom was moderate and the treatment was continued. In the other the dysgeusia was improved on dose-reduction.

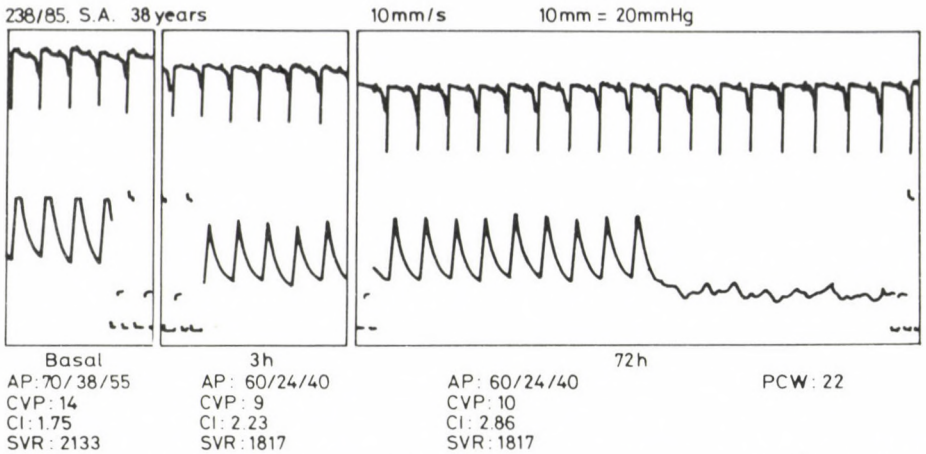

Fig. 2. The acute (3 hours) and short-term (72 hours) effects of 12.5 mg and 3 × 25 mg Captopril resp.

Abbreviations: AP = pressure in pulmonary artery (mmHg)
CVP = central venous pressure (water cm)
CI = cardiac index (l/min/m²)
SVR = systemic vascular resistance (dyn × sec × cm^{-5})
PCW = pulmonary capillary wedge pressure (mmHg)

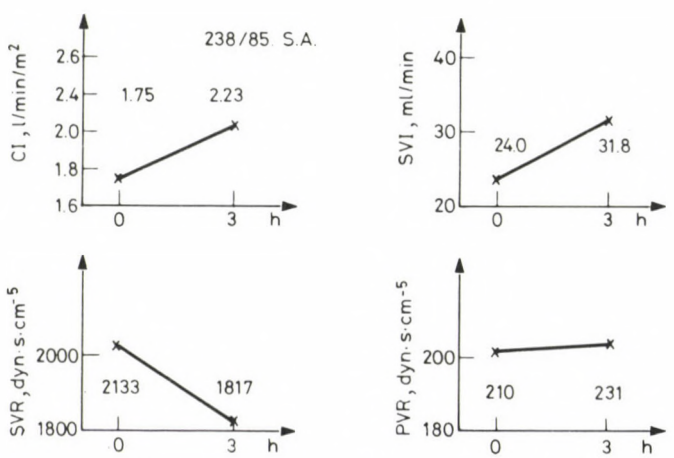

Fig. 3. The acute changes of the haemodynamical parameters of a patient in response to 12.5 mg oral captopril

Abbreviations: see Fig. 2.
SVI = stroke volume index = CI/ heart rate, (ml/min)
PVR = pulmonary vascular resistance (dyn. sec. $cm.^{-5}$)

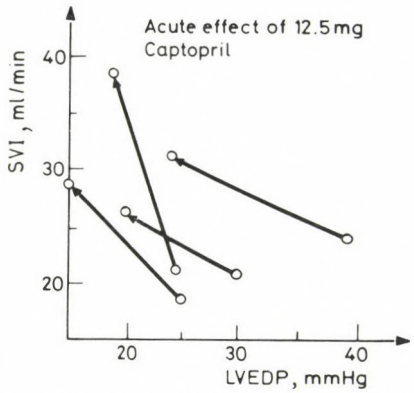

Fig. 4. The changes of filling pressure (LVEDP) and stroke volume index (SVI) in 4 patients controlled haemodynamically after taking 12.5 mg Captopril
Abbreviations: LVEDP = left ventricular end-diastolic pressure = PCW

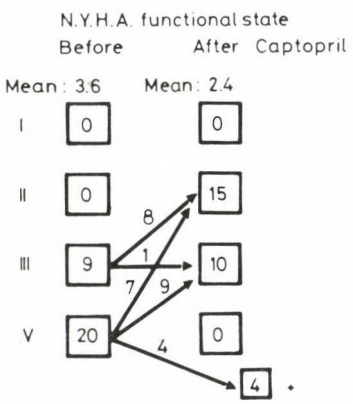

Fig. 5. Changes in New York Heart Association (NYHA) functional classes [12] after captopril treatment. (Follow up for 6 days to 2 years)

In the acute cases there were considerable changes in serum electrolytes. Serum potassium levels of hypokalemic patients who have been treated previously with high doses of diuretics became normalized soon on Tensiomin-treatment. Hyperkalaemia (5.8 mmol/l) was observed in one case treated with the combination of Tensiomin and aldactone. It was an interesting observation that, when using the combination of Tensiomin and furosemide, serum sodium level was also normalized without sodium substitution in 4 patients with dilution hyponatraemia.

