„VICTOR BABES" UNIVERSITY OF MEDICINE AND PHARMACY TIMISOARA
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PhD THESIS SUMMARY

PARTICULARITIES IN MANAGEMENT OF CARDIOVASCULAR DISEASE IN PATIENS TREATED BY HEMODIALYSIS
USE OF ECHOCARDIOGRAPHICAL PARAMETERS IN THE EVALUATION OF THERAPEUTIC INTERVENTIONS

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CONTENT

1. Introduction

In recent years all studies have shown a close relationship between cardiovascular and renal pathology, with important impact on prognosis. It is of paramount importance addressing the problem as a whole: cardiovascular, renal, metabolic, and neurological, all with a huge impact on patient's evolution.

Regarding dialysis patient, the cardiovascular risk is unanimously recognized. The prognosis of these patients is determined by the associated heart disease and possible infections that may occur in this complex situation. The therapy raises special problems of pharmacokinetics and pharmacodynamics, beyond the co morbid peculiarity.

The most common clinical scenarios faced by cardiologists in renal patients are acute coronary syndromes, rapidly evolving valvulopathies with extensive degenerative changes, potential for alteration of phosphocalcic metabolism, endomyocardial calcifications that may be a source of arrhythmias and which precipitates the evolution to heart failure. Results from retrospective studies and clinical trials are the basis of current recommendations, due to the lack of prospective studies on patients with CKD. Future research concerning the metabolic effects of renal dysfunction will be able to bring new information about therapy and diagnosis for renal patients with cardiovascular disease. Hypertensive disease is also a problem in renal patients as a cause - hypertensive nephroangiosclerosis with progression to end stage CKD, but at the same time primary renal pathology may cause secondary hypertension, or malignant, or resistant hypertension with wide chamber reaction and precipitation of heart failure. The therapy of hypertension in patient with renal pathology is a real challenge for cardiologist and must be individualized according with evolution of renal impairment and vascular morpho-functional changes.

GENERAL PART

Uremic cardiomyopathy is responsible for the high rate of morbidity and mortality in patients with chronic kidney disease (CKD) or end-stage renal disease (ESRD), although early onset of dialysis or kidney transplantation may stop its progression.

The high cardiovascular risk in dialysis patients is due to the synergistic interaction between traditional risk factors (age, hypertension, sex, dyslipidemia, diabetes, obesity, sedentary lifestyle, smoking, family history), non-traditional cardiovascular risk factors (homocysteine, lipoprotein, C-reactive, hypercoagulability), modified in CKD, and new risk factors related to chronic kidney disease (uremic toxins, oxidative stress, inflammation, anemia, hypervolemia, insulin resistance, mineral and bone disorders) that cause rapid cardiovascular disease progression .

The most common cardiovascular abnormalities in patients with ERSD are left ventricular hypertrophy (LVH), left ventricular dilation, systolic and diastolic dysfunction of the left ventricle. Serial echocardiographic evaluation of dialysis patients showed that the course of LVH was associated with increased mortality and cardiovascular events, regardless of ventricular mass or other cardiovascular risk factors - thus, patients with increased ventricular mass had a worse prognosis (Zoccali et al. 2004). Uremic cardiomyopathy is the result of pressure overload (due to hypertension, atherosclerosis and valvulopathies), volume overload (anemia, hypervolemia, arteriovenous fistula) and uremic status.

Volume and pressure loading lead to left ventricular hypertrophy, initially as an adaptive response. Later persistence of LV overload leads to changes in cardiomyocytes and their death by decreased perfusion. Together with myocardial fibrosis, uremia and hyperparathyroidism, LV dilation with diastolic and systolic dysfunction develops. In other words, in advanced stages, uremic cardiomyopathy presents as LV dilation with systolic, diastolic dysfunction and low ejection fraction.

Bone mineral disorders (CKD-MBD) are involved in the pathophysiology of uremic cardiomyopathy. Phosphotoxicity is considered the leading cause of cardiovascular mortality. Vascular calcification is an active process in which calcium and phosphate salts are deposited, especially in the muscular tunic of vessels (coronary and systemic) and heart valves. In

addition, hyperphosphatemia has a toxic effect on endothelial cells leading to endothelial dysfunction, strong procoagulant action and endothelial cell apoptosis.

There is a biunivocal relationship between the evolution of chronic kidney disease and cardiovascular disease, the pathophysiological key being represented by endothelial dysfunction. It occurs early in the course of kidney disease. There is a reduction in the clearance of the asymmetric inhibitor of endothelial nitric oxide synthetase, which reduces the availability of endothelial nitric oxide, activates angiotensin II by inducing oxidative stress and vasoconstriction. At the same time, chronic inflammation is generated and self-sustaining in a dyslipidemic environment and deficient in endothelial growth factors. Endothelial dysfunction contributes significantly to the onset and progression of cardiovascular disease in renal patients and precipitates renal decompensation, leading to a vicious circle.

