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OPTIMAL TREATMENT IN RENOPARENCHYMATOUS ARTERIAL HYPERTENSION AND CHRONIC RENAL FAILURE

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Abstract. Chronic renal diseases are often accompanied by systemic hypertension, which, in turn, accelerates progression of renal dysfunction. The vast majority of actual guidelines recommend ACEI and/or ARB as first choice of antihypertensive treatment. The study presented compares the evolution of 157 patients with chronic renal failure and renoparenchymatous hypertension treated with different antihypertensive regimens.
Keywords: CKD, renoparenchymatous hypertension, proteinuria, treatment

Introduction

Chronic renal diseases are often accompanied by systemic hypertension, which, in turn, accelerates progression of renal dysfunction [1].

Several mechanisms are involved in the genesis of renoparenchymatous hypertension [3]:

- excessive renal salt and water retention as a result of pressure-natriuresis disturbance with expansion of extracellular volume – the main mechanism of hypertension in acute glomerulopathies, acute oliguric renal failure, chronic renal failure.
- inappropriate stimulation of the vasopressor system (especially renin) due to renal ischemia – the main cause of hypertension in chronic glomerulopathies, chronic tubulointerstitial nephropathies, polycystic kidney diseases, diabetic nephropathies.
- decreased secretion of medullipin or other medullar depressor factors is an additional factor in the genesis of hypertension in diseases with severe destruction of medullar cells: cystic diseases, chronic pyelonephritis, obstructive uropathies, analgesic nephropathies.
- as CKD progresses to ESRD, additional mechanisms contribute to the increases of hypertension through: increase in plasma levels of endothelin, decrease in the synthesis of nitric oxide (NO).

In conclusion, hypertension in CKD is multifactorial, but volume expansion and salt sensitivity are predominant [1,4]. Excessive stimulation of RAAS, endothelin production and impaired NO generation during volume expansion not only contribute to hypertension, but also generate atherosclerosis, cardiac hypertrophy, accelerated renal sclerosis [4]. Thus, a vicious spiral is created culminating in severe hypertension and progressive kidney damage with requirement of dialysis. Therefore appropriate and early management of hypertension is very important in the attempt to slow the rate of progression of CKD.

The actual guidelines recommend ACEI and/or ARB as first choice of antihypertensive treatment [2]. The study presented compares the evolution of 157 patients with chronic renal failure and renoparenchymatous hypertension treated with different antihypertensive regimens.

Material and methods

A 3 years prospective study included 157 patients with renoparenchymatous hypertension and chronic renal failure (72 chronic glomerulopathies, 44, tubulointerstitial nephropathies, 18 polycystic diseases and 23 ischemic nephropathies). Inclusion criteria:

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serum creatinine above 1.2mg/dl in 2 measurements at 1 month interval and BP above 140/90 mmHg in 3 measurements at 1 week interval. Exclusion criteria: other causes of hypertension, severe systemic disorders (hematologic, neoplastic, hepatic, pulmonary), diabetic nephropathies.

At 3-months interval, in addition to routine evaluation, the volemic status of patients has been measured by transthoracic vascular bioimpedance (Hotman).

The patients were divided in 3 groups depending on the initial value of creatinine and proteinuria (table I). The 3 groups received different antihypertensive regimens:

Group A, in the light of actual guidelines: ACEI/ARBs±CCB±diuretics or ACEI/ARBs±BB±diuretics or ACEI/ARBs±clonidine±diuretics.

Group B: 30 patients received one of the regimens described above (group B1) and the rest of the 39 regimens did not include ACEI or ARBs (group B2).

Group C: CCB/BB/clonidine±diuretics.

Results And Discussions

Group A:

- in chronic glomerulopathies, proteinuria decreased <1g/day in 21 patients, diuresis decreased from 1143 ml/day to 808.6 ml/day, serum creatinine increased from 2.18 mg/dl to 4.9 mg/dl and volemia increased from 125% to 148% (mean values); after 1.1 years (1.5 months – 1.8 years) – 18 patients necessitated initiation of dialysis.
- chronic tubulointerstitial nephropathies: proteinuria decreased <1g/day in all 5 patients, diuresis decreased from 1840 ml/day to 1720 ml/day, serum creatinine increased from 1.72 mg/dl to 2 mg/dl (mean values); all patients were euvolemic during the study; duration of treatment 2.1 years (treatment stopped because of other side effects than progression of renal dysfunction); none of the patients reached dialysis therapy until the end of the study.

