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Treatment of hypertensive patients with chronic nephropathy with angiotensin converting enzyme inhibitors

High Blood Pressure (HBP) is a frequent complication of Chronic Renal Failure (CRF). In different clinical investigations it is observed that chronic renal parenchymal diseases are the main cause of secondary hypertension and these diseases cause 5% of HBP in general population (1).

Many patients with CRF develop HBP due to primary renal diseases, e.g. in chronic glomerular diseases 15-80% of patients have HBP. Patients with polycystic kidneys almost always have HBP in the stage of CRF. Also tubulo-interstitial diseases have a high incidence of HBP when CRF developes (1).

On the other hand, HBP is an indipendent risc factor for CRF. So, Hypertensive Nephrosclerosis causes 25% of CRF (end stage) in USA and 8% in Europe (2.3.4.5.)

The study of HBP in Chronic Renal Diseases is realised through the pattern of uninephrectomy and salt loading (6). This model suggests that extracelular volume can cause HBP but in reality the pathogenesis of HBP is more complex.

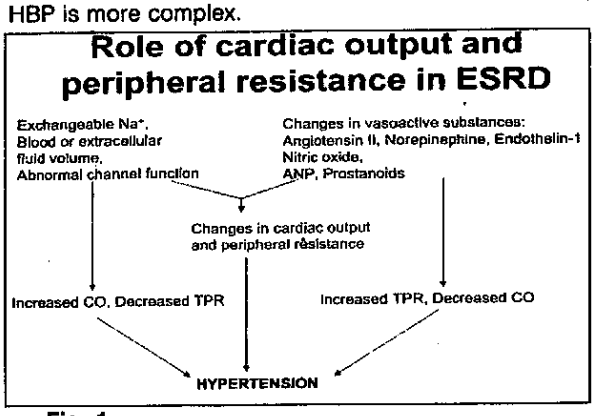

Fig. 1

Role of excessive extracelular volume.

Many reports suggest the role of extracelular volume and balance of sodium in HBP during end-stage CRF. In earlier stages, plasma volume and extracelular fluid volume are normal. But later this volume increases considerably. Infusion of salt solutions aggravates HBP of patients with CRF. The mecanism how the increased volume can influence on BP is not known but an explanation for this can be the theory of Autoregulation.

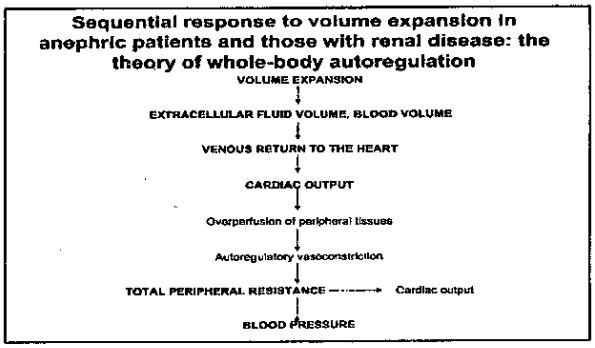

Fig.2

In fact many factors can influence the genesis of HBP during CRF [1]. HBP and hypervolemia if they are present for a long time, can damage the blood vessels and HBP can no longer be influenced by the treatment. This phenomenon occurs alco by decreased level of vasodilators or by increased vasoconstrictors.

Sympathetic System

It is observed that there is a sympathetic hyperactivity in HBP and renal diseases including Nephrotic Syndrome. This hyperactivity influences the increased cardiac output and total peripheric resistance [7].Norepinephrine and plasma renine activity are increased more in hypertensive patients with CRF than in normotensives with CRF or in normal subjects. It has been shown that bilateral nephrectomy decreases sympathetic activity, vascular resistance and improves BP in CRF [8]. The administration of Debrisoquin that is a postganglionic sympathetic blocker, lowers in a considerable way BP in hypertensive patients in Dialysis but not in normotensives in Dialysis.

Endotelins.

ET-1 influences the genesis of HBP during CRF. Patients with end - stage CRF have increased levels of ET-1. It is considered that there is a decreased ET-1 cleareance in CRF and this can be explaned by the decreased urinary ET-1 exretion.