Blood pressure control in the dialysis patient is mandatory, and obviously has particularities related to pharmacodynamics, volume loading, tolerability, elastic or not elastic response of the negative remodeled vessel, circadian profile of blood pressure values.

Uremic toxins, hyperkalemia and bone mineral disorders contribute as risk factors for atrial or ventricular arrhythmias, altering the duration of action potential and electrophysiological characteristics in both the excitoconductive tissue and the working myocardium. Moreover, there are changes in anisotropic conduction of the electrical impulse, in conduction velocity with the appearance of macro and micro-reentrant circuits, as well as alterations of automatism. Given the pathological substrate of left ventricular hypertrophy, ventricular dilation, heart failure and valvular disease, the incidence of arrhythmias is higher in patients with CKD, including bradyarrhythmias and atrio-ventricular blocks. Dose adjustment of antiarrhythmic drugs is required in renal patients. Moreover, the presence of CKD may cause increasing of defibrillation threshold, which may lead to the failure of implantable cardiac defibrillator therapy, as well as increasing of stimulation threshold and of fibrosis in those with pacemakers. Patients with CKD have an increased risk of sudden cardiac death, but also a significantly higher risk of death.

The present paper aims to follow the biunivocal impact of severe renal pathology and cardiovascular pathology correlating risk factors and evaluating echocardiographic parameters in dialysis patients with prognostic impact on morbidity and mortality. We also aim to establish a link between the above mentioned parameters and therapeutic measures destined to favorably influence evolution of these patients.

Chronic kidney disease causes changes in the heart and blood vessels with extensive implications for prognosis and treatment. Uremic heart disease, hypertension, valvular abnormalities, arrhythmias recognize a complex etiopathogenesis and precipitate the evolution to heart failure.

3. Special part

The special part of this thesis focuses on the association of risk factors, especially diabetes and the prognostic impact of comorbidities. The second part aims to assess serial echocardiographic evaluation and the follow-up of the morphological and functional parameters for the stratification of the risk of these patients. The last two parts evaluate the treatment for risk reduction, positive cardiac remodeling and the therapeutic impact of the use of renin angiotensin aldosterone system blockers and loop diuretic.

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Material and method

Each stage of our study included dialysis patients in whom consent was obtained, patients in whom echocardiographic examination was performed during the dialysis program. Depending on the issue, we included a number of patients to obtain statistically significant results. We collected data like age, comorbidities, duration of dialysis and drug treatment from

patient records, and echocardiographic exploration was performed on the same Siemens Accuson P300 echocardiograph.

The comparison between the groups was made using the t and Fisher tests. Correlations were performed using the Pearson test. Values were considered significant if $p < 0.05$.

Results and discussions

3.1 Considerations regarding chronic kidney disease, cardiovascular disease, dyslipidemia in the diabetic patient

On the investigated group, in order to reproduce the results, we considered that patients had diabetic kidney disease (DKD) if GFR <60ml / min / 1.73m2 for a duration> of 90 days. The prevalence of diabetic kidney disease (DKD) in the investigated group was 35% (147 cases). In our group, BCV was present in 50% of patients. The prevalence of stroke, BC and PVD was significantly higher in patients with DKD stages 3,4,5.

Depending on the lipid profile of the investigated patients (410), the group was divided into 4 groups: patients without dyslipidemia, patients with hypercholesterolemia, patients with hypertriglyceridemia and patients with mixed dyslipidemia. The results obtained regarding the association with DKD and CVD are presented in the following table:

	without DL n=82	H colest. n=118	H Tgl n=98	DL mixta n=112
BRD	20,35%	25,24%	24,25%	30,16%
AVC	15,65%	37,5%	26,5%	20,35%
BC	12,15%	48,35%	25,17%	24,33%
BVP	18,38%	44,67%	16,05%	20,90%

Table no. 3.1.3: Prevalence of DKD and CVD in patients with dyslipidemia

All forms of dyslipidemia, but especially intensely atherogenic ones, are associated for reasons already well known with chronic kidney disease and diabetes. As can be seen in the table, the highest prevalence of CVD is evident in hypercholesterolemia and the highest proportion of patients with DKD is found in mixed dyslipidemias. These seem to explain the increased prevalence of CVD patients and the high cardiovascular mortality of both diabetic patients and patients with diabetic kidney disease. In reality, the table above imposes another idea, in patients without DKD the prevalence of dyslipidemias reaches 75.29% of cases, while in patients with DKD the percentage of those with dyslipidemias (of any form) reaches 88.44%. These results support Tonelli's findings from the PPP study and explain at least in part that statin treatment has entered the standards of good practice in CKD treatment. Whether the cardiovascular benefit of statins is currently proven in both patients with chronic kidney disease and people without chronic kidney disease is still unclear whether lipid metabolism disorders negatively influence the progression of CKD or not.

In this study we correlated the renal function of the investigated patients with the monitored parameters, both in patients with diabetic kidney disease (DKD) and in those without DKD.