Primary renal disease		**Group A:** creatinine<4mg/dl, P>1 – **ACEI±ARBs ±diuretics**	**Group B1:** creatinine<4mg/dl, P<1 – **ACEI/ARBs ±diuretics**	**Group B2:** creatinine<4mg/dl, P<1 – **CCB/BB/ clonidine±diuretics**	**Group C:** creatinine<4mg/dl, P<1 – **CCB/BB/ clonidine±diuretics**
GN	72	29	13	9	21
TIN	44	5	15	10	14
PKD	18	2	2	5	9
IN	23	0	0	15	8
total	**157**	**36**	**30**	**39**	**52**

Table I. Treatment applied to the patients depending on the initial serum creatinine and proteinuria

In the majority of the patients, in order to control blood pressure, there have been used 2 or 3 antihypertensive drugs. In 49 of the total of 105 patients with creatinine<4mg/dl, control of hypertension was initially obtained with 1 agent; depending on the volemic status appreciated with the Hotman apparatus, diuretics were added in all hypervolemic patients. ACEI and ARBs were not used in ischemic nephropathy or in patients with multiple risk factors (generalized atherosclerosis, smoking, dyslipidemia).

In group A and B1, ACEI or ARB drugs were stopped when serum creatinine raised above 4mg/dl; this situation occurred after 1.1 years in 18 patients in group A and 1.8 years in 10 patients in group B1.

Evolution of patients was appreciated by comparing: evolution of serum creatinine, diuresis, volemic status, proteinuria. The obtained data were analyzed with the following statistic tests: T, $\chi 2$ or Z.

- polycystic renal diseases: proteinuria decreased <1g/day in all patients, diuresis decreased from 2250 ml/day to 2150 ml/day, serum creatinine increased from 2.6 mg/dl to 3.8 mg/dl (mean values); all patients were euvolemic during the study; duration of treatment 2.1 years (treatment stopped because of other side effects than progression of renal dysfunction; creatinine >4mg/dl in 1 patient); none of the patients reached dialysis therapy until the end of the study.

Statistic analysis of results using the T test showed that the decrease of diuresis and increase of serum creatinine were statistically significant, greater in patients with glomerulonephritis than in patients with the other primary renal diseases. In the same time, duration of ACEI/ARBs treatment was significantly smaller in patients with chronic glomerulonephritis versus other etiologies.

Statistic importance of data and discussions:

Although proteinuria diminished in most of the patients with **glomerulonephritis**, this was concomitant with decreased diuresis and increased serum creatinine, in conclusion it was secondary to renal failure progression and not to the antiproteinuric effect of ACEI. This assumption is supported by the fact that, until the end of the study, 18 patients wits GN needed initiating of dialysis and overall, in all patients with GN, the duration of treatment was 1.1 years (mean value, with limits between 1.5 months and 1.8 years).

Patients with **chronic tubulointerstitial disorders** seemed to be less affected by ACEI treatment: proteinuria decreased after ACEI treatment, but this was not accompanied by significant decrease of diuresis or significant increase of serum creatinine. The explanation might be that the tubulointerstitial fibrosis and preservation of glomerulotubular feedback are able to preserve diuresis and limit aggravation of renal dysfunction. Another assumption may be that the initial proteinuria was secondary to a chronic infection and not due to the final glomerulosclerosis seen in the late course of chronic tubulointerstitial nephropathies. A better evolution with ACEI therapy in these chronic diseases is demonstrated by the fact that none of the patients have reached the need for dialysis until the end of the study, although in 2 patients the therapy needed to be stopped because of severe other side effects. The mean duration of ACEI treatment was 2.1 years.

Patients with **cystic renal diseases** had a similar evolution with those with chronic tubulointerstitial nephropathies; this fact was foreseeable, because cystic diseases affect mainly the renal tubules. The mean duration of ACEI treatment was 2.1 years.

Group B:

We compared the evolution of group B1 versus group A and the evolution of group B1 versus B2. The variables that we monitored were: serum creatinine, diuresis, volemia, and the duration of treatment until the patients initiate dialysis.