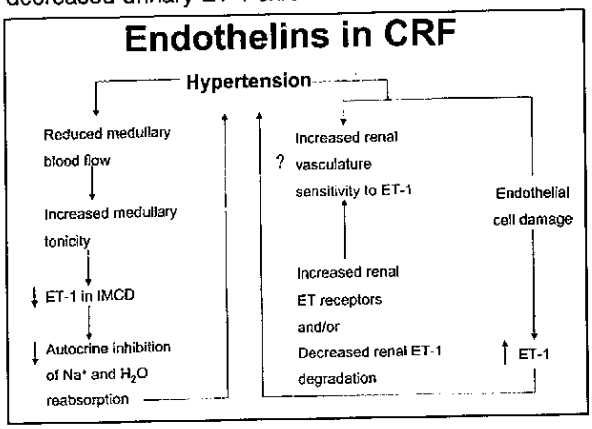

Fig. 3

On fig.3 it is shown that Et-1 can influence the BP in patients with a mild or a moderate level of CRF.

The renine-angiotensine system

The patients with mild or moderate CRF have increased levels of the activity of plasma renin, which correlates with HBP [9]. The administation of Saralasine in hypertensive patients with CRF causes a decrease of BP, which is proportional with the basal activity of plasma renin. ACE-I and β-blockers that decrease the secretion of renin have similar antihypertensive effects in patients with moderate CRF.In fact the majority of patients with HBP in end-stage CRF manifests a sensitive decrease of BP only by fluid removal through ultrafiltration in dialysis. In these patients the levels of Angiltensine-II and plasma renin are normal but they are considered increased in relation with exchangeable sodium and with volemia. On the other hand a group of patients with and-stage CRF that do not respond to the removal of sodium, have high levels of renin and of Angiotensine-II. These patients respond quite well to Saralasine and ACE-I. The strong correlation that exists between the activity of plasma renin, Angiotensine-II and HBP in patients with CRF, support the important role of renin-Angiotensine system in the genesis of HBP.

The role of Angitensine-II in renal "scarring".

Recently an important role is given to the Tubulo-interstitial "scarring" and to the vascular sclerosis [10]. In order to understand better the mode of action of ACE-I in chronic renal diseases we think that it would be better to look just a little the contribution of Angitensine-II in the development and progression of renal "scarring".

First of all let us see what is the renal "scarring".

a) Glomerulosclerosis. - The actual understanding of mechanism of glomerulosclerosis has been enlightened by Brenner et al. They postulated that glomerular hyperperfusion and hyperfiltration occur in the remnant nephrones whenever there is a loss of the functional mass of the kidney [11]. These hypotheses were advanced further including the adaptive increase of the intraglomerular capillary pressure (glomerular hypertension). Anyway till now the hemodynamic hypothesis of glomerulosclerosis is avaible but it has some limits because glomerulosclerosis occurs even when glomerular hemodynamic changes are absent [10-12]. Another interesting hypothesis evaluates the important role of lipids in the progression of glomerulosclerosis [13]. This hypothesis stimulated the research that suggests that increased ingestion of lipids hastened the progression of glomerulosclerosis, while the decreased dietary lipids or drugs that influence the lowering of the blood level of lipids, exert protective role. These investigations drew attention in the similarity between glomerulosclerosis and atherosclerosis.

In the last decade it was enlighten the role of "growth" factors and of cytokines in renal "scarring". The treatment with neutralizing anticorps and antagonists of these factors improves the severity of experimental glomerulosclerosis [14].

b) Tubulo-interstitial "scarring" - In fact it's not correct to consider glomerulosclerosis as an isolated phenomenon because it rarely progresses in the absence of conconitant tubulo-interstitial "scarring". Today it is observed that the progression of chronic renal diseases is a function of the level of the tubulo-interstitial "scarring" more than glomerulosclerosis. There are some hypothesis today to explain the tubulo-interstitial "scarring". First it was thought of a hyperfunction and hypermetabolism of remnant tubules [15]. Also it was suggested the implication of proximal reabsorbtion of sodium and amoniogenesis. Some authors suggest the role of free radicals of oxygen [16]. Recently the investigations were concentrated in the interaction between tubular cells and inflamatory cells and fibroblasts [17].

c) Vascular sclerosis. - This plays an important role

in the pathogenesis of progressive renal deseases. The narrowing of vascular lumen first of all causes glomerular ischemia and that contributes in glomerulosclerosis [18]. Also it is suggested that perivascular myofibroblasts can contribute in the development of tubulo-interstitial fibrosis [19].