	RFG – BRD (-) n=273		RFG – BRD (+) n=147	
	r	p	r	p
age	- 0,3214	0,001	- 0,3124	0,001
Colesterol ser	- 0,1945	0,001	- 0,1324	0,001
Proteinurie			- 0,2014	0,001

Tablel No.3.1.4: Correlation of GFR with dif parameters in patients with and without DKD

Our results highlight that GFR is negatively correlated with age in both diabetic patients without CKD and those with CKD. The phenomenon is explained by the fact that renal function decreases with age regardless of the underlying pathology.

The negative correlation highlighted between GFR and proteinuria in patients with CKD is a well-known phenomenon and proteinuria is a risk factor / marker of CKD progression regardless of age and etiology. A result worth mentioning is the inverse correlation between GFR and cholesterol in both patients with DRD and those without DRD. The administration of statins in these categories of patients does not improve the progression of CKD but reduces the cardiovascular risk. Currently, the guidelines of nephrology societies, although they include statins in the standard treatment of reducing the progression of CKD, in reality, there is insufficient evidence to support this therapeutic approach.

In our group, 42.1% (n = 64) of patients developed DKD in these 4 years, significantly more than the data published in UKPDS 64. The phenomenon could be attributed to the fact that the entire group from which we selected the patients included in this study had a known evolution of type 2 DM for more than 10 years. From the patients who developed DKD (64) 45.3% (29) developed albuminuria without reduction of GFR, 20.3% (13) developed albuminuria and GFR <60ml / min / 1.73m2, 34.3% (22) developed GFR reduction <60 in the absence of albuminuria. The results seem to confirm those obtained by Tsalamandris. Taking in account that patients were not investigated by renal biopsy, we see that there are 3 possible evolutions to DKD and only the first two could be explained by the classical theory of DKD genesis.

3.2. Predictive value of echocardiographic parameters for cardiovascular events in dialysis patients with heart failure with preserved or mid-range EF

Our study group is a typical group for Romania. (350 patients with a mean age of 63 years and a mean duration of hemodialysis treatment of 4.5 years). The percentage of patients with heart failure (present symptoms and preserved or mid-range ejection fraction) is 17.4%, which is high. In this prospective study, we enrolled 61 patients with ERSD treated by hemodialysis (duration of HD therapy> 90 days) with preserved or mid-range ejection fraction according to the European Guide for acute and chronic heart failure. Patients with cardiovascular events showed an increased prevalence of diabetes and cardiovascular history, significantly increased LVEDD values, significantly lower mean values of ejection fraction, and diastolic and systolic dysfunction.

The most frequent ultrasound diagnoses on the group we investigated were:

a. Diastolic LV dysfunction (85.1%), expressed in the value of the E / A ratio

b. Systolic dysfunction (27.8%), expressed by the value of the ejection fraction.

c. Dilatation of the left atrium in almost half of patients (48.2%), expressed by assessing the diameter of the LA and its volume (LAV)

d. Left ventricular hypertrophy (84.9%) objectified by parietal thicknesses

e. Dilatation of the left ventricular cavity (21%) objectified by telesystolic and telediastolic intracavitary diameters

f. Increased left ventricular mass in direct correlation with LV dilation and LV hypertrophy.

Evaluating the data of our patients, we notice that the "improvement" of the ejection fraction is actually due to the association of significant regurgitation, responsible for volume loading and, according to Laplace's law, increase of the ejection fraction and shortening fraction.

Valvular diseases have an increased prevalence in patients with severe CKD and in those on dialysis (64), an association that is important from a prognostic point of view. It was observed that the presence of valvulopathies is associated with a worse prognosis, with

increased mortality - mortality at 5 years in dialysis patients with aortic stenosis or mitral regurgitation, is 50% higher compared to patients without CKD.

Serial echocardiographic determinations performed in our patients showed an increased prevalence of valvular calcifications, which corresponds to data from the literature. The prevalence of aortic valvular sclerosis is about 25% in the population over 65 years, and tight aortic stenosis 3%. Valvular calcifications and endomyocardial calcifications increase proportionally with the decrease of the active nephron population, respectively with the GFR. The prevalence of mitral regurgitation at enrollment was 16% and, at the end of the study, it reached 31%; in the case of aortic insufficiency, the prevalence of the severe form increased from 11% to 16%.

It should also be noted that in the case of dialysis patients there is an increased incidence of endomyocardial calcifications and valvular calcifications, in the absence of significant valvulopathy. Calcifications are due to altered phosphocalcic metabolism, hyperparathyroidism, altered levels of vitamin D, need for administration of anticoagulants antivitamin K warfarin or acenocoumarol, amyloid deposits, with the addition of the classic factors that precipitate valve calcifications, mechanical stress, activated mechanical stress, dyslipidemia. These calcifications correlate with a poorer prognosis.