Group B1:

- serum creatinine increased from a mean value of 1.93 mg/dl (GN 2.09 mg/dl, TIN 1.79 mg/dl, cystic diseases 1.85 mg/dl) to a mean of 2.97 mg/dl (GN 4.22 mg/dl, TIN 1.99 mg/dl, cystic diseases 2.15 mg/dl).
- volemia increased from a mean of 105% (GN 117%, TIN 94.8%, cystic diseases 104%) to a mean of 120.86% (GN 139%, TIN 105.86%, cystic diseases 115%).
- diuresis decreased from a mean value of 2018 ml/day (GN 1196 ml/day, TIN 2646.6 ml/day, cystic diseases 2650 ml/day) to a mean of 1825 ml/day (GN 884.6 ml/day, TIN 2543.3 ml/day, cystic diseases 2550 ml/day).

Statistic importance of data and discussions

Statistic validation of the results with the T test showed that in group B1, as in group A, patients with glomerulonephritis had a greater decrease of diuresis and a greater increase of serum creatinine when compared with patients with the other 2 etiologies treated with the same antihypertensive regimens (ACEI or ARBs). Comparing group A (with proteinuria) with group B1 (no proteinuria), with the same antihypertensive regimens, the decline of renal function was more rapid in patients with proteinuria (group A) than in those without proteinuria (T test); this fact may be explained by the harmful effect of proteinuria per se on the kidney. **These results are in an obvious conflict with many other studies which sustain that ACEI are more efficient in proteinuric patients; in the present study, the proteinuria has indeed decreased but with the price of degradation of residual renal function.**

The results also showed that in all patients with creatinine <4mg/dl treated with ACEI there was an increase in volemia and this was the reason for increasing the dose of diuretics or for adding diuretics. The increase in volemia with ACEI therapy was significantly greater in proteinuric GN patients than in proteinuric patients with TIN or PKD, but was smaller than in nonproteinuric patients with GN (T test).

		Group B: proteinuria, 1g/day, serum creatinine <4mg/dl			
		Group B1	Group B2		
Primary renal disease		**ACEI±ARBs±diuretics**	**CCB±diuretics**	**BB±diuretics**	**Clonidine±diuretics**
GN		13	4	3	2
TIN		15	4	4	2
PKD		2	0	0	5
IN		0	6	6	3
Total	**69**	**30**	**14**	**13**	**12**

Table II. Treatment applied in nonproteinuric patients with initial serum creatinine <4mg/dl

Group B2

Group treated with CCB:

- serum creatinine increased from an initial mean value of 2.63 mg/dl (GN 3.5 mg/dl, TIN 2.275 mg/dl, NI 2.3 mg/dl) to a mean of 3.91 mg/dl (GN 5.2 mg/dl, TIN 2.5 mg/dl, IN 4 mg/dl).
- volemia increased from a mean value of 120% (GN 138%, TIN 94%, IN 126%) to a mean of 136.5% (GN 152%, TIN 104%, IN 148%).
- diuresis decreased from a mean value of 1728.5 ml/day (GN 1262.5 ml/day, TIN 2450 ml/day, IN 1558.3 ml/day) to a mean of 1525 ml/day (GN 937.5 ml/day, TIN 2300 ml/day, IN 1400 ml/day).

Group treated with BB:

- serum creatinine increased from a mean of 2.32 mg/dl (GN 3.63 mg/dl, TIN 1.52 mg/dl, IN 2.2 mg/dl) to a mean of 3.8 mg/dl (GN 5.4 mg/dl, TIN 1.97 mg/dl, IN 4.2 mg/dl).
- volemia increased from a mean of 127.7% (GN 151.3%, TIN 103.7%, IN 131.8%) to a mean of 137.9% (GN 159%, TIN 107%, IN 148%).
- diuresis decreased from a mean of 1788.5 ml/day (GN 1200 ml/day, TIN 2750 ml/day, IN 1441.6 ml/day) to a mean of 1423 ml/day (GN 800 ml/day, TIN 2500 ml/day, IN 1016.6 ml/day).

Group treated with clonidine:

- serum creatinine increased from a mean value of 2.38 mg/dl (GN 3.55 mg/dl, TIN 2.15 mg/dl, PKD 2.22 mg/dl, IN 2.03 mg/dl) to a mean of 4.2 mg/dl (GN 5.7 mg/dl, TIN 3 mg/dl, PKD 4 mg/dl, IN 4.2 mg/dl).
- volemia increased from an initial mean value of 106% (GN 88.5%, TIN 107%, PKD 102%, IN 123.3%) to a mean of 134.4% (GN 136%, TIN 118%, PKD 128%, IN 155%).
- diuresis decreased from a mean of 2204.16 ml/day (GN 1000 ml/day, TIN 2425 ml/day, PKD 2790 ml/day, IN 1883.3 ml/day) to a mean value of 1837.5 ml/day (GN 600 ml/day, TIN 2100 ml/day, PKD 2430 ml/day, IN 1500 ml/day).

