UNIVERSITY OF MEDICINE AND PHARMACY CRAIOVA

DOCTORAL SCHOOL

PhD THESIS

-ABSTRACT-

LEFT VENTRICULAR MASS INDEX AND ARTERIOVENOUS FISTULA FLOW AS CARDIOVASCULAR RISCK FACTORS IN CHRONIC KIDNEY DISEASE PATIENTS, STAGES 3-5D

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TABLE OF CONTENTS

INTRODUCTION

Chronic kidney disease (CKD) is a major health problem and has a growing prevalence in Romania and worldwide. The concept of chronic kidney disease (CKD) is defined by abnormal kidney function and/or structure persisting for more than 3 months, influencing patients health [1].

NHANES study (2005-2010) revealed a prevalence of 13.1% for patients with stages 3 and 4 CKD in the USA, and 8.5% prevalence of heart failure [2]. In Australia, AusDiab study revealed a prevalence of 4.8% for patients with glomerular filtration rate below 60 ml/min/1.73m2 between 2011-2012 [3].

People with CKD are at risk of developing end-stage renal disease requiring transplant or other renal replacement therapies. In Romania there has been a rise in dialysis patients from 5800 in 2003 to 10,470 at the end of 2012 [4].

Patients with chronic kidney disease have a 20-30 times greater risk for cardiovascular morbidity and mortality than similar individuals without chronic kidney disease [2, 5-8]. Increased cardiovascular risk is due to high prevalence of traditional and non-traditional (urea own factors) cardiovascular risk factors.

I chose this research topic because, in patients with CKD and end-stage renal disease, impaired cardiovascular function directly influences vital prognosis.

Keywords: left ventricular hypertrophy, chronic kidney disease, cardiovascular risk factors, arterio-venous fistula

1. **Summaries of the main parts**

1.1. State of knowledge

People with CKD are at risk of developing end-stage renal disease requiring transplant or other renal replacement therapies. In Romania there has been a rise in dialysis patients from 5800 in 2003 to 10,470 at the end of 2012 [4]. Patients with chronic kidney disease have a 20-30 times greater risk for cardiovascular morbidity and mortality than similar individuals without chronic kidney disease [2, 5-8]. According to NHANES 2005-2010, there is 42.9% prevalence of heart failure in patients with CKD, the prevalence of stroke (CVA) is 26.7% and the prevalence of heart failure is 15.1% [2].

Approximately 15% of CKD patients starting dialysis have left ventricular systolic dysfunction [9]. The prevalence of diastolic dysfunction at the start of dialysis is not completely known but is assumed to be high. Increased cardiovascular risk is due to the high prevalence of traditional and non-traditional (urea own factors) cardiovascular risk factors.

1.2. Cardiovascular risk factors in chronic kidney disease

Important epidemiological and interventional trials conducted in healthy population revealed that certain risk factors are associated with an increased rate of cardiovascular events. Same risk factors are reproducible in patients with renal impairment. (Table 1)

Table 1. Cardiovascular risk factors in CKD patients

Traditional risk factors	Uraemia specific risk factors	Dialysis related risk factors
Age	Hemodynamic overload	Modificări intra- şi interdializă a umplerii cardiace
Sex - male	Secondary hyperparathyroidism	Blood presure fluctuations
High blood presure	Anemia	Electrolyte fluctuations
Diabetes	Hypoalbuminemia	Arterio-venous fistula
Hyperlipidemia	High fibrinogen	Dialysis substance impurity
Obesity	Hyperhomocysteinemia	Incompatibility
Menopause	Dyslipoproteinemia	
Smoking	Resistance to insulin	
Inactivity	Increased Ca x P	
	Metabolic acidosis	
	Chronic inflammatory condition	
	Oxidative stress	
	Carbonyl stress	

After: Ursea N, Insuficienţa renală cronică, Tratat de nefrologie, Ediţia a II a, vol. I, Editura Fundaţiei Române a Rinichiului, 2006

1.3. Cardiovascular risk stratification in chronic kidney disease

Due to continuous growing trend of cardiovascular morbidity and mortality in the general population, it was necessary to implement algorithms for cardiovascular risk assessment.