The role of Angiotensin-II in glomerulosclerosis

Since the beginning of the eighties it was observed that Angiotensine-II has a central role in the pathogenesis of hyperfiltration and glomerular hypertension. It is thought that Angiotensine-II causes constriction of efferent arteriole and by this way is caused and increase of intraglomerular capillary pressure, which ensues in glomerulosclerosis. Others have attributed the protective effect of ACE-I to the inhibition of the renal and glomerular hypertrophy [20].

The role of Angiotensine-II in tubulo-interstitial "scarring"

Angiotensine-II increases tubular hypertrophy and tubulo-interstitial fibrogenesis. Angiotensin-II can contribute in the renal tubular hyperfunction because it stimulates proximal Na+/H+ exchange and amoniogenesis. The activation of these processes influences the pathogenesis of tubulo-interstitial "scarring". Today it is proven the tubulo-interstitial fibrogenic effect of Angiotensine-II. It was shown that incubation of tubular cells with Angiotensine-II stimulates the synthesis of collagen of type IV [21]. By this way Angiotensine-II exerts an important role in the pathogenesis of tubulo-interstitial fibrosis.

Angiotensine-II and vascular Sclerosis.

The role of Angiotensine-II in the pathogenesis of vascular sclerosis is verified in vitro as well as in vivo. Angiotensine-II stimulates the proliferation of myo-vascular cells. The hypertensive effects of Angiotensine-II contributes in vascular sclerosis. Further the administration of Angiotensine-II in rats increases the cellularity of small renal erteries and causes fibrinoid necrosis of small renal arterioles [20].

Angiotensine-II and fibrogenic "growth" factors

Angiotensine-II stimulates the production of Endohelins and Cytokins and also of "growth" factors by renal cells [21].

Angiotensine-II causes the proliferation and hypertrophy of smooth muscle vascular cells by stimulation of PDGF and of TGF-b. This stimulation influences the synthesis of collagen.

Today exist some data that "growth" factors, mainly bFGR (basic fibroblast growth factors) are capable to stimulate the production of Angiotensine-II [21].

HBP not rarely is complicated by hypertensive nephrosclerosis of interlobular and afferent arteries but also by global glomerulosclerosis [22,23,24]. This damage of the kidneys in hypertensive patients is linked with the existence of the gene of "renal sensitivity" and only when this genetic alteration is present, the hypertensive nephrosclerosis developes, indipendently by the presence or the level of HBP. In these genetically hypertensive subjects consequently to HBP, occures an exaggerated contraction of afferent preglomerular arterioles. This decreases very much the glomerular blood flow and glonerular ischemia develops. Consequently, the normal activity of glomerular endothelial cells is altered and they produce in an exaggerated way vasocontrictors such as angiotensine II and endohelin and the production of vasodilators like nitric oxide decreases. Beyond that the phenomenon of apoptosis is deranged and the reaction to cytokine is decreased. [1,26,27]. The intrarenal activation of renine Angiotensine-system that takes place as a consequence of decreased afferent blood supply stimulates the cytokine TGF-b that explodes the fibrotic cascade.

Inhibition of Angiotensin-II and the progression of CRF.

As i mentioned previously it is logical to reason that the prevention of progression of CRF and of "scarring process" in the kidneys can be achieved by inhibiting the production of Angiotensin-II or by inhibiting its action. In many studies it is proven that inhibition of ACE decrease the BP and proteinuria and prevents the progression of "renal scarring". Similar results has been observed using antagonists of Angiotensin-II receptors. In humans it was observed a slower progression of diabetic nephropathy and non diabetic nephropathy [10].

ACE-I decrease the proteinuria independently by the effect on BP. Their effect actually is considered better than that of other antihypertensive drugs. But some authors explains the superior protective effect of ACE-I with a better 24 hours profile of its antihypertensive effect.