Statistic relevance of data and discussion

The above results showed that **the increase of serum creatinine in nonproteinuric patients with initial creatinine <4mg/dl is significantly smaller in those treated with nonACEI/ARBs regimens than in the patients treated with ACEI/ARBs** (T test). CCB and BB are accompanied by a smaller rate of creatinine when compared with clonidine (test T). **Ischemic nephropathy is characterized by the most rapid increase of serum creatinine when compared with other primary renal diseases** (T test); this result is not influenced by the type of antihypertensive treatment (T test) and, we believe, nor by the severity of hypertension (known to be, in ischemic nephropathy, mild and easy to control), but by the coexistent cardiovascular comorbidities.

Therapy with clonidine is accompanied by the greatest increase in volemia when compared with CCB and BB (T test) and this effect is more pronounced in patients with chronic GN; the patients with tubular nephropathies (euvolemics or, more frequently, hipovolemics). BB are accompanied by the best volemic control among the three types of antihypertensive therapy (T test).

Diuresis is best preserved with CCB than with the other two types of treatment (T test).

An interesting observation is that, **among patients with ischemic nephropathies, those treated with BB presented a more rapid decrease of diuresis when compared with patients treated with the other regimens** (T test); we believe that the cardiodepressant effect of BB is responsible for this result: BB decrease cardiac output and secondary there is a decrease in renal blood flow.

Group C

The comparisons were made between the three types of antihypertensive regimens (table III).

Patients treated with CCB:

- initial mean serum creatinine 5.16 mg/dl (GN 5.72 mg/dl, TIN 4.62 mg/dl, PKD 5.03 mg/dl, IN 4.9 mg/dl) increased to a mean of 7.38 mg/dl (GN 8.01 mg/dl, TIN 6.4 mg/dl, PKD 7.43 mg/dl, IN 7.4 mg/dl).
- initial mean volemia 135.7% (GN 154.7%, TIN 122.4%, PKD 107.3%, IN 142%) increased to a mean of 163% (GN 188%, TIN 138%, PKD 129% and IN 180%).
- only 4 patients out of 18 were monitored for the whole 3 years period of study (3 with TIN and 1 with PKD); the rest of them (all patients with GN and IN, 2 patients with TIN and 2 patients with PKD) necessitated initiation of dialysis.

Patients treated with BB:

- initial mean serum creatinine 5.16 mg/dl (GN 5.66 mg/dl, TIN 4.54 mg/dl, PKD 6.1 mg/dl, IN 4.4 mg/dl) increased to a mean of 7.63 mg/dl (GN 8.3 mg/dl, TIN 6.5 mg/dl, PKD 7.3 mg/dl, IN 7.5 mg/dl).
- initial mean volemia 131.7% (GN 151.1%, TIN 97%, PKD 118%, IN 136.3%) increased to 154.3% (GN 175%, TIN 112%, PKD 136%, IN 169%).
- as in the above group, only 4 patients were monitored until the end of the study (3 with TIN and 1 with PKD); 14 patients began dialysis earlier: all patients with GN, IN and 2 with TIN.

Patients treated with clonidine:

- initial mean serum creatinine 5.175 mg/dl (GN

	Group C: serum creatinine >4mg/dl		
Primary renal disease	**CCB±diuretics**	**BB±diuretics**	**Clonidine±diuretics**
GN	7	9	5
TIN	5	5	4
PKD	3	1	5
IN	3	3	2
Total	**18**	**18**	**16**

Table III. Treatment applied in patients with initial serum creatinine >4mg/dl

5.54 mg/dl, TIN 4.6 mg/dl, PKD 5.44 mg/dl, IN 4.75 mg/dl) increased to a mean of 7.72 mg/dl (GN 8.6 mg/dl, TIN 6.5 mg/dl, PKD 7.6 mg/dl, IN 8.3 mg/dl).

- volemia increased from a mean of 123% (GN 151.6%, TIN 95.5%, PKD 119%, IN 116.5%) to a mean of 150.5% (GN 187%, TIN 113%, PKD 139%, IN 163%).
- 12 patients necessitated initiation of dialysis before the end of the 36 months period of study: all those with GN and IN, 2 with TIN and 3 with PKD; 2 patients with PKD and 2 patients with TIN terminated the full period of study.