DISCUSSION

Since the first report of Gavras et al. /19/ a bulk of data, subsequently also confirmed by haemodynamic measurements, has accumulated on the benefits of the captopril treatment in heart failure refractory to conventional treatment /1, 5, 6, 7, 8, 10, 13, 16, 17, 19, 24, 25, 26, 28/. As an acute effect the left ventricular filling pressure is decreased, the ejection function is improved and the cardiac output is increased; these changes result in a rapid improvement of the clinical symptoms. The increase in the cardiac output is due almost exclusively to the increase of regional blood flows to the kidney and the brain, /15, 29/ therefore patients with relatively low blood pressure can also tolerate captopril. It is particularly favourable that the well-balanced effect, i.e. reduction of both the preload and the afterload is not accompanied by any increases in myocardial oxygen demand, in the double product wich is directly proportional

to it /7, 20, 30/ or in myocardial oxygen consumption. The haemodynamic effects of hydralazine, prazosine and captopril and the changes in oxygen consumption were compared by Chatterjee et al /7/. Of the three vasodilator drugs, captopril produced the greatest reduction in myocardial oxygen consumption (approx. 20%) wich was directly proportional to the decrease of oxygen demand, i.e., the double product. The coronary blood flow was proportionally decreased along with the reduced demand. While the level of circulating catecholamines is elevated by other vasodilators it is significantly decreased (by approx. 30%) by captopril /5, 8, 9, 16, 23, 24, 26, 30, 31/. There is no rebound effect on captopril withdrawal /26/.

These unique regional myocardial effects which are more favourable than those of the other vasodilators allow the heart failure associated with acute myocardial infarction to be treated with captopril /3, 4/. The haemodynamic improvement is not accompanied by aggravation of the anginas and arrhythmias. It is a promising experimental finding that captopril decreases the size of infarction in animal experiments /14/.

Combining captopril with dobutamine up to a dose of 5 μg/kg b.w./min may further improve the haemodynamic parameters; at higher inotropic doses oxygen demand is also increased, thus angina and arrhythmia may ensue /22/. The acute and chronic responses to captopril have been classified by Packer et al. /28/.

Permanent improvement can be achieved in 50% of the patients; the long-term result is satisfactory after a transient decline of the therapeutic response in 15% of the patients (so called triphasic response). If the acute response is proper, permanent, improvement can be expected in the majority of cases; the appearance of late tolerance can be expected in 15% of all cases. The remaining 20% respond poorly even at the beginning of treatment.

The lasting favourable haemodynamic changes, demonstrated also by catheterization, are accompanied by an increased tolerance to exercise and a considerable improvement of the NYHA functional class /1, 2, 5, 6, 8, 10, 13, 16, 18, 24, 26, 28, 30, 32/ although mortality improves only moderately /11, 26/ during long-term observation.

Captopril may be effective for the treatment of heart failure refractory to other vasodilators /2, 18/. Due to the mechanism of action of angiotensin converting enzyme inhibitors, the secondary aldosterone overproduction which is one of the factors causing tolerance to other vasodilators does not develop /2/.

This aldosterone effect explains the positive potassium balance. Due to the risk of hyperkalaemia captopril in combination with potassium sparing diuretics should be given only with caution. Captopril normalizes the low sodium level in dilution hyponatraemia by more complex mechanisms /13, 16, 21/.

The most serious side effect is extreme hypotension occuring especially after the first dose. Such a response can be expected in patients who had been treated previously with large doses of diuretics and have relative hypovolaemia and may have hyponatraemia. To avoid this side effect low initial doses (6.25 mg), cautiously repeated according to the requirements, are advised. The maintenance dosage is lower than the usual doses applied in the treatment of hypertension: it rarely exceeds 100 mg daily in heart failure (In our cases the average daily dose was 54.3 mg).