Anyway, HBP is a major problem of chronic progressive renal diseases and its treatment aims the prevention of renal function loss. In experimental studies it has been shown that ACE-I and CA (Calcim Antagonists) are superior to other drugs in preserving the renal function and in improving the glomerular hypertension. It has been shown that the prolonged treatment with captopril slows the progression of diabetic nephropathy but till now does not exist data for the non diabetic nephropathy. The mechanism of glomerular damage in systemic hypertension can hardly be explored in humans but experimental data suggest that hypertension of glomerular capillaries is a critical determinant for the hemodinamically mediated glomerular damage. In an experimental work of Omata et al (30) done in hypertensive rats that had been nephrectomised in 5/6 of their renal mass, it was observed the effect of oral administration of Temocapril. 12 weeks of treatment, resulted in a significant improvement of systolic BP. The level of serum creatinine, urinary exretion of albumins and the index of glomerular sclerosis were lower on Temocapril treated than in the untreated rats.

Table 1.

Parameters following treatment with temocapril for 12 weeks in 5/6 nephrectomized spontaneously hypertensive rast *(SHR/Izm)*

N	SBP mmHg	S_{Cr} mg/dl	$U_{alb}V$ mg/day	IGS
Temocapril 7	156 ± 3[a]	0.8 ± 0.1[b]	24.8 ±2.5[b]	0.94 ±0.01[b]
Vehicle 7	265 ±8	1.3 ±0.2	32.3 ±2.1	1.34 ±0.12

Results are expressed as means ± SE.SBP, systolic blood pressure; S_{Cr}, serum creatinine; $U_{alb}V$, urinary albumin excretion; IGS, index of glomerular sclerosis.

[a] *p<0.0001 compared with vehicle (two way analysis of variance)*

[b] *p<0.05 compared with vehicle*

(Omata et.al. Kidn.Int. 1996, 49, supp.55 pp S-57-5-62)

These results suggest that the reduction of systolic BP with Temocapril preserves the renal function and improves the renal damage in hypertensive rats with subtotal nephrectomised kidneys. In 5/6 nephrectomised rats it was shown that hyperfiltration in remnant nephrons is mediated by consistent rise of glomerular capillary pressure and this is followed by the progressive rise of albuminuria, the development of glomerulosclerosis and finally by the declining of the renal function (31). In these models the treatment with different ACE-I gave similar results in the prevention of albuminuria and the incidence of sclerotic glomeruli (32.33.34). The increased pressure of glomerular capillary has an important role in the progression of glomerular damage. ACE-I can normalize the hydraulic pressure of glomerular capillary and they restrict the development of structural damage.

In patients with accelerated HBP or with diabetes the reduction of BP prevents CRF. In diabetic nephropathy ACE-I are considered as therapy of choice (35.36). Anyway in primary renal diseases the benefit of slowing CRF by HBP treatment is not proven yet quite well (37).Some reasons why in these cases the progression of CRF is not retarded adequately can be as follows:

1. The therapeutic control of BP may be not adequate, that is the target BP aimed, is very high.
2. Antihypertensive drugs used were not able to improve the capillary glomerular pressure.
3. The renal damage occurs as a consequence of an independent primary basal derangement.

Anyway there are two questions to be unsuered yet:

1. How much be lowered the BP in order to protect the kidney?
2. What must be the drug chosen?

According to the recommendation of the Group for the National Education of HBP Program (37), the level of BP must be under 140/90 mmHg in order to preserve the kidney. The ambulatory monitoring of BP practically has a favorable impact on the treatment. This is particularly useful for the evaluation of the effects like: white coat effect, target organ damage, BP during sleeping and therapeutic response.

Generally the recent studies have defined the level of BP aimed by antihypertensive treatment and the way this antihypertensive therapy has to be done.