The need of new computing systems to assess cardiovascular risk, wich include the presence or absence of uremia, had emerged. Currently, only QRISK2 includes CKD in estimating cardiovascular

risk along with age, sex, smoking status, total cholesterol/HDL-cholesterol ratio, body mass index (BMI), ethnicity, family history, the presence of rheumatoid arthritis, atrial fibrillation, diabetes and antihypertensive therapy [10].

1.4. Left ventricular hypertrophy

Left ventricular hypertrophy, defined as left ventricular mass index (LVMi) >131 g/m in men and >100 g/m in women, is the main manifestation of uremic cardiomyopathy and may contribute to the onset of extensive cardiovascular pathology in patients with CKD. LVH was observed in nearly 75% of patients at the start of dialysis.

LVH and heart failure represent an adaptive response to increased cardiac output. The volume and pressure overload act synergistically resulting in ventricular hypertrophy in patients with end-stage renal disease. Also traditional risk factors and uremia-related risk factors give their imput to LVH pathophysiology..

1.5. Arterio-venous fistula

Permanent vascular access is essential to perform adequate hemodialysis in uraemic patients. Arterio-venous fistula (AVF) is a surgically created connection between an artery and a vein, in order to be punctured repeatedly during hemodialysis sessions. Preffered placement of an AVF is [11]: radiocephalic fistula, brahiocephalic fistula, transposed brahiobasilic fistula.

Creation of permanent vascular access, represented by AVF, produces local and general changes in normal hemodynamics (Table 2) [12].

Tabel 2. Local and general hemodynamics changes due to AVF creation

Local hemodynamic disturbances	General hemodynamic disturbances
venous hypertension with turgid draining veins	increased preload to the right heart
venous arterialization	decrease in mean arterial pressure by reducing peripheral resistance
increase in venous oxygen saturation at 94-98%	increased heart rate
occurrence of turbulence phenomena expressed by thrill and bruit	increased cardiac output

After Ursea N and al. Rinichiul artificial și alte mijloace de epurație extrarenală. Fundația Română a Rinichiului, București, 39-147, 1997

2. Personal Research

2.1. STUDY I. Evaluation of uremic cardiomyopathy in chronic kidney disease patients, stages 3 - 5D

2.1.1. Objectives

We aimed to assess cardiovascular risk factors in patients with chronic kidney disease. We examined the prevalence and type of LVH, the role of anemia, diastolic dysfunction, age, body mass index (BMI) and albumin as risk factors for progression of chronic kidney disease. We calculated the risk of cardiovascular events for 10 years, accounted stroke or heart failure using QRISK2-2014 and highlighted its relationship with major cardiovascular risk factors.

2.1.2. Methods

We conducted a retrospective study that included 130 patients with chronic kidney disease (eGFR <60 ml min/1.73m2), who were hospitalized in the Nephrology Clinic of the Emergency County Hospital Craiova, between 1 January 2010 and June 1, 2014.

The subjects were divided into 4 groups according to the GFR, as follows:

Group A – stage 3 CKD - eGFR = 59 - 30ml/min/1,73m^2

Group B – stage 4 CKD - eGFR = 29 - 15ml/min/1,73m^2

Group C – stage 5 CKD - eGFR < 15ml/min/1,73m^2

Group D – stage 5D CKD - patients on hemodialysis under 3 months

Echocardiographic measurements were performed according to recommendations of the American Society of Ecocardiography (ASE) [13].

2.1.3. Results

Demographic, paraclinic and echocardiographic parameters of study group are presented in Table 3.

Table 3. Demographic, paraclinic and echocardiographic parameters

	Stage 3 CKD n=28	Stage 4 CKD n=30	Stage 5 CKD n=27	Stage 5D CKD n=45	P
Age (years)	60.3±12.2	60.7±13.6	57.9±16.4	56±22	0.63
Women (%)	8(29)	10(33)	12(44)	25(56)	0.09
HTN (%)	24(85)	24(80)	27(100)	33(73)	**0.03**
SBP (mmHg)	139.3±10.9	143.2±11.6	152.8±6.7	146.5±21.2	**0.009**
DBP (mmHg)	69.1±6.7	75±6.9	78.4±4.1	73.6±12.8	**0.003**
Diabetes (%)	16(57)	11(36)	2(7)	8(17)	**0.0001**