Our patients improved by 1.2 classes on the average according to the NYHA classification. This is significantly higher than the pooled data of C.M.R.G. (Captopril Multicenter Research Group /6/) where an average increase of 0.5 class has been found as compared to placebo. The difference can be explained by the fact that in more than half of our patients the primary disease was an acute ischaemic event and the spontaneous improvement of pump function also contributed to the improvement of our patients' classes. Further examinations in a larger number of patients would be neccesary to ascertain whether early vasodilator treatment improves the pump function also in the postinfarction period.

The present results indicate that captopril can be safely administered in the treatment of heart failure occuring during an acute ischaemic event. The balanced vasodilator effect verified also by right-side catheterization was not accompanied by any increases in myocardial oxygen consumption. The incidence of side effects could be reduced to minimum with correct indication and cautious dosage.

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INDICATIONS AND EFFECTS OF CAPTOPRIL THERAPY IN CHILDHOOD

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Chronic effects of captopril were studied in 29 patients (age, 4 months to 16 years; mean, 6.9 years) suffering from digitalis and diuretic resistant congestive heart failure (CHF) or hypertension of different etiology. Twenty two patients with CHF (13 dilated, 4 restrictive cardiomyopathy, 5 congenital heart defects) and 7 cases with hypertension were treated for 1 to 31 months (mean, 9 months). The dose of captopril varied from 1 to 3 mg/kg/day (mean, 2.2 mg) in CHF and from 1.1 to 6.8 mg/kg/day (mean, 3.7 mg) in hypertension. In CHF digoxin therapy was maintaned while the dose of diuretics could be reduced or discontinued. In 4 severely hypertensive patients the addition of a diuretic or beta blockers was necessary. In CHF clinical improvement was observed in 13 patients (59%), while there was no response in 4 and 5 patients died. The survivors exhibited a significant decrease of the cardiothoracic index ($p<0.05$), the PEP/LVET ratio ($p<0.05$) and an increase of the echocardiographic linear ejection fraction ($p<0.001$). If hypertension was present, blood pressure decreased in all patients ($p<0.05$). Captopril was well tolerated by all patients except one who developed anaemia. This side effect disappeared after having discontinued the drug.

These findings suggest that captopril is of benefit in controlling chronic CHF. Captopril alone or in combination with other drugs is effective in the management of severe hypertension.

Keywords: congestive heart failure, cardiomyopathy, hypertension, renal artery stenosis

The new vasodilator agents developed in the recent years have gained a significant role in the treatment of congestive heart failure and hypertension. Due to their site of action they can be applied rationally according to the haemodynamic state /4/. Captopril, the inhibitor of the enzyme converting angiotensin I to angiotensin II proved to be a potent vasodilator agent and was shown to be effective even in the treatment of cases refractory to other vasodilators /2, 6/. There are however a few data about its pediatric application, indications, dosage and long-term effect /1, 11/.

The aim of our study was to establish the efficacy of captopril during long-term administration in congestive heart failure (CHF) refractory to digitalis

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and diuretic treatment and in systemic hypertension of various origin, to establish the effective dosage which can be well tolerated and to observe the side effects.

Captopril tablets of 25 mg (Tensiomin) produced by EGIS Pharmaceuticals were administered. The infants were treated by a powder prepared from the tablets.

PATIENTS AND METHODS

The patients were divided into two groups

1. Patients suffering from congestive heart failure of various origin
2. Patients suffering from systemic hypertension of various origin.

The distribution according to diagnoses and age of the patients is presented in Table 1.

Table I

Distribution according to diagnosis and age

Diagnosis	N	Age (year)	Mean (year)
DCM	13	0.5—16	7
RCM	4	6—16	10.3
Congenital heart defect	5	0.3— 6	3.9
Hypertension	7	2,5—15	7.2
Total	29	0.3—15	5.5

Male / Female = 1.23
DCM = dilated cardiomyopathy
RCM = restrictive cardiomyopathy

In heart failure captopril was administered only in cases which were refractory to digitalis and diuretics, as a second choice drug. All the patients suffering from dilated (DCM) and restrictive cardiomyopathy (RCM) were chronic cases; subjects with acute myocarditis were not included. The diagnosis of cardiomyopathy was established by the clinical symptoms, ECG, X-ray examination, mechanography, M-mode, two dimensional and Doppler echocardiography. Of the 17 patients 10 underwent heart catheterization an angiocardiography and in 7 patients endomyocardial biopsy was also performed. In 5 patients with DCM the biopsy specimen showed chronic myocarditis and myocardial fibrosis. In 2 patients with RCM endocardial fibroelastosis was established by biopsy and later on at autopsy as well.

