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THE EFFECT OF ANGIOTENSIN CONVERTING ENZYME INHIBITION ON EFFECTIVE RENAL PLASMA FLOW IN PATIENTS WITH DIFFUSE RENAL PARENCHYMAL DISEASES AND HYPERTENSION

UTICAJ INHIBICIJE ANGIOTENZIN-KONVERTUJUĆEG ENZIMA NA EFEKTIVNI BUBREŽNI PROTOK PLAZME KOD BOLESNIKA SA DIFUZNIM PARENHIMSKIM BOLESTIMA BUBREGA I HIPERTENZIJOM

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Summary

Introduction. Angiotensin converting enzyme inhibitors are commonly used to treat various hypertensive conditions and in addition to lowering blood pressure these drugs affect the local renal hemodynamic status, thereby influencing the glomerular filtration rate and effective renal plasma flow. The study was aimed at determining whether angiotensin converting enzyme inhibitors can produce significant changes in effective renal plasma flow in patients with parenchymal renal disease and to assess whether the changes depend on the pre-existing functional status of the kidney. **Material and Methods.** The study included 80 subjects, 40 subjects with hypertension associated with diffuse renal parenchymal disease and 40 subjects with essential hypertension. All study subjects underwent the baseline effective renal plasma flow measurement and the repeated effective renal plasma flow measurement after administration of captopril. Effective renal plasma flow was determined by 131 I-hippuran clearance in blood samples taken at 20 and 30 minutes. **Results.** Angiotensin converting enzyme inhibitors caused significant effective renal plasma flow changes in 55% of subjects with diffuse renal parenchymal disease and in 75% of subjects with essential hypertension. The effective renal plasma flow changes were more significant in subjects with preserved renal function (normal baseline effective renal plasma flow) compared to subjects with reduced baseline effective renal plasma flow. **Conclusion.** The application of angiotensin converting enzyme inhibitors in patients with diffuse renal parenchymal disease and in individuals with essential hypertension may result in significant hemodynamic changes in the kidney, accompanied by changes in effective renal plasma flow. The extent of the changes caused by angiotensin converting enzyme inhibitors depends on the preexisting functional status of the kidney.

Key words: Angiotensin-Converting Enzyme Inhibitors; Peptidyl-Dipeptidase A; Renal Plasma Flow, Effective; Kidney Diseases; Hypertension; Renin-Angiotensin System

Sažetak

Uvod. Lekovi iz grupe inhibitora angiotenzin-konvertujućeg enzima često se koriste u lečenju svih hipertenzivnih stanja, a ovi lekovi, pored toga što snižavaju krvni pritisak, utiču i na lokalni hemodinamički status bubrega utičući na vrednosti jačine glomerulske filtracije i efektivnog bubrežnog protoka plazme. Cilj ovog istraživanja bio je da se utvrdi da li kod bolesnika sa parenhimskim bolestima bubrega i hipertenzijom, primena inhibitora angiotenzin-konvertujućeg enzima može izazvati značajnije promene efektivnog bubrežnog protoka plazme i da li nastale promene zavise od postojećeg funkcionalnog statusa bubrega. **Materijal i metode.** Istraživanje je sprovedeno kod 80 ispitanika, 40 ispitanika sa udruženim difuznim parenhimskim bolestima bubrega i hipertenzijom i 40 ispitanika sa esencijalnom hipertenzijom. Kod svih ispitanika izvršeno je merenje efektivnog bubrežnog protoka plazme u bazalnim uslovima i ponovljeno merenje nakon premedikacije kaptoprilom. Za merenje efektivnog bubrežnog protoka plazme korišćena je metoda određivanja klirensa 131J-hipurana uz vađenje dva uzorka krvi u 20. i 30. minuti. **Rezultati**. U grupi ispitanika sa difuznim parenhimskim bolestima bubrega i hipertenzijom, primena inhibitora angiotenzin-konvertujućeg enzima u 55% slučajeva rezultirala je značajnim promenama protoka, dok u grupi ispitanika sa esencijalnom hipertenzijom primena inhibitora rezultirala je značajnijim promenama protoka u 75% slučajeva. Promene efektivnog bubrežnog protoka plazme bile su izraženije kod pacijenata sa očuvanom funkcijom bubrega (normalne bazalne vrednost protoka) u odnosu na ispitanike sa izrazito redukovanim bazalnim vrednostima protoka. **Zaključak**. Primena inhibitora angiotenzin-konvertujućeg enzima kod bolesnika sa difuznim parenhimskim bolestima bubrega i hipertenzijom, kao i kod bolesnika sa esencijalnom hipertenzijom, može rezultirati značajnim promenama hemodinamičkih uslova u bubregu, praćenih promenama vrednosti efektivnog bubrežnog protoka plazme, pri čemu promene zavise i od funkcionalnog statusa bubrega.