Hb (g/dl)	12.1±1.3	9.7±1.2	10.2±1.4	9.5±0.9	**<0.0001**
eGRF (ml/min/1.73m^2)	42.6±8	20.5±4.3	14.5±1.2	7.6±1	**<0.0001**
Uric acid (mg/dl)	6.31±1.41	6.97±1.79	7.55±1.72	8.09±6.13	**0.001**
C reactive protein (mg/dl)	1.16±1.30	1.33±1.87	2.85±2.46	3.53±2.17	**<0.0001**
Proteinuria (mg/24h)	45.61±25.01	153.72±139.07	250.24±241.54	490.57±368.06	**<0.0001**
IVS (mm)	13.1±1.9	12.9±1.9	13.5±1.7	13.2±1.7	0.64
PWT (mm)	11.7±1.6	12.5±1.8	12.8±1.8	13.9±2.3	**0.0001**
LVEDD (mm)	46±4.2	50.1±7.4	52.2±6.5	47±5.3	**<0.0001**
LVESD (mm)	34.3±6	38.7±10.1	41.8±7.2	34.2±3.9	**<0.0001**
LVMi (g/m^2)	119±23.1	165.1±56.1	198.1±64.6	248.6±126.5	**<0.0001**
LVH (%)	12(42)	21(70)	25(92)	37(82)	**0.0001**
LVVi (g/m^2)	42.19±18.77	59.40±37.51	64.20±37.06	39.41±18.37	**0.001**
RWT	0.52±0.11	0.51±0.11	0.49±0.08	0.60±0.13	**0.003**
mitral E velocity(m/s)	0.63±0.18	0.66±0.17	0.69±0.12	0.60±0.20	0.15
mitral A velocity (m/s)	0.65±0.12	0.69±0.11	0.76±0.15	0.79±0.09	**<0.0001**

Analysis of factors associated with LVH in the studied group

Overall prevalence of LVH was 73% and the degree of renal dysfunction (median eGFR) was higher in patients with CKD and LVH compared with patients without LVH (Student test p = 0.000923 - S). Concentric hypertrophy has been prevalent in our study (55%).

Although the number of hypertensive patients in the group with LVH is significantly higher as in the group of hypertensive patients without LVH (p Chi-χ2 = 0.02), the difference between the LVH degree in hypertensive vs. non-hypertensive patients, expressed by mean ± standard deviation of LVMI, does not reach statistical significance between the two groups (p = 0.631240 Student test - S).

Comparing several clinical and laboratory parameters between patients with LVH and those without LVH in the batch represented by CKD stages we observed that hemoglobin level was significantly higher in stage 3 CKD patients without LVH (p=0.01), CRP was significantly higher in stage 5D patients without LVH (p=0.01) and proteinuria was significantly lower in those without LVH in stage 4 CKD (p=0.01) and higher in those with stage 5D without LVH (p=0.008).

Serum hemoglobin levels and proteinuria are independent risk factors for LVH expressed as LVMi. CRP and proteinuria are directly correlated with the LVMi ($p<0.0001$), while the serum hemoglobin correlates inversely with LVMi ($p <0.0001$).

Anemia, diastolic dysfunction and LVMi were the most important risk factors for CKD progression ($p<0.0001$) and age, BMI and proteinuria had no prognostic value.

Analysis of LV dilatation and its role in uraemic cardiomyopathy

LVVi correlates directly with SBP, DBP, mitral E velocity and E/A and inversely with BMI. Only E/A ratio is an independent risk factor for LVVi progression ($p=0.006$).

We evaluated the predictive power of LVVi for LVH, hypertension and diastolic dysfunction by using the ROC curve. For all cases we reached statistical significance.

Analysis of diastolic dysfunction in patients with CKD

Diastolic dysfunction was present in 69% of patients and was directly correlated with the decline in eGFR ($p<0.0001$). Comparing the average E/A ratio in patients with LVH vs those without LVH, although there is a numerical difference, it does not reach statistical significance. However, it is clear that there are more patients with diastolic dysfunction in the LVH group ($p=0.05$).

We compared velocities, and for mitral A velocity differences were greater ($p<0.0001$) than for mitral E velocity ($p=0.381$). We examined the variability of mitral A velocity, and it is lower in stage 3 CKD than in stage 5 and 5D CKD. Also, mitral A velocity in stage 4 CKD is significantly lower than in stage 5 and 5D.