There is a significantly increased prevalence of hemodynamically significant valvulopathies: 32 ± 5.1% compared to 21.1 ± 1.8% (p 0.018) in the group of patients who presented cardiovascular events compared to those who had a favorable evolution. Also, the prevalence of endomyocardial calcifications was higher in the group of those with cardiovascular events: 27.4 ± 3.7% vs. 19.5 ± 5.1% (p 0.027), and the severity score of calcifications was also significantly higher in those with cardiovascular events: 4.9 ± 1.5 vs. 2.8 ± 0.4 (p 0.017).

In our study, patients with cardiovascular events had pathological values of the e / e' ratio and of the global longitudinal strain. In the group of patients with cardiovascular events the value of the e / e' ratio was 15.5 ± 5.3 compared to those with good evolution without cardiovascular events in which the value of the ratio was 11.6 ± 4.9 (p 0.046). LV systolic dysfunction, translated by the speed of systolic movement of the mitral ring was present in 49.6% in those with cardiovascular events compared to 21.6% in those without events (p 0.028). Tissue Doppler parameters may have a potential prognostic role, but in any Doppler investigation they are limited by angular dependence and of course influenced by translational movement.

In our experience, the deformation parameters would be useful in assessing the hemodynamic risk, respectively in the correct assessment of cardiac performance, but establishing the optimal operative moment for the dialysis patient remains an ideal desideratum, knowing that a surgery in their case involves a high operative risk with an immediately poor prognosis, with risk of infection and severe hemodynamic decompensation.

3.3 Intervention on the Renin-Angiotensin-Aldosterone System in dialysis patients. Impact on mortality and echocardiographic morpho-functional changes

Our study addresses a particular problem: it is appropriate to resume treatment with ACEI or ARB after initiating dialysis. Another question we want to answer is whether treatment with ACEI / ARB decreases the risk of CV mortality of the dialysis patient.

We enrolled in this study 1200 patients with ERSD of various etiologies treated with hemodialysis for over 90 days (stable) with a mean age of 57.8 ± 2.3 years (52% men). The average duration of dialysis on the investigated group was, at enrollment, 6.5 +/- 2.3 years. To keep the ultrasound evaluation as simple as possible (taking into account the large number of patients and the relatively short time) we used in this study the size of LV and the walls of left ventricle, LV mass, ejection fraction determined after one hour of hemodialysis. We repeatedly evaluate the presence of endomyocardial calcifications and the existence of valvular degenerative changes translated by possible regurgitations.

At inclusion, only 11% of the investigated patients had normal ultrasound parameters. Left ventricular hypertrophy was present in 74%, LV dilation in 43%. Degenerative valve

changes were present in 41% of cases, ischemic valve regurgitation was present in 18% and endomyocardial calcifications in 19% of cases. Pericardial fluid and pulmonary hypertension were also highlighted. The results of the ultrasound data are presented in the table

ECO CHANGES	PREVALENTA (%)
Normal parameters	11
Left ventricle hypertrophy	74
Dilatation of LV cavity	43
Degenerative valvular lessions	41
Ischemic valvular lessions	18
Ejection fraction >50%	35
Ejection fraction 40-49%	48
Pericardial effusion	28
Endomyocardial calcification	19
Pulmonary hypertension	28

Table No. 3.3.4 The echocardiographic parameters at inclusion

	without	IECA		with IECA		
	includere	final	p	includere	final	p
LA (mm)	48,3±2,7	56,4±3,1	0.0041	49,5±1,8	54,4±2,1	0.037
EDD(mm)	56,23±3,1	59,2± 4,2	0,0037	53,29±2,9	55,45±1,8	0,049
ESD (mm)	39,21±2,1	43,67±3,7	0,007	37,56±3,7	41,78±2,9	0,009
IVS (mm)	13,4±0,9	15,8±1,2	0,004	13,9±1,1	14,1±1,1	0,051
EF %	49,2±3,1	42,1±2,8	0,002	50,1±2,1	51,3±2,1	0,03
EF≥50	53,2±2,3	50,4±0,3	0,031	54,2±2,6	55,7±3,6	0,041
EF ≤49	44,4±2,5	41,34±3	0,028	43,5±2,4	47,1±0,9	0,006
LV mass g	356±89	478±88	0,003	374±67	434±39	0,003

Table No. 3.3.5 The echocardiographyc parameters at patients with or without ACE/ARB

The echocardiographic parameters of the surviving patients indicate that this group of patients had smaller LVs, an ejection fraction close to normal and which did not vary significantly during the surveillance period, in other words they had stable ultrasound parameters. The patients who died had increased telesystolic and telediastolic diameters, a thickened interventricular septum 15 ± 2.8 mm and a reduced average ejection fraction 41 ± 3.7%.

When comparing the effect of ACE inhibitors / ARBs with the other groups of lowering blood pressure agents, we noticed that the best results on changing the ultrasound parameters were obtained with the medication that intervenes on the RAAS.