Of the 5 patients with congenital heart defect and CHF a four month old infant had ventricular septal defect and pulmonary hypertension; two little girl of five and six years suffered from left ventricular dysfunction following the operation of Fallot's tetralogy and double outlet right ventricle, respectively. Two little boys had congenital mitral incompetence.

The hypertensive group included 7 patients; 3 patients had renovascular hypertension, 2 had generalized disease of the small arteries and 2 patients had persistent hypertension after having been operated on with coarctation of the aorta (Table II). Haemodynamic studies and angiography were performed in all patients.

According to the hitherto published data /5, 13, 15, 16/ the administration of captopril may be deleterious in patients with impaired renal function, haematological disorders and hepatic dysfunction; such abnormalities were cautiously excluded. Baseline and control laboratory examinations were as follows: urinalysis, blood picture, serum potassium, sodium, creatinine, BUN, GOT, GPT, LDH, and cholesterol levels. These parameters were checked in the firts week of treatment, then every other week, in case of long-term treatment once a month, then every other months. The treatment was always initiated during hospitalization.

Table II

Hypertensive group

Case No	Age (year)	Diagnosis	Blood pressure		Follow up months	Dose mg/kg daily
			at the start	during therapy		
1	7.5	unilateral stenosis of renal artery	150/100	120/80	31	3.5
2	9	bilateral stenosis of renal artery	240/140	150/80	1.5	4.5
3	6.5	bilateral stenosis of renal artery	140/90	110/70	12	1.1
4	2.5	autoimmune arteritis	240/160	140/80	20	6.8
5	7	unknown (Recklinghausen's disease)	190/115	125/80	12	5.0
6	15	postoperative state (coarctation of the aorta)	170/95	140/80	16	3.0
7	3	postoperative state (coarctation of the aorta)	160/120	110/70	3	1.7
$\bar{x}$ = 7.2		$p<0.01$			$\bar{x}$ = 13.6	$\bar{x}$ = 3.7

Blood pressures in mmHg

The initial dosage of captopril was 0.5 mg/kg a day divided into 2–3 doses. At the start of treatment blood pressure, heart rate and ECG were checked hourly. When the decrease of blood pressure in normotensive patients did not exceed 10 mmHg and dizziness, orthostatic collapse or other side effects did not occur, the dosage was increased every other day. The final dosage which varied in the different groups was reached in 7–10 days depending on the development of the desired effect. In hypertension an initial daily dose of 1–1.5 mg/kg was administered and the dosage was increased according to the level of blood pressure (Table III).

In the decompensated group the improvement of complaints, general state and exercise tolerance, the decrease or cessation of systemic and pulmonary congestion,the decrease or disappearance of the mitral or tricuspid insufficiency, the possibility of reducing the dosage of the diuretic were evaluated to establish the eficacy of captopril. As non-invasive parameters the changes of the cardiothoracic index (CTI), the PEP/LVET ratio and the echocardiographic linear ejection fraction (EF) were determined. In hypertension the decrease of blood pressure was the decisive indicator. The data were statistically analyzed by Student' paired "t"-test.

Table III

The dosage of captopril

Diagnosis	N	mg/kg daily	mean
DCM.	13	1.4—3.0	2.2
RCM	4	1.5—3.0	2.6
Congenital heart defect	5	1.0—3.0	1.7
Hypertension	7	1.1—6.8	3.7

RESULTS

The improvement of subjective complaints and the clinical state is presented in Table IV.

Five patients died due to intractable heart failure; three suffered from endocardial fibroelastosis and two from myocardial fibrosis. Their treatment lasted from 3 to 4 months, only one patient with RCM survived for 16 months. He presented a transitory improvement during captopril therapy.

The data of the non-invasive investigations of the 24 survivors were evaluated. In CHF the favourable effect could be observed after treatment for 1 or 2 weeks, however significant improvement was observed only after several month's treatment.

The decrease of the CTI was significant ($p<0.05$). In the RCM cases this was not apparent; they were characterized mainly by disturbances of distensibility as well as by systemic and pulmonary congestion and not by cardiomegaly (Fig. 1).

Figure 2 shows the significant decrease of the PEP/LVET ratio in 16 patients ($p<0.05$). In two small children the baseline values are missing because of technical difficulties.