E/A ratio was significantly lower in stage 5D CKD than in other stages of the CKD ($p=0.001$).

Heart failure patients with CKD

Overall prevalence of heart failure was 72%. We analyzed the predictive power of the LVMi and diastolic dysfunction for heart failure, using ROC curve. Both cases reached statistical significance ($p <0.0001$).

Cardiovascular risk in the study population

I estimated the cardiovascular risk with QRISK2, by age groups and found that cardiovascular risk increases with age ($p <0.0001$). Cardiovascular risk estimated with QRISK2 directly correlated with eGFR ($p=0.037$), SBP ($p=0.001$), DBP ($p=0.001$) and age ($p<0.0001$). Medium and increased cardiovascular risk, stratified by CRP, was associated with increased prevalence of LVH (p Chi-χ2=0.001).

2.1.4. Discussion

There were no statistically significant differences regarding age or sex. Male gender prevailed in our study similar with other studies [14] but discordant with the USRDS, where the percentage of women with GFR <60 ml/min/1.73m2 was higher that that of men, and with recent data from England, Canada and the Netherlands [15, 16, 17]. More than half of the patients had concentric LVH. Eccentric hypertrophy and concentric remodeling were present in equal quantities. There was a fairly significant number of patients with concentric remodeling, which is an important predictor of predisposition to impaired LV morphology and appearance of either concentric or eccentric LVH.

LVH concentric type morphology betrays the presence of hypertension as pression overload factor and in our study the group of hypertensive patients with LVH was significantly higher than those without LVH.

However comparing the average value of LVMi among hypertensive patients and those without hypertension didn't find statistically significant differences. This can only mean that other co-factors in the etiology of LVH such as loss of elasticity of the blood vessels or the presence of vascular calcification leading to increased pulse pressure were present. LVMi has proved a highly predictive factor for LVH and hypertension.

Asymptomatic LV dilatation is associated with increased cardiovascular risk [18], and now left atrial volume (LAV) has a major impact in terms of mortality in patients with LVH and end-stage renal disease [19, 20].

In our study mitral A velocity has increased progressively with CKD stage. E/A ratio was significantly greater in patients with less impaired renal function. Lower value of mitral A velocity in stage 3 vs stage 5 and 5D, and also stage 4 vs 5 and 5D, as more severe degree of diastolic dysfunction in end-stage CKD patients suggest that LV filling pressure is higher in stage 5D (hemodialysis) patients. This is possible probably due to the phenomenon of volume overload in patients on hemodialysis.

We applied the QRISK2 score for patients in our study and found a strong correlation with age and systolic and diastolic blood pressure values. It also correlated with eGFR but although we expected that average number of cardiovascular risk to be higher as eGFR decline (negative correlation), this does not happen, probably because of the close correlation with age, as in our study in stages 5 and 5D medium age is lower than in stages 3 and 4 CKD.

We stratified cardiovascular risk with CRP values according to the AHA/CDC classification and found that medium and increased cardiovascular risk associated with the LVH prevalence. Also patients in stages 5 and 5D CKD have an increased cardiovascular risk.

2.1.5. Conclusions

- Echocardiographic changes of LV are present in most patients with CKD.

- The prevalence of LVH increases with the degree of renal function decline.

- Cardiovascular mortality and morbidity are influenced by the presence of LVH, diastolic dysfunction and LV dilatation.

- LV diastolic dysfunction is present in all patients with renal impairment, was more frequent with the degree of renal dysfunction and is an independent predictor of new onset heart failure.

- Hypertension, anemia and inflammation are factors with a negative impact on LVH and on cardiovascular risk in patients with CKD.

- The emergence of new methods of assessment and evaluation of cardiovascular risk in patients with CKD is useful but still requires greater adaptation to the "needs" of patients with CKD.

2.2. STUDY II. Hemodynamic impact of arteriovenous fistula in hemodialized end-stage renal disease patients

2.2.1. Objectives

Serial echocardiographic monitoring of dialysis patients can provide useful information in detection of cardiac changes that may result in adverse cardiovascular events. Doppler ultrasound evaluation of the vascular bed prior to the arteriovenous fistula placement should be required to make a successful vascular access, as well as maturing and evolving.

We aimed to evaluate echocardiographic changes in a group of hemodialysis patients and assess by Doppler sonography relationships between the fistulas flow and cardiac output.