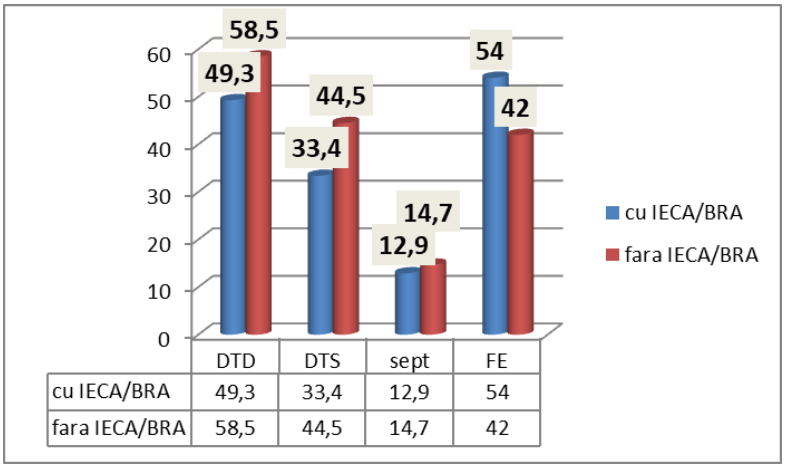

Figura Nr. 3.3.2: Modificarile parametrilor ecocardiografici la pacienti care au reluat terapia cu IECA/BRA

In this study we evaluated the effect of ventricular rate and ACE inhibitor / ARB treatment on dialysis patients followed for a period of 3 years and who underwent ACE inhibitor therapy and had a heart rate below 70 b/min, patients without ACE inhibitor treatment but with controlled frequency, patients on active treatment with ACE inhibitors with a frequency of more than 80 and those with no treatment with ACE inhibitors or controlled heart rate. I mention that the controlled frequency was obtained in the vast majority of cases with beta-blocker: bisoprolol, carvedilol, metoprolol succinate or nebivolol.

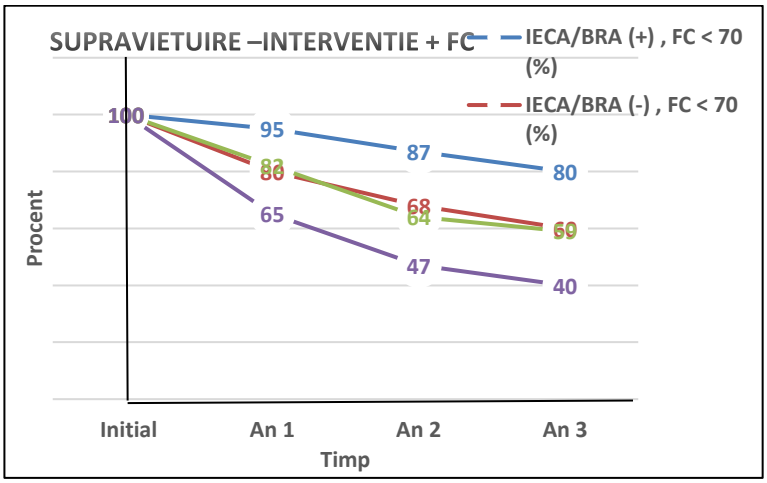

Figura Nr. 3.3.3: Supraviețuirea la 1,2,3 ani la cele 4 grupuri de pacienți

We observed that the best evolution had patients with ACE inhibitor therapy and heart rate below 70. Heart rate above 80 b / min practically potentiates the favorable effect of the use of ACE inhibitors / ARBs. It should be noted at this point that we did not discriminate between the effect of beta-blocker therapy and ventricular rate outside of therapy with these drugs.

3.4. Furosemide in the treatment of the dialysis patient - Friend or enemy

We included in this study 101 patients with chronic kidney disease (CKD) stage 5, treated by hemodialysis for at least 6 months, 3 sessions / week, 4 hours per session, who had a residual diuresis between 250 and 650 ml / day and sinus rhythm.
The results obtained are illustrated in the tables below:

	Parametri	Initial	3 luni	6 luni	9 luni	12 luni	24 luni	P
Grupul martor	FE(%)	61.1±11.0	62.8±13.6	61.3±12.5	60.6±14.4	58.9±15.6	57.1±18.5	NS
	FS (%)	37.7±11.5	37.1±13.2	35.3±11.4	36.6±12.2	34.3±10.6	34.8±11.8	NS
	E(m/s)	0.9±0.3	1.2±0.5	1.1±0.2	0.8±0.4	1.0±0.1	1.2±0.5	< .001
	A (m/s)	0.7±0.4	0.9±0.2	0.7±0.5	0.9±0.2	0.8±0.3	0.5±0.4	< .0001
	E/A	1.9±0.8	1.8±1.1	2.0±1.5	2.2±1.8	2.1±2.0	2.2±1.2	< .0001
	DT (ms)	170.2±25.4	174.9±29.6	167.3±31.8	181.4±41.3	189.2±33.4	191.3±49.5	< .0001
	LAV(ml)	68.1±17.5	62.1±16.0	76.5±26.2	61.7±13.6	88.8±19.4	80.3±29.2	< .0001
	VAS (cm)	3.9±2.6	4.2±1.8	4.5±1.8	4.7±2.7	4.6±2.3	4.4±1.4	< .0001
	CW TR (m/s)	2.4±0.6	2.3±0.7	2.6±0.5	2.8±0.8	2.9±0.7	3.3±0.5	< .0001
	Masa VS (g)	191.9±39.5	186.5±26.8	193.3±42.4	195.5±47.1	198.1±47.2	210.6±43.1	.0993