Ključne reči: ACE inhibitori; Angiotenzin konvertujući enzim; Efektivni bubrežni protok plazme; Bolesti bubrega; Hipertenzija; Renin-Angiotenzin sistem

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Abbreviations
ACE – angiotensin converting enzyme
GFR – glomerular filtration rate
ERPF – effective renal plasma flow
CrCl – creatinine celarance

Introduction

Regulation of renal blood flow is very complex and involves the nervous and humoral factors as well as the autoregulatory mechanism. It is predominantly influenced by the activity of three regulatory systems: the renin-angiotensin-aldosterone system, the prostaglandin system, and the kallikrein-kinin system. The latter two are a part of the renal vasodilator system, whereas the renin-angiotensin system represents the renal vasoconstrictor, with the vasodilator systems modulating vasoconstrictive effects of angiotensin II on one hand, and angiotensin II stimulating the secretion of vasodilatory components on the other, which prevents substantial increase in the renal vascular resistance. The relationships and dynamic balance of these interdependent systems determine the renal blood flow and blood redistribution in the kidney. Angiotensin II is biologically the most active factor of the renin–angiotensin system. In the kidney, it causes strong vasoconstriction of the efferent arteriole and moderate vasoconstriction of the afferent arteriole, directly stimulates the reabsorption of sodium ions in the proximal tubule, thereby contributing to an increased volume of extracellular fluid and the development of hypertension [1,2]. The inhibitors of angiotensin converting enzyme (ACE) act by modulating the activity of the rennin-angiotensin system. By blocking angiotensin converting enzyme, ACE inhibitors significantly block the conversion of angiotensin I to angiotensin II, thus lowering blood pressure via reducing the production of the strong vasoconstrictor. ACE inhibitors are frequently used to treat various hypertensive conditions, and besides antihypertensive effects, these drugs have local protective effects on the kidney, by reducing intraglomerular pressure and exerting the antiproliferative effect, thereby slowing down the progression of renal failure and preventing the development of more severe forms of renal failure [3]. The antihypertensive effects of ACE inhibitors are associated with the inhibition of local and systemic effects of angiotensin II on the vascular structures, stimulation of the local vascular kinin system with the secondary stimulation of the prostacyclin system, as well as the effects on renal hemodynamics and excretory functions.

Changes in total effective renal plasma flow (ERPF) in the setting of ACE inhibition result from the changes in local hemodynamic conditions in the kidney due to changed ratios and interactions between the components of the regulatory vasoconstrictor and vasodilator systems of the kidney [4,5].

The aim of the study was to determine whether application of ACE inhibitors in patients with diffuse renal parenchymal disease and hypertension can produce significant changes in ERPF and to assess to what extent the changes in ERBF depend on the preexisting functional status of the kidney.

Material and Methods

The study included a total of 80 subjects, 40 patients with diffuse renal parenchymal disease associated with hypertension and 40 patients with essential hypertension. Out of the 40 patients with diffuse renal parenchymal disease, 14 had been diagnosed with glomerulonephritis and 26 with tubulointerstitial disease. The study design was prospective. The study protocol included baseline measurement of ERPF in all subjects, along with determination of glomerular filtration rate (GFR), serum urea and creatinine levels, blood pressure, and repeated ERPF and blood pressure measurements after administration of captopril. Serum urea concentrations were determined using standard methods on an Olympus AU400 biochemical analyzer and commercial sets produced by Olympus. For the inhibition of angiotensin converting enzyme in the kidney, the subjects were administered 25mg captopril one hour

Table 1. Baseline values of 40 patients with diffuse renal parenchymal disease
Tabela 1*. Bazalne vrednosti kod 40 pacijenata sa difuznom bubrežnom parenhimskom bolesti*