Table IV

The result of captopril treatment

Diagnosis	N	Improved	Unchanged	Died	Follow up months
DCM	13	8	2	3	3—24 $\bar{x}$ = 7.5
RCM	4	1	1	2	3—20 $\bar{x}$ = 9.5
Congenital heart defect	5	4	1	—	1—10 $\bar{x}$ = 5.6
Hypertension	7	7	—	—	1.5—31 $\bar{x}$ = 13.6

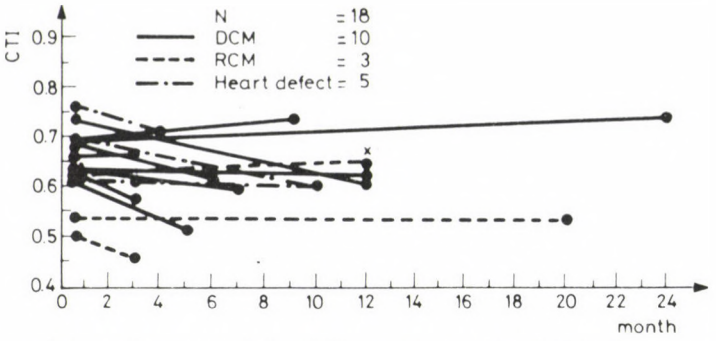

Fig. 1. Changes of the cardiothoracic index (CTI) in patients with CHF Diff. × = −0.043; $p<0.05$

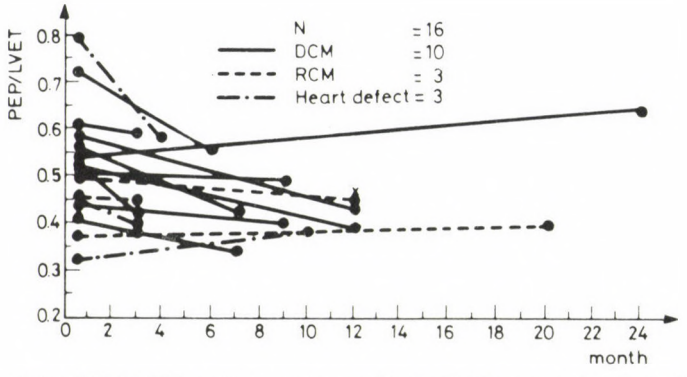

Fig. 2. Changes of the PEP/LVET ratio in patients with CHF Normal value for children is 0.31 Diff. × = −0.063; $p<0.05$

Figure 3 presents the echocardiographic EF values. The improvement was strongly significant ($p<0.001$). In three patients the values could not be calculated because of the paradoxical septal movement. In some congenital heart defects (mitral incompetence, ventricular septal defect) and in the initial stage of RCM the EF can be normal in spite of the forward failure, but its increase is in agreement with the clinical improvement. That was observed in our four cases.

The patients with hypertension responded unambigously well. The decrease of systolic and diastolic blood pressure was significant ($p<0.05$ for both) (Table II). In three milder cases captopril alone proved to be sufficient; in four more severe cases combined therapy was necessary. The therapy was supplemented with a diuretic in three cases and diuretic+beta blocker in one case.

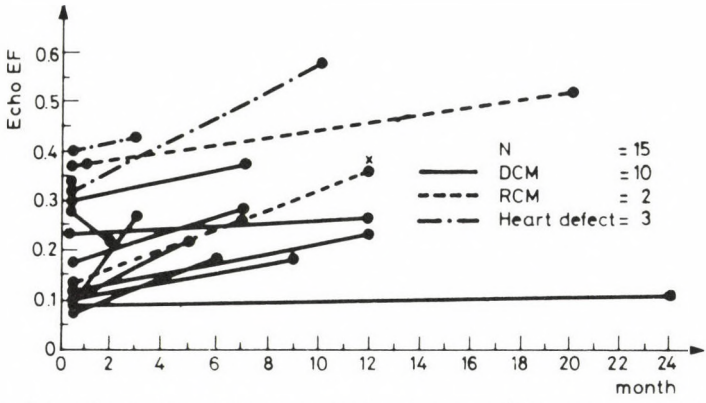

Fig. 3. Changes of the echocardiographic linear ejection fraction (EF) in patients with CHF. Normal value for children is 0.34 Diff. × = 0.098 $p<0.001$

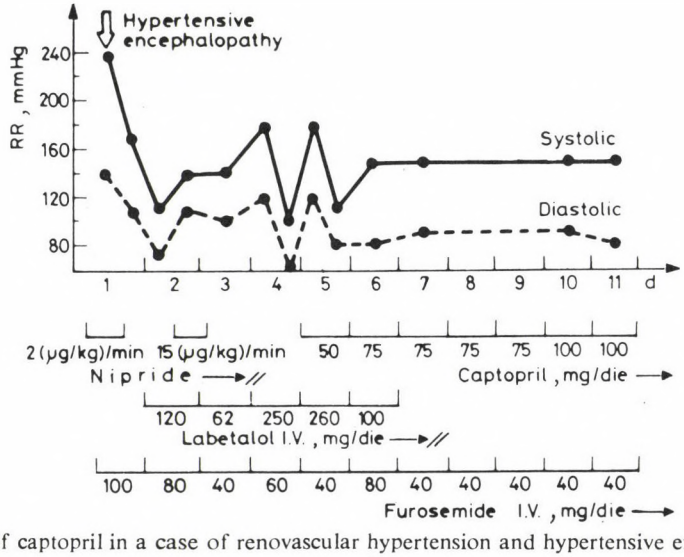

Fig. 4. Effect of captopril in a case of renovascular hypertension and hypertensive encephalopathy see text)