	TAS (mmHg)	143.8±22.1	150.0±18.2	152.5±16.2	133.5±74.3	150.4±16.3	152.0±14.2	NS
	TAD (mmHg)	82.0±11.0	8l.0±9.7	89.4±9.3	79.5±9.8	86.5±10.6	89.5±12.5	NS
Grupul Cu furosemid	FE (%)	62.1±11.6	62.2±8.9	64.3±10.7	60.4±8.5	60.1±18.6	59.4±12.3	NS
	FS (%)	38.2±11.8	39.4±9.4	38.1±9.7	37.8±8.9	36.2±11.5	35.5±5.0	NS
	E(m/s)	0.7±0.3	0.9±0.2	0.8±0.4	1.1±0.2	0.9±0.2	1.0±0.1	.0005
	A (m/s)	0.7±0.2	0.8±0.3	0.6±0.2	0.6±0.3	0.8±0.2	0.9±0.1	.005
	E/A	1.1±0.3	1.4±0.5	1.3±0.6	1.4±0.7	1.3±0.6	1.4±0.7	.0031
	DT (ms)	164.2±23.4	184.9±29.6	187.3±31.8	191.4±41.3	169.2±53.4	181.3±49.5	.0318
	VAS(ml)	58.1±17.5	62.1±16.0	56.5±16.2	61.7±13.6	58.8±19.4	60.3±19.2	NS
	DAS (cm)	2.9±1.1	3.3±1.9	3.5±1.6	4.8±2.0	3.7±1.4	3.9±1.1	< .001
	CW TR (m/s)	2.0±0.6	2.0±0.7	2.4±0.5	2.7±0.8	2.6±0.7	3.0±0.5	< .0001
	MASA VS(g)	181.9±35.5	176.6±29.6	190.3±43.2	185.5±48.4	199.1±37.2	201±48.6	.0545
	TAS (mmHg)	143.3±20.5	147.5±22.2	143.7±26.9	145.8±24.0	144.2±21.5	141.8±22.8	NS
	TAD (mmHg)	76.2±7.5	70.0±11.5	78.7±10.3	73.7±13.8	79.7±14.9	77.9± 17.9	NS
Grupul martor	Parametri	Initial	3 luni	6 luni	9 luni	12luni	24 luni	P
	E´(cm/s)	5.8±1.4	6.3±1.6	5.9±1.5	5.9±1.7	7.1±1.8	7.2±1.7	< .0001
	A´ (cm/s)	5.0±2.4	4.6±2.3	4.7±1.9	5.1±1.8	5.6±2.0	6.5±2.2	< .001
	E´/ A´	0.9±0.4	1.7±1.2	1.5±0.8	2.0±0.5	1.4±0.7	1.5±0.5	< .0001
	E/E´	21.1±18.8	28.8±13.3	22.0±14.5	26.1±14.2	36.0±16.8	32.9±18.2	< .0001
	IVRT (ms)	108.9±32.5	95.6±24.2	93.5±23.8	104.2±33.3	109.5±19.3	111.4±28.8	< .0011
	ePCWP (mmHg)	15.8±2.7	13.9±1.8	16.8±2.6	17.9±2.3	15.4±2.1	18.2± 3.4	< .0001
Grupul Cu furosemid	E´(m/s)	4.8±1.9	4.5±2.3	5.1±2.1	4.9±1.8	4.7±2.3	5.7±2.3	< .0001
	A´ (m/s)	6.4±1.2	5.5±1.5	5.8±1.7	5.7±1.5	6.1±1.8	6.6±1.8	< .05
	E´/ A´	0.8±0.4	0.7±0.3	0.9±0.5	0.9±0.2	1.1±0.3	1.2±0.4	NS
	E/E´	17.5±7.5	22.2±7.6	24.0±12.9	25.4±11.9	26.3±15.6	20.1±6.2	< .0001
	IVRT (ms)	122.6±41.2	118.9±32.3	124.3±36.9	115.4±32.2	121.0±44.7	119.0±24.0	<0.01
	ePCWP (mmHg)	11.7±1.6	12.9±2.3	10.4±1.6	13.9±2.5	14.0±2.1	13.2± 2.6	<.0001

Conclusions

CKD is currently a major public health problem in many countries. The prevalence between 9 and 15% in western countries and positive epidemiology has led to steadily increase in patients requiring renal replacement therapy: hemodialysis (HD) and peritoneal dialysis (PD).