2.2.2. Methods

Between February 1, 2014 and August 15th 2014, we conducted a prospective observational study that included 33 patients on hemodialysis. All patients were performing hemodialysis for at least 6 months, 3 sessions per week at IHS Haemodialysis Centre in Craiova.

Permanent vascular access had 3 locations: radio-cephalic (Group A), brahio-cephalic (Group B) and brahio-basilica (Group C).

All patients were evaluated by standard 2-D, M-mode and Doppler cardiac and AVF ultrasound. We used a Siemens Sonoline Prima SLC device in the Internal Medicine Clinic of Military Emergency "Dr. Stefan Odobleja" Craiova Hospital.

2.2.3. Results

There were 17 women and 16 men, mean age 49.64 ± 15.72 years. The average duration of renal replacement therapy from the onset and until inclusion in the study was 29.30±15.84 months. There were no statistically significant differences between the 3 types of fistulas average duration, although radio-cephalic and brahio-cephalic fistuls had a longer duration of use.

Comparative analysis of clinical, laboratory and ultrasound parameters at baseline according to the distribution of the groups

There were no statistically significant differences in terms of age, systolic or diastolic blood pressure, presence of hypertension or diabetes, but the prevalence of females is remarkable both in the overall group, as well as lots brahiocephalic and brahiobasilic fistulas (p = 0.009).

IVS and PWT were significantly higher in patients with radiocephalic fistula vs those with brahiobasilic fistula (p=0.015). The volume index of LV (LVVi) was significantly higher in patients with brahiocephalic fistula vs those with radiocephalic and brahiobasilic fistulas (p=0.048).

Vein diameter and area were significantly lower in patients with radiocephalic fistula vs brahiobasilic and brahiocephalic fistulas (p=0.002). This together with the fact that the average flow for a radiocephalic vein was significantly lower than that of veins flows in brahiobasilic and brahiocephalic fistulas (p <0.0001), means that at level 0 vascular bed is reduced in size.

Regarding the feeding artery of the fistula, velocity indices and its diameter were significantly higher in patients with brahio-basilica and brahio-cephalic fistulas, than those with radio-cephalic fistula. Flow showed no significant changes.

Overall prevalence of LVH at time 0 was 55% and concentric LVH predominated (43%). Normal LV geometry had 36% of patients and 12% of them had eccentric LVH. Pressure and volume overload are acting on dialysis patients and I noticed that the ejection fraction and SBP are factors of LVH progression.

LV dilation expressed as the LVVi >90 g/m^2 was present in 18% of patients at baseline. Diastolic dysfunction represented by the ratio E/A <1 was present in 58% of patients at baseline.

A percentage of 36% of patients had heart failure. Fistula's venous flow was significantly higher in patients with heart failure than in patients without heart failure (p<0.001).

I wanted to know fistula's flow threshold from which heart failure occurs. This value is 1170, with Sn (85.71%) and Sp (80.0%), representing a viable threshold to discern between patients with or without heart failure, Figure 1.
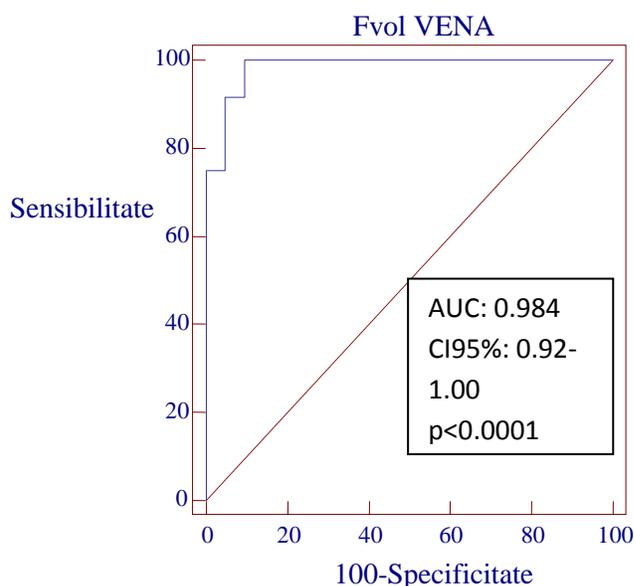
Fvol VENA

AUC: 0.984
CI95%: 0.92-
1.00
p<0.0001

Sensibilitate

100-Specificitate

Figure 1. ROC curve for fistula's flow and heart failure

Comparative analysis of clinical, laboratory and ultrasound parametres at visit 1 according to the group distribution

In patients with brahiobasilic fistula, PWT and IVS were higher than those with radio-cephalic fistula (p=0.047). In patients with brahiocephalic fistula, LVVi was higher than patients in the other two groups (p=0.041). Mitral A velocity was higher in patients with brahiocephalic fistula than those with brahiobasilic and radiocephalic fistulas (p=0.008).