In Fig. 4 the effect of captopril in renovascular hypertension is demonstrated in a 9 year old male patient with bilateral renal artery stenosis. He had not been treated previously with antihypertensive agents. Soon after his admission a blood pressure of 240/140 mmHg and severe hypertensive encephalopathy was recorded. Although intravenous nitroprusside-Na and the subsequent labetalol treatment were effective, the blood pressure could be stabilized only with captopril. The initial daily dose was 4.5 mg/kg. The dose of furosemide could be decreased simultaneously by 60%. Since then the patient undervent successful operation.

Side effect was observed only in one patient who developed progressive anaemia during three months' treatment. This side effect disappeared after the drug having been discontinued. The gradually increased doses were well tolerated by each age-group. In normotensive patients the fall in blood pressure did not exceed 10 mmHg. The laboratory examinations showed normal values throughout the study; proteinuria, reduced renal function, leukopenia did not occur.

DISCUSSION

The mechanism of action of captopril is complex /3, 5, 16/. As the inhibitor of ACE its effect is exerted partly through the renin-angiotensin-aldosterone system. It decreases the angiotensin II production and as a consequence, aldosterone secretion is also reduced. The converting ezyme is identical with the kininase II which catalizes the degradation of bradykinin. Thus the inhibition of ACE facilitates the activity of prostaglandins, too. Due to the decrease of angiotensin II levels, sympathoadrenergic activity is also reduced. All these changes contribute to the marked peripheral vasodilation.

Captopril exerts its effect mostly on the arteriolar system (decrease of afterload) but it acts also on the venous side (decrease of preload). Its favourable effect is manifested especially in the decrease of peripheral vascular resistance, the increase of the ejection fraction and cardiac output, as well as the reduced pulmonary capillary pressure /1, 4, 6, 8, 10/. Due to the decrease of aldosterone production, sodium and fluid retention is less pronounced which is favourable both in congestive heart failure and hypertension.

Captopril has been found to be effective also in adult cases of heart failure refractory to other vasodilators. Tolerance does not develop /2, 6/. The drug has been shown to favourably influence the regulation of regional blood flow. The blood flow to the kidney and brain is increased by captopril, while this is not apparent in the vascular system of the liver and the limbs /8/. However the results of acute pharmacological studies are not always in agreement with the long-term effects /9, 10/. Occasionally, the favourable effect

appears only after treatment for several months. The increase of exercise tolerance, the decrease of cardiomegaly and the improvement of the clinical state are regarded as best indicators of success in long-term therapy /6, 9, 12/.

In the present study the long-term effect of captopril was analysed; we, too, found that the above mentioned parameters were the most characteristic indicators of therapeutic benefit. The usually modest improvement of pump function in our patients is explained by the very severe, sometimes premortal disease.

The hypertensive patients responded invariably well to the treatment. In more severe cases, instead of raising the dosage of captopril adjuvant diuretic or beta blocker treatment was administered as it has been recommended for adults /13, 15, 16/. Renal insufficiency caused by captopril has also been reported in renovascular hypertension /7/; however, its administration is considered to be favourable by others /3, 14/. In our three cases satisfactory clinical response was observed; there was no indication of drug-induced impairment of renal function.

The side effects are mostly dose-dependent; when using lower doses (below 150 mg in adults) they are infrequent and, if present, they disappear on dose-reduction /4, 13, 15, 16/.

The question arises as to the proper timing of the initiation of vasodilator treatment. According to observations in humans and data of animal experiments vasodilator treatment may induce regression of myocardial hypertrophy and result in a sustained favourable effect through the reduction of tension of the left ventricular wall /5/. It is possible that, when having more experience with this therapy, we shall administer it more frequently and at earlier stages.

Comparing our experience with the data in the literature on the pediatric applications of captopril /1, 11/ it appears that the administration of this drug is reasonable in the following cases: acute and chronic myocarditis, dilated cardiomyopathy, severe mitral and aortic regurgitation, congenital heart defects with large left-to-right shunt and postoperative left ventricular failure; thus in general, low cardiac output syndromes with normal blood pressure (increased peripheral resistance) and the combination of low cardiac output with pulmonary congestion. It is also indicated in hypertension of various origin.