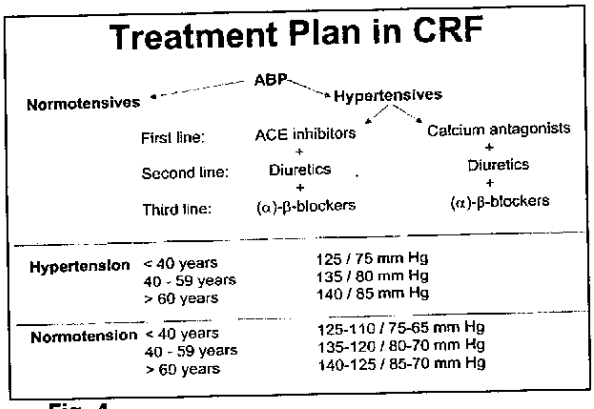

Fig. 4

ACE-I like Captopril, Enalapril, Alacepril, Delapril, Cilazapril, Lisinopril, Imidapril and Temocapril are almost equally effective in the reduction of BP.

Many studies have been performed in humans for the evaluation of clinical efficacy of ACE-I in comparison with CB (Calcium Blockers)[27.38.39.40]. Zucchelli et al[40].reported the results of a 4 years multicenter prospective randomized study in hypertensive patients with established CRF. The treatment with ACE-I and CB improved the worsening of renal function. The slowing of progression of CRF was similar using two kind of drugs. CB differently from ACE-I dilates mainly the afferent arterioles. In another study it was shown that in spite of treatment with CB the progression of renal damage continued [30]. This can be explained by the fact that if the theragy lowers the systemic BP inadequately, the widening of afferent arteriole causes an increase of glomerular capillary pressure that ensues with progressive glomerular sclerosis. Otherwise, if the treatment with CB is efficacious in lowering considerably the systemic BP, then in spite of the widening of afferent arteriole, it produces a decrease of perfusion pressure. The renal protective effect of ACE-I is not linked with the systemic antihypertensive effect. ACE-I dilates the efferent arterioles causing a reduction of glomerular pressure. So the mechanism of renal protection of ACE-I is linked with the reduction of postglomerular loading.

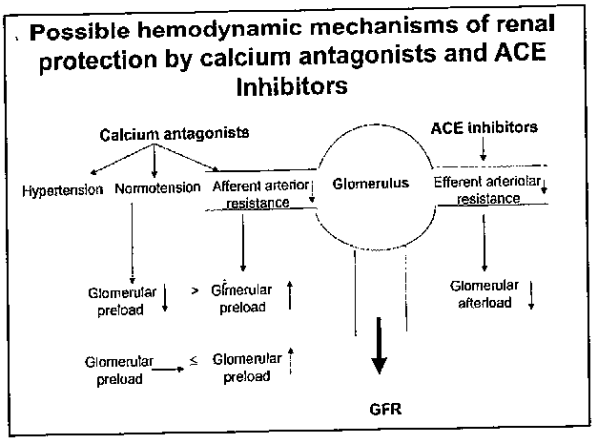

Fig. 5

In the hypertensive nephrosclerosis that develops as a consequence of essential HBP, if the consept of primary glomerular ischemia is correct then, the CB would be drugs of choice because of their ability to dilate the

afferent arteriole. Anyway actually the most rational treatment is the combination of CB with ACE-I (2). If the CB dilate the afferent arteriole, the ACE-I reduces the glomerular capillary pressure. ACE-I in a more effective way prevents the fibrosis and remodeling of preglomerular microvessels (28.). Further the inhibition of the effects of Angiotensine II is more complete by the combination of ACE-I with AT-receptor-blockers. These last drugs neutralize the effect of that part of Angiotensine II that is produced not through the line of converting enzyme (29).

In reality the actual pathogenesis of renal disease progression includes the systemic HBP and hemodynamic factors, and also the metabolic and coagulation factors as well as the mediators of inflammation (41). The precise mechanism of renal protection by ACE-I and CB is not entirely explained.

Actually one of the most common chronic nephropathy world wide, is beyond doubt the diabetic nephropathy (DN). In USA, the DN and essential HBP constitutes together the most frequent cause of end-stage CRF that needs to be treated by Hemodialysis. The DN is un doubtedly a consequence of diabetic micro and macroangiopathy and the basic mechanism of their development is the chronic hyperglycemia[42]. But in Diabetes the prevention of diabetic complications is realized through other alternative strategies beyond the control of glycemia.