Statistic importance of results. Discussions

Due to severe renal dysfunction, patients from group C have been monitored until dialysis was necessary.

In this group, t**he proportion of patients who initiated early dialysis did not differ between the three types of antihypertensive treatment** (χ^2 test); in the same time **the period from the beginning of the study to the moment of initiating dialysis did not significantly differ between the three types of treatment (T test). These results demonstrate that, in late stages of CKD, efficacy of antihypertensive treatment is extremely poor.**

Although the moment of beginning dialysis din not correlate with the type of antihypertensive treatment, there **was a strong correlation between the rate of progression of CRF and primary renal diseases**: regardless of the antihypertensive treatment, patients with chronic tubulointerstitial nephropathies had the slowest rate of progression to ESRD (Wilcoxon Z test) and those with ischemic nephropathy the fastest (T test). Surprisingly, **although they had the smallest diuresis during the study, the patients with chronic glomerulopathies did not aggravate renal dysfunction as rapidly as those with ischemic nephropathies** (23 months versus 19 months – mean values) (T test); possible explanations might be that long-term oliguria determined a better compliance of patients regarding water and salt restrictions or that in glomerular patients there were less severe cardiovascular comorbidities/complications as in patients with ischemic nephropathies; patients with chronic glomerulonephritis are often younger and have a better endurance of water and salt excess.

Although the patients treated with different types of treatment aggravated the renal function in a similar rhythm, in the monitored variables there have been a lot of differences demonstrating that indication of dialysis has indeed differed depending on the treatment. Thus, **in patients treated with CCB, although the rate of serum creatinine increase was the slowest** (T test), hypervolemia was the main factor imposing initiation of dialysis. **Patients treated with BB had the best volemic preservation** (T test), but serum creatinine increased more rapidly: the negative inotropic effect of BB decreased the cardiac output and renal flow. Although **in group B2 patients treated with clonidine experienced the most severe increase in volemia** (T test), in group C treated with the same drug, the raise of volemia was smaller, comparable with the raise produced by CCB (T test), because of the increased number of tubular nephropathies (especially PKD in which clonidine was recommended with antalgic intention) who experienced a smaller increase of volemia. Initiation of dialysis in group C treated with clonidine was not only due to creatinine increase and/or hypervolemia, but to dyselectrolytemia as well (especially hyponatremia).

Conclusions

Hypertension in CKD has a multifactorial causality and has a negative effect on the cardiovascular system and the residual renal function. Therefore, controlling HT is essential from the early stages of CKD.

Using ACEI as first line of antihypertensives in all patients, regardless of primary renal disease, diuresis, serum creatinine and/or volemic status, may lead to several side effects, but the main is aggravation of renal dysfunction. In our opinion,

there are a lot of antihypertensive drugs with the same efficacy as ACEI, but with less harmful effects on residual renal function. In the same time, we consider that choosing an antihypertensive agent must take into account the primary renal diseases and the comorbidities as well. Chronic tubulointerstitial nephropathies are expected to have a slow progression to ESRD, while ischemic nephropathies have a rapid deterioration of renal dysfunction; iatrogenic effects of antihypertensive drugs may be partially reversible in TIN because diuresis is preserved and the cardiovascular complications or comorbidities are rare, but these are often irreversible in IN because of severe cardiovascular and cerebral atherosclerosis. Patients with chronic glomerulopathies often have well tolerated oliguria; prescription of an antihypertensive drug that will aggravate oliguria may precipitate pulmonary edema and emergency dialysis may be necessary.

In late stages of CKD, controlling of HT is often impossible regardless of the antihypertensive drugs associations. Early initiation of dialysis prevents loosing residual renal function and severe cardiovascular complications.

Abbreviations:

P>1 = proteinuria >1g/day; P<1 = proteinuria<1g/day
CKD = chronic kidney disease
CRF = chronic renal failure
ESRD = end stage of renal diseases
HT = hypertension
GN = glomerulonephritis
PKD = polycystic kidney diseases
TIN = tubulointerstitial nephropathies
IN = ischemic nephropathies
ACEI = angiotensin converting enzyme inhibitors
ARBs = angiotensin-receptor blockers
BB = betablockers
CCB= calcium-channel blockers

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