One has to keep in mind that captopril influences only the course of the disease, therefore the possible causal therapy should not be delayed.

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IMMUNOLOGICAL EFFECTS OF CAPTOPRIL

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The effect of captopril treatment on natural killer activity and mitogen-induced lymphocyte blastogenesis was studied in man. No significant change in immune reactivity was found either in short term (one hour after ingestion of 25 mg) or long term (after two weeks, 50 mg daily) treatment.

Keywords: captopril, NK-cell activity, mitogeninduced blast transformation

Captopril, an inhibitor of angiotensin converting enzyme, affects the kallikrein-kinin-prostaglandin system /10, 13, 15/, thus influencing inflammatory processes. The molecular structure of captopril is similar to that of penicillamine, a drug with known antiphlogistic properties. Although D-penicillamine has been used for many years in the treatment of rheumatoid arthritis, the mechanism of its action remains obscure /3/. Both compounds influence mitogen-induced blastogenesis in vitro /4, 7, 11/. D-penicillamine—by means of its thiol group—scavenges free radicals produced by phagocytes /1, 12/; a possible mechanism of action of captopril may also be suggested.

Captopril, similarly to penicillamine, has been shown to be effective in the treatment of rheumatoid arthritis /9/. In scleroderma renal crisis, captopril was found to be beneficial /8, 14, 16, 17/.

We studied the immunosuppressive effect of captopril in vitro and in vivo.

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MATERIALS AND METHODS

Patients

Four patients with progressive systemic sclerosis were treated with 50 mg captopril (2×25 mg) daily. Blood was drawn immediately before starting therapy, and after 2 weeks. Twelwe healthy subjects were involved in another study. Their blood was drawn before and after 1 h of ingesting 25 mg captopril.

Lymphocyte proliferation assay

Mitogen-induced lymphocyte blastogenesis was performed using the "whole blood assay", as described earlier /2/. The ^{3}H-thymidine incorporation of cells was measured after 72 h in culture, and was expressed as counts per minute (cpm). The mitogens, phytohaemagglutinin (PHA; Leukoagglutinin, Pharmacia), and concanavalin A (Con A, Pharmacia) were used in concentrations of 2, 10, and 25 ug/ml.

Natural killer (NK) cell activity

NK cell activity was measured according to the method of Jondal and Pross /5/ with minor modifications /6/ using ^{51}Cr-labelled K-562 targets and 50:1 and 25:1 effector to target cell ratios in a 4 hour assay. Cytotoxicity was expressed as citotoxicity index (CI%)

RESULTS AND DISCUSSION

There was no significant change in mitogen-induced blastogenesis after the oral intake of 25 mg captopril (Table I). Similarly, there was no change in NK activity or blastogenesis after 2 weeks of treatment (Table II). In these tests no immunosuppressive effect of captopril was demonstrated. A more detailed study, including its free-radical scavenging potential, is required to elucidate its exact immunological mechanism of action.

Table I

Effect of captopril on lymphocyte transformation (1 h; mean cpm +/− SEM)

Mitogen	Taking the drug	
	before	1 h after
2 μg/ml PHA	3850+/−790	4420+/−980
10 μg/ml PHA	6230+/−1120	8160+/−1340
25 μg/ml Con A	2810+/−865	3980+/−1019

Table II

Effect of captopril treatment (50 mg daily for two weeks) on NK activity and lymphocyte transformation (mean+/−SEM)

Test	2 weeks of treatment	
	before	after
NK activity (CI%) (25:1)	6.8+/−2.1	6.3+/−1.7
NK activity (CI%) (50:1)	11.9+/−2.3	16.2+/−3.7
Lymphocyte transformation (cpm)		
2 μg/ml PHA	5520+/−1237	4830+/−1786
10 μg/ml PHA	11456+/−2322	11123+/−3562
25 μg/ml Con A	7824+/−2089	7410+/−2546

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– heart failure (cases refractory to digitalis+ diuretic)
– in certain form of cardiomyopathy (congestive cardiomyopathy)
– as diagnostic tool in renovascular hypertension and Conn syndrome.