The best treatment of diabetes actually is antihypertensive treatment particularly for the prevention of end stage renal-disease. The first reports in this direction in the beginning of 90-es have compared the ACE-I with CB [43,44]. In these studies were analyzed the effects of those groups of drugs on BP, Albuminuria and GFR. After one year of follow-up there were not seen differences in both groups on these parameters. So in the study done in non-insulin dependent diabetics with incipient nephropathy were compared the results using Enalapril and Nifedipine [44]. The rate of slowing of albuminuria was similar in both groups. But in an earlier report [45] it was observed that Nifedipine has a smaller effect than Captopril in decreasing the Albuminuria. Recently in a multicenter study realized in Italy [46] the insulin-dependent diabetics with normal BP and microalbuminuria used CB and ACE-I. It was shown the same rate of progression of proteinuria in both groups.

Studies using angiotensin - converting enzyme inhibition *vs*. calcium channel blockade in diabetes with a follow-up period of at least 1 year and with two end-points: rate of change of AER and rate of change of GFR

Study	Pedents	Duration (years)	Drug	AER (ug/min) Baseline	End	P	GFR (ml/min) Baseline	End	P
MDNSG	43 IDDM & NIDDM	1	Peridropril	34	25	n.s.	135	132	n.s.
Ref 11			Nifedipine	44	35		134	131	
Chan et al.	102 NIDDM	1	Enalapril	48	22	< 0.006	65	55	n.s
Ref 12			Nifedipine	45	40		70	68	
Cropaldi et al.	82 IDDM	2	Lisinopril	51	29	n.s.	122	123	n.s.
Ref. 18			Nifedipine	70	58		118	120	
Velussi et al.	18 NIDDM	3	Cilazapril	49	36	n.s.	76	74	n.s.
Ref. 16			Amlodipine	39	27		74	72	
Bakris et al.	36 NIDDM	6	Lisinopril	1475	1763	n.s	66	61	n.s.
Ref. 15			Verapami-Alluzem	3125	1736		61	55	
Rossing et al	IDDM	1	Nifedipine	1047	554	< 0.01	85	73	< 0.01
Ref. 17				754	671		86	80	

Table.2

Actually it is accepted that ACE-I and CB have the same efficacy in preserving the kidney from the progression of renal damage in diabetic. This is accepted even in the conclusions of "6th National Committee on Diagnosis Definition and Treatment of HBP". There it was suggested that ACE-I and CB are equally effective in the treatment of diabetic patients and it was determined that the values of BP must be 130/85 mmHg for the intended treatment.

It must be said that the renal protective effects of ACE-I and CB are not linked only with their hypotensive effect. As the renal protective mechanisms are different between ACE-I and CB, then it would be reasonable the combination of ACE-I and CB for the prevention of the progression of chronic renal diseases.

Summary

Treatment of hypertensive patients with chronic nephropathy with angiotensin converting enzyme-inhibitors.

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Chronic renal parenchymal diseases are frequent causes of secondary hypertension. Nearly 5% of patients (pts) with High Blood Pressure (HBP)have chronic renal parenchymal diseases that are the main causes of secondary hypertension. Beyond that HBP is an independent risk factor for progression of Chronic Renal Failure (CRF).

In pts with Chronic Renal Diseases (CRD) the level of BP is determined by changes of cardiac output and total peripheral resistance. Autoregulation theory can explain at least partially how Hypervolemia determines HBP in CRD. Also an important role is given to factors as Sympathetic system, Endohelins, and Renin - Angiotensin system (RAS).

There is a strong link between renal scarring and increased activity of RAS which influences the hemodynamic changes in the Glomerulus. Renal scarring is also influenced by fibrogenic "growth" factors, mainly PDGF and TGF - β. Angiotensin - II stimulates directly the production of PDGF and TGF - β. From the above mentioned reason it can be concluded that inhibition of ACE improves HBP, proteimuria and renal "scarring".

The effect of ACE-I in chronic renal failure is superior to that of other antihypetrensive drugs. Especially ACE-I is therapy of "choice" in diabetic nephropathy. Some think that the effect of ACE-I is comparable with that of Calcium Antagonists (CA) in slowing the progression of CRF, but it seams that the best therapy is the combination of CA and ACE-I. In diabetic pts the aimed level of BP is 130/85 mmHg. In CRF, the target should be 125/75 mmHg when proteinuria>1 gr/d and 130/80 mmHg in pts without proteinuria.

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