	$\bar{X}$	SD	Min	Max
Age (years)/*Godine starosti*	51.25	10.88	23	66
ERPF (ml/min/1.73 m^2)/*EBPP(ml/min/1.73 m^2)*	360	110	120	631
Deviation of ERPF from expected (ml/min) *Odstupanje EBPP od očekivanog (ml/min)*	-195	105	-11	-509
Deviation of ERPF from expected (%) *Odstupanje EBPP od očekivanog (%)*	-35	16	-2	-70
GFR (ml/min/73 m^2)/*JGF(ml/min/73 m^2)*	72	22	22	109
Creatinine (μmol/l)	118	62	69	373.20
Urea (mmol/l)	8.5	3.6	4.6	17.8

ERPF - effective renal plasma flow/*EBPP - efektivni bubrežni protok plazme*
GFR - glomerular filtration rate/*JGF jačina glomerulske filtracije*

prior to blood sampling/measurements. ERPF was determined by the clearance of 131 I-hippuran in two blood samples, which were taken at 20 and 30 minutes according to Blaufox's method [6]. The normal ERPF values were calculated using regression equations by Schernthaner et al. [7] as following:

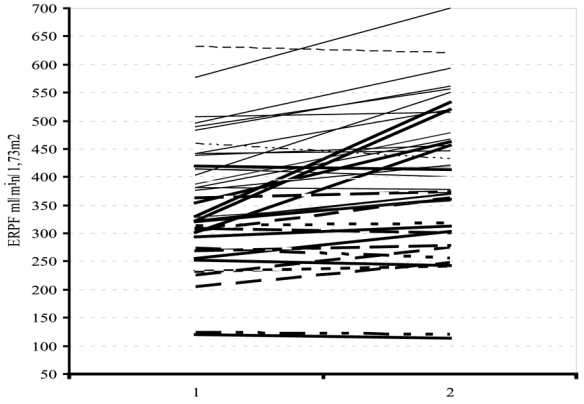
For women : ERPF= 673,3 - (2.92*years of age)

For men: ERPF = 854,2-(5.4*years of age)

The ERPF values were expressed as ml/min/1.73 m^2 and variations in the ERPF values compared to reference values (expected values for the sex and age) were given as ml/min and percentage. A change in the hemodynamic status was regarded significant if ERPF after inhibition was increased by ≥ 10% compared to the baseline values. GFR was estimated by measuring endogenous creatinine clearance (CrCl), by 24h urine collection. The calculated values of CrCl were normalized relative to the body surface of 1.73 m^2. Serum creatinine and the concentrations of creatinine in urine were determined using standard methods (modified Jaffe's method) on an Olympus AU400 biochemical analyzer and commercial sets produced by Olympus. The results were processed using standard statistical analyses (t-test, Spearman's rank correlation).

Results

The baseline values in the subjects with diffuse renal parenchymal disease associated with hypertension and the subjects with essential hypertension are presented in **tables 1, 2**, respectively. A significant change (improvement) in ERPF after administration of ACE inhibitors was recorded in 55% of the subjects with diffuse renal parenchymal disease, whereas ERPF did not change significantly in 45% of them **(Graph 1).** In the group of patients with essential hypertension, ACE inhibition resulted in significant improvements in ERPF compared to the baseline values in 75% of subjects, whereas no significant changes were detected in 25% of them **(Graph 2).** In 76% of the subjects (n=29) with the baseline normal ERPF values, ACE inhibition produced significant ERPF changes. In only 35% of the 20 subjects with the reduced baseline ERPF (defined as >40% of reference values) had significant changes in ERPF after ACE inhibition. Related/dependent samples t-test showed a highly significant decrease in mean systolic and diastolic pressures before and after administration of ACE inhibitors in both groups of subjects (systolic pressure p = 0.000; and diastolic pressure, p = 0.000). The analysis of correlation between the variables using Spearman's rank correlation showed a statistically highly significant correlation between systolic and diastolic pressures (baseline and after ACE inhibition) and ERPF (ρ = -0.450, p = 0.004; ρ = -0.456, p = 0.003 for systolic pressure; and ρ = -0.433, p = 0.005; ρ = -0.378, p = 0.016 for diastolic pressure).