CONTRAINDICATIONS: *Absolute:* pregnancy, lactation (if the administration can not be avoided the lactation should be discontinued)
Relative: leuko- and thrombopenia

ADMINISTRATION: It should be individualized.
Hypertension: Usual dosage for adults: initial dosage 12.5 mg 3 times daily. If the decrease of blood pressure is not satisfactory after 2-day' treatment the dosage may be raised to 50 mg 3 times daily. For further reduction

of blood pressure thiazide type diuretic, beta-blocker and/or other vasodilator (Ca-antagonist, prazosin, dihydralazine) may be administered.
The incidence of side effects is significantly increased over a daily dose of 300 mg but the blood pressure lowering effect is not increased thus is not recommended to exceed this dose-level.

Renovascular and renoparenchymatous hypertension: 6.25—12.5 mg 3 times daily.
The maintenance dose may be gradually increased to 25 mg 3—4 times daily; doses higher than that are rarely required.
In case of reduced renal function, the maximum daily dose:

Creatinine clearance			Dose mg
ml/min/m²	ml/sec/m²	ml/sec*	
80—41	1.33—0.68	2.31—1.18	300
40—21	0.66—0.35	1.15—0.61	150
20—11	0.33—0.18	0.57—0.31	75
10	0.17	0.29	37.5

* The value calculated on the averave adult body surface (1.73 m²)

Heart failure: Initial dosage: 6.25 mg 3 times daily; it should be increased gradually.

In pediatry: It should be used in well-established cases (especially in renovascular and renoparenchymatous hypertensions). Recommended daily dose: 1—2 mg/kg body weight.
The tablets should be taken 1 hour before meals. The therapy should be started by a specialist of internal medicine in hospitalized patients, if possible.
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The doses of other drugs administered in combination should be adjusted individually.

SIDE EFFECTS: In case of usual dosage (50—150 mg a day) the incidence of side effects is very low. Higher doses do not increase the effectiveness but the side effects become more frequent.
The potential side effects are as follows:
– proteinuria which may be accompanied by membranous glomerulopathy; nephrosis syndrome
– neutropenia/agranulocytosis due to myeloid hypoplasia with secondary infections
– rash, rarely angioneurotic edema, flushing
– transient, more severe hypotension especially in patients with heart disease treated previously with diuretics.
Very rarely tachycardia, chest pain, palpitation (especially in volume depleated patients)
– loss of appetite, dry mouth, metallic, salty taste (it disappears spontaneously in the 2nd and 3rd month of the therapy), aphtous ulcers on the oral mucosa, nausea, vomiting, peptic ulcer, cholestasis, abdominal pain, diarrhea, constipation.
– headache, dizziness, sleep disturbances, paresthesia
– increase of hepatic enzyme, blood urea nitrogen, creatinine and potassium values in the serum, false positive urine keton-test.
The side effects are more frequent in patients with autoimmune discorder therefore the regular control of blood picture and renal function is recommended.

DRUG INTERACTIONS: Concomitant administration with drugs increasing the serum potassium level (e.g. potassium sparing diuretics such as spironolactone, amiloride, triamterene) should be avoided (risk of hyperkalemia).

It can be combined with caution
– with diuretics in volume depleted patients or in the presence of Ca-antagonists its effectiveness is increased.

TREATMENT OF OVERDOSAGE: The hypotension can be treated with intravenous infusion of normal saline. Captopril can be removed from the circulation by hemodialysis.

WARNINGS: In case of more severe renal impairment the dosage should be started with lower doses (6.25 mg 3 times a day) and the increase should be carried out with caution.
Prior to therapy then once a month protein excretion should be determined. If the protein excretion exceeds the value of 1 g/day or it is increasing the continuation of the treatment should be considered. (The appearance of proteinuria may be expected in the first 8 months of the therapy, thus from the 9th month the urinary protein should be checked only in every third/sixth month).
Salt and/or volume depleted patients should be treated with extreme caution since the hypotensive effect is enhanced because of the increased renin-release. During the initiation of treatment hypotension occurs more frequently in patients with heart failure following the first doses so the initiation should be performed in hospitalized patients. In patients treated previously with diuretics the recommended initial dosage is 6.25 or 12.5 mg 3 times a day. White cell count should be checked once a month in the first 3 months of the therapy then in every third month. In patients with autoimmune disorder white cell count should be checked in every second month.
When the white cell count is below $4 \times 10^9/l$ ($4000/mm^3$) differential counts should be performed. It the number of neutrophils is lower than $1 \times 10^9/l$ ($1000/mm^3$) the therapy should be discontinued.
If the first symptom of infection appears blood count should be checked at once.
If hypotension occurs during surgery it should be corrected by volume expansion.
The patient should be informed:
– when edema or infection occurs the patient should consult a physician.
– to warn the patient against the discontinuation of treatment without the physicians advice
– to avoid extreme physical effort or increased dehydration (perspiration, vomiting, diarrhea).

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