The presence of CKD amplifies the overall mortality 8.8 times due to the fact that it is a major cardiovascular risk factor. Mortality in CKD increases with renal disease evolution (and loss of renal function). The most important cause of advanced CKD, respectively end stage CKD (ESRD) is DM. DM (especially type 2 diabetes) has a positive epidemiology in the general population and in the population of patients with CKD (diabetic kidney disease DKD). It seems that DKD is becoming the main cause of ESKD treated by HD and PD.

In the first section of the special part, we evaluated a significant and typical group (from Timiș County) of patients with diabetes in whom we followed complications, comorbidities, cardiovascular risk, prevalence and progression of CKD. The purpose of this section was to

highlight the pathological complexity of the case and to demonstrate some of the reasons for the high mortality in that group of patients.

The conclusions to be drawn from this first section are as follows:

1) The prevalence of CKD was 35% at an average age of 57 years and an average duration of DM of 11 years, significantly higher than in general population (between 9-10%)

2) On the investigated group, the progression of DKD was significantly faster than that suggested by the international literature. In 4 years, 42.1% of patients without DKD developed chronic kidney disease. It should be noted that 34% had decrease renal function in the absence of albuminuria, which suggests: either the existence of alternative mechanisms in the genesis of albuminuria, or the existence of additional renal pathology about which we have no information in the absence biopsy.

3) On the investigated group, the prevalence of CVD was significantly higher compared to the general population (50%) due to the increased prevalence of major cardiovascular risk factors and the effect of amplifying the prevalence due to DKD. An example is dyslipidemia whose prevalence is significantly higher in patients with DKD compared to patients with diabetes without DKD (88.44% vs 75.29%) and this prevalence tends to increase as renal function decreases.

4) We managed through this section of the thesis to prove that diabetic patients who get dialysis are not 'innocent' of a severe cardiovascular disease and are burdened by high cardiovascular mortality since the earlier periods of DKD. Taking into account the complex background pathology and extrapolating the data from international statistics, we can say that patients who will survive long enough to reach renal replacement treatment (hemodialysis), from the studied group, is below 2% of the whole investigated group and the main cause mortality is cardiovascular mortality.

In the second section of this thesis we explored the role and place that should be occupied by serial ecocardiographic evaluation of patients with CKD. The identification of patients at risk is, along with appropriate treatment, a continuous goal to be improved in the care of these patients. Uremic heart disease, alteration of mineral and bone metabolism (CKD-MBD), the association of hypertensive disease, coronary heart disease, valvular disease causes cardiac morphofunctional changes that are diagnosed echocardiographically and stratified as risk and impact on prognosis, by the same method.

Our group of 61 dialysis patients with heart failure with preserved ejection fraction or mid- range ejection fraction, with a mean duration of HD treatment of 39 ± 14 months, was evaluated prospectively over an average period of 20.4 ± 11.3 months. During this period we followed clinical, biological and ultrasound parameters that could be predictive for the development of cardiovascular events during the surveillance of the investigated patients.

The results obtained led to the following conclusions:

1) On the group of 350 dialysis patients, the presence of mid-range and preserved ejection fraction of heart failure (according to recent guidelines) was particularly high 17.4%.

2) In this category of patients the prevalence of cardiovascular events was 18%. Cardiovascular events were mainly associated with the presence of diabetes, BCV previously known and not with smoking, total cholesterol, BP or body mass index. These findings support the concept of reverse epidemiology of dialysis patients regarding hypertension, dyslipidemia, and obesity.

3) Ultrasound parameters associated with the prevalence of CV events were: significantly increased LVEDD values, significantly low mean values of ejection fraction, diastolic and systolic dysfunction.

4) The main predictive parameter of cardiovascular prognosis in dialysis patients was EF.

5) 48% of the studied patients registered an increase of the ejection fraction. In 29.1% of cases, the increase of the ejection fraction was due to progression of valvular lesions. In other situations, the increase in ejection fraction was relatively small (up to 10%) and was

attributable to the modulation of cardio protective treatment, reduction of hydration and reduction of heart rate by beta blockers.

On our data, echocardiographic surveillance seems to be a predictor of cardiovascular events and in this context, in addition to its diagnostic use, we propose the use of the method in order to follow the cardiac effects of cardio protective medication in dialysis patients. The value of the method would consist in serial evaluations that do not require waiting for the completion of strong endpoints for reorienting the therapy.

The third section of the special part of the thesis deals with the reiteration of cardio protective treatment with ACE inhibitors or ARBs in hemodialysis patients. The working hypothesis we launched was that in the context of the increased prevalence of heart failure in dialysis patients (see section II) the cardio protective effect of ACE inhibitors / ARBs could reduce cardiovascular mortality. At the same time, we followed the effect of therapy by serial echocardiography in order to confirm the method proposed in section II. It is common knowledge that patients in ESKD are not" innocent" patients. They have an impressive number of comorbidities and life-threatening complications due to the underlying (most commonly DM, hypertension) and CKD (resistant hypertension, microinflammatory status, CKD-MBD, renal anemia, hyperuricemia, CVD, etc.). It appears that these risk factors progress as survival in hemodialysis. Our group is not apart from those presented above, nor is it an initiation group in hemodialysis (the average duration of HD treatment was 6.5 +/- 2.3 years.).