Graph 1. The values of ERPF (ml/min/1.73 m^2) basal (1) and after administration of ACE inhibitors (2) in patients with diffuse parenchymal kidney disease

Grafikon 1*. Vrednosti efektivnog bubrežnog protoka plazme (ml/min/1,73 m^2) bazalno (1) i nakon primene inhibitora angiotenzin-konvertujućeg enzima (2) kod pacijenata sa difuznom parenhimskom bolesti bubrega*

Discussion

ACE inhibitors are widely used to treat various hypertensive conditions and in addition to lowering hypertension, these drugs affect the local renal hemodynamic conditions, thereby affecting GFR and ERPF. A number of clinical studies on the role of ACE inhibitors in decelerating the progression of

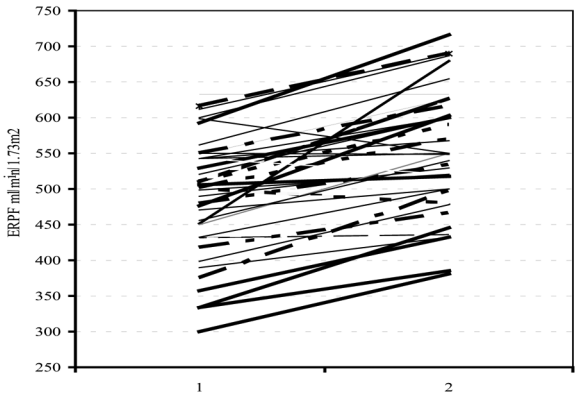
Table 2. Baseline values in 40 patients with essential hypertension

Tabela 2*. Bazalne vrednosti 40 pacijenata sa esencijalnom hipertenzijom*

	$\bar{X}$	SD	Min	Max
Age (years)/*Godine starosti*	46.1	15.7	18	65
ERPF (ml/min/1.73 m^2)/*EBPP(ml/min/1.73 m^2)*	466.10	84.03	300	632
Deviation of ERPF from expected/*Odstupanje EBPP od očekivanog (ml/min)*	-30.45	62.74	0	-222
Deviation of ERPF from expected (%)/*Odstupanje EBPP od očekivanog (%)*	-7	8.11	0	-20
GFR (ml/min/73 m^2)/*JGF(ml/min/73 m^2)*	101.1	21.65	70	164
Creatinine (μmol/l)	81.54	14.64	56	105
Urea (mmol/l)	5.57	1.50	2.7	7.9

ERPF - effective renal plasma flow/*EBPP - efektivni bubrežni protok plazme*

GFR - glomerular filtration rate/*JGF jačina glomerulske filtracije*



Graph 2. The values of ERPF (ml/min/1.73 m^2) basal (1) and after administration of ACE inhibitors (2) in patients with essential hypertension

Grafikon 2. *Vrednosti efektivnog bubrežnog protoka plazme (ml/min/1,73 m^2) bazalno (1) i nakon primene inhibitora angiotenzin-konvertujućeg enzima (2) kod pacijenata sa esencijalnom hipertenzijom.*

renal disease have been published, and among the first were those conducted by the Melbourne Diabetic Nephropathy Study Group, the ACE Inhibition in Progressive Renal Insufficiency (AIPRI) Study Group, and the North American Microalbuminuria Group. The results of those studies indicate that ACE inhibitors have a protective role, by decreasing microalbuminuria and slowing down the progression of renal disease [5, 8, 9].

Our results in the subjects with essential hypertension, i.e., significantly increased ERPF and decreased systolic and diastolic pressures, also corroborate the significant role of ACE inhibitors in the protection of renal function in these subjects. The relationship between arterial hypertension and renal function has been long established and well proved. The kidney may initiate arterial hypertension, as well as suffer the consequences of full-blown arterial hypertension. Chronic/constant arterial hypertension is at early stages characterized by increased renal vascular resistance, normal or slightly decreased renal blood flow and increased GFR. The development of renal failure due to arterial hypertension is believed to result both from ischemia due to changes in preglomerular arteries and arterioles and from the effects of increased intraglomerular pressure (hyperperfusion), which inevitably leads to functional and subsequently structural glomerular changes and progressive loss of renal function. Considering the fact that arterial hypertension represents one of the leading causes of end-stage renal failure in our country as well as worldwide, it is clear that timely protection of renal function in patients with essential hypertension is of great importance. Blood pressure regulation, with its maintenance at levels below 130/80 mmHg, and inhibition of the renin-angiotensin system in order to reduce renal vascular resistance and intraglomerular pressure are therefore frequently recommended [10,11].