Our results impose some important conclusions:

1) Patients survival depends on the severity of the morphological and functional changes pre-existing at the beginning of the study (the intervention on RAAS) and for an important part of the patients, the resumption of the treatment with ACE inhibitors / ARBs.

2) In general, higher mean values of LA and LV, a thicker interventricular septum, a higher LV mass and a lower ejection fraction appear to be predictors of mortality for patients at the initiation of RAAS intervention.

3) Ultrasound-detectable morphological and functional lesions tend to progress as the duration of hemodialysis therapy is prolonged. The more important progression of ultrasound parameters seems to be predictive of mortality.

4) ACE / BRA treatment decreases the rate and frequency of ultrasound and functional changes and thus favorably influences the survival of patients, although the initiation of ACE / BRA therapy was in most cases distant from the initiation of hemodialysis.

5) The intervention on RAAS and the average ventricular rate below 70b / min offers the best survival in our group, the weakest survival rate is encounted in patients with higher frequencies without treatment on RAAS. (Interestingly, higher heart rates in patients treated with ACE inhibitors appear to reduce the beneficial effect of SRAA intervention and generate a similar prognosis with untreated patients but with lower heart rate).

The conclusions expressed in this paragraph should be interpreted with caution as lower heart rates were largely obtained by beta-blocker treatment and in this context we cannot discriminate between the beneficial cardiovascular effect of beta-blockers and the beneficial effect of lower heart rates per se. For the same reason, but also due to the small number of cases, we cannot draw conclusions about the intervention with ivabradine.

Our data state that there is a benefit for patient survival when initiating / restarting ACE inhibitor / ARB therapy in dialysis patients regardless of the period of initiation of treatment (starting HD or in patients in chronic HD treatment). More extensive randomized and controlled studies are needed to confirm our findings, but serial echocardiographic evaluation may modulate the design of such studies.

The last section of the special section addresses the usefulness of continuing treatment with furosemide in dialysis patients with residual renal function and residual diuresis. The use of furosemide in dialysis patient has been and continues to be a source of controversy. Residual diuresis means residual renal function that is intended to be exploited. On the one hand the main problem of the dialysis patient and the source of an important part of

comorbidities is the lack of diuresis or inefficient diuresis, on the other hand the loop diuretic therapy was considered useless (fluid elimination is ensured by hemodialysis) and sometimes toxic. Heterogeneity of patients, interdialytic variation of volume loading, alteration of vasomotor and vascular elasticity and comorbidities make a therapeutic strategy extremely difficult to establish. This in no case can be uniform, having to deal with a large number of variables. Hydration control significantly corrects high blood pressure. Assessing hyperhydration beyond the patient's weight can allow individualization of treatment.

Echocardiographic techniques for morphological and functional assessment provide objective data on volume loading, systolic and especially diastolic performance of the left ventricle and the impact of these changes on the heart.

Treatment with furosemide in the investigated group led to the following conclusions:

1) The treatment improved the ventricular filling parameters and induced a better hydroelectrolytic balance. In addition, it contributed to the positive remodeling of the heart cavities.

2) Serial determination of echocardiographic parameters provided valuable hemodynamic quantification data, and identified earlier volume loading, while allowing individualization of treatment.

3) The relatively short follow-up period did not allow us to draw conclusions about mortality or the assessment of residual renal function.

PERSONAL CONTRIBUTIONS

In this thesis we proposed the development of a methodology in order to broaden the indications of classical echocardiography and TDI from diagnosis to prognosis estimation and to monitor the effects of medications with potential prognostic impact.

The method involves the use of standard echocardiography and TDI with repeated determinations over time. Combined with strong and secondary endpoints, this method will allow the selection of ultrasound markers to identify early changes and detect early factors that may influence prognosis of dialysis patients.

Where the objective clinical situation does not allow it, markers could function as surrogate endpoints (as is the case in end stage CKD treated by hemodialysis).

The proposal is an important step for the individualization of dialysis treatment, the choice of concentrates, the evaluation of the individual consequences of ultrafiltration, the active intervention with cardio protective medication, in order to reduce the mortality of patients treated by hemodialysis (and not only).

Although in the current stage of development of the medical system in our country this method seems to lack an optimal cost / efficiency ratio, the increase in the number of doctors (ultrasound technicians) and devices I think will make the difference in favor of the proposed method.

Obviously, randomized and controlled studies on a large number of cases that provide statistical power are needed before implementing the method in order to establish appropriate ultrasound markers

Regarding the interventional sections of the thesis, the results of my studies support the intervention with ACE inhibitors / ARBs in dialysis patients beyond blood pressure control and support the use of furosemide in dialysis patients with delayed renal function to improve hydration parameters. I believe that both interventions can reduce long-term mortality in treated patients.