Different renal diseases that cause damage to individual segments of the nephron (blood vessel, glomerulus, tubule or interstitium) lead to structural and functional changes, as well as to local hemodynamic changes in the kidney. Regardless of the etiological factor involved, the pathogenetic mechanisms underlying the progression of renal disease are the same and include abnormal glomerular hemodynamics (intraglomerular hypertension and glomerular hyperfiltration), hypoxia, proteinuria, and effects of various vasoactive substances (e.g. cytokines, growth factors). Furthermore, a critical role in the pathogenesis of renal impairment is played by angiotensin II, one of its main effects being regulation of renal hemodynamics. The effect of angiotensin II on renal blood flow in the setting of renal parenchymal impairment is determined substantially by its relationship with other vasoactive systems in the kidney. Considering the role of angiotensin II in the progression of renal disease, it is clear that application of ACE inhibitors can be expected to have protective effects on the renal function [12,13]. On the other hand, in the setting of relatively preserved renal function, i.e. when fewer functioning nephrons are affected by pathological processes, the vasoregulatory systems are also relatively intact, so any changes in renal hemodynamics under the influence of ACE inhibition are expected to be more substantial. Likewise, in our study ERPF changes after ACE inhibition differed between the subjects with preserved renal function and those with reduced ERPF. The majority (76%) of subjects with preserved renal function had more significant ERPF changes after ACE inhibition, as opposed to subjects with reduced functional reserve of the kidneys, in whom the majority (65%) did not show any significant changes in renal hemodynamics after ACE inhibition. In the patietns with hypertension and preserved renal function, ACE inhibition is usually associated with increased total ERPF, resulting from decreased resistance to blood flow at the level of glomerular capillaries and efferent arteriole and consequent increase in blood flow at the level of peritubular capillaries. The absence of a significant hemodynamic response to ACE inhibition in our subjects with more severe functional impairment is probably due to the existence of very complex interrelationships between angiotensin II and other regulatory mechanisms involved in the regulation of renal blood flow. Considering the integral parts of all three regulatory systems in renal hemodynamics, the vasoconstrictor activity prevails either due to the stimulation of renin-angiotesin-aldosteron system, or due to the inhibition of prostaglandin and kallikrein-kinin systems that participate in the

maintenance of the optimal hemodynamic conditions in the kidney via their vasodilatory effects. In the setting of significantly reduced functional reserve of the kidney, i.e. with reduced numbers of functioning nephrons, there is a significant decrease in the production of vasodilator prostaglandins. Hence, the significant impairment of renal function entails a significant disturbance of dynamic balance between the vasoregulatory systems, and the renal response to ACE inhibition is indeed determined by a complex interplay of these systems. Another possible explanation is the incomplete inhibition of renin-angiotensin system, since ACE inhibition does not cut off other alternative ways of angiotensin II production. Dragović et al. showed that the individual hemodynamic response in the patients with diabetic nephropathy in the condition of renin-angiotensin system blockade is genetically dependent, as well as focusing on individual therapeutic strategies for the purpose of more effective prevention and prognosis of diabetic nephropathy [14].

Previous research was directed to dual blockade of the renin-angiotensin system, i.e. the simultaneous inhibition of ACE and blockade of angiotensin II receptors. The results obtained suggest that the dual blockade has more significant antiproteinuric and antihypertensive effects compared to monotherapy [15-17]. Finally, the answers should be sought not only within the renal vascular system, but also in the numerous factors outside the kidney that may affect the hemodynamic response.

Conclusion

Angiotensin converting enzyme inhibition by means of angiotensin converting enzyme inhibitors may significantly affect renal hemodynamic conditions and effective renal plasma flow in patients with diffuse renal parenchymal disease and in individuals with essential hypertension, and the extent of the hemodynamic changes depends also on the functional status of the kidney.

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