There were statistically significant differences between fistula's flow ultrasound parameters through the artery and the vein:

- PI of the vein was higher in patients with brahiocephalic fistula vs. radiocephalic fistula patients (p=0.046)
- PSV from the vein was lower in patients with radiocephalic fistula vs. brahiocephalic and brahiobasilic fistulas (p=0.002)
- TAMX and MDV of vein were higher in patients with brahiobasilic fistula vs. brahiocephalic and radiocephalic fistulas (p<0.0001 and p=0.002)

- vein diameter and area were lower in patients with radiocephalic fistula vs. brahiocephalic and brahiobasilic fistulas (p=0.030 and p=0.010)

- vein TAV and Fvol were lower in patients with radiocephalic fistula vs brahiocephalic and brahiobasilic fistulas (p<0.0001)

- PSV, MDV and TAMX of the artery were lower in patients with radiocephalic fistula vs. brahiocephalic and brahiobasilic fistulas (p<0.0001)

- diameter and area of the artery were lower in patients with radiocephalic fistula vs. brahiocephalic and brahiobasilic fistulas (p=0.038 and p=0.027)

- Fvol and TAV of the artery were lower in patients with radiocephalic fistula to brahiocephalic fistula (p=0.052 and p=0.016)

It was observed that ejection fraction and shortening fraction are factors of progression of LVH.

Comparative analysis of clinical, laboratory and ultrasound parameters at visit 2 depending on group distribution

Notably, at the time of the final evaluation, after six months from the time of enrollment, paraclinical parameters revealed the following situations:

- IVS and PWT were lower in patients with brahiobasilic fistula to those radiocephalic fistula (p=0.011); LVMI was lower in patients with brahiobasilic fistula to patients with radiocephalic and brahiocephalic fistulas (p=0.016 and p=0.006)

- ejection fraction and shortening fraction of LV are lower in patients with brahiocephalic fistula vs. patients with radiocephalic fistula (p=0.006 and p=0.003)

- vein PSV, MDV and TAMX are higher in patients with radiocephalic fistula vs brahiobasilic and brahiocephalic fistulas

- veins flow volume was lower in patients with radiocephalic fistula vs. brahiocephalic and brahiobasilic fistula (p = 0.004, p = 0.043)

- PSV, MDV, TAMX, TAV and Fvol of the artery were significantly lower in patients with radiocephalic fistula vs. brahiobasilic and brahiocephalic fistula

It was observed that cardiac output, ejection fraction and shortening fraction are factors of progression of LVH.

Comparative analysis of clinical, laboratory and ultrasound findings in dynamic

Although several variables have an up or down trend, statistically significant differences were only for resistivity index (RI) in the vein, which increases progressively with time and that DBP

decreases gradually with time. The increase in the IR means an increased resistance to blood flow at the periphery. We observed decrease in PSV and MDV but without statistical significance.

Mean hemoglobin values increased during monitoring (p=0.004), which shows a better management of anemia in dialysis patients. The mean serum albumin also increased.

Comparing the mean value of LVMi, we found a decrease in LViI between baseline and visit 2, without statistical significance (p=0.819). LVVi also decreased during follow-up butwe reach no statistically significant differences (p=0.555).

Diastolic dysfunction, represented by the average ratio E/A, has remained relatively constant. Both ejection fraction and shortening fraction of LV had an increasing trend over time, without statistical significance.

Cardiac output decreased during the 6 months of follow-up, but without statistical significance. Cardiac output was higher in patients with brahio-cephalic and radio-cephalic fistulas. Venous flow in the radiocephalic fistula was significantly lower than the other fistulas (p=0.0001) and had a discrete upward trend. Statistically significant correlations between cardiac output and fistula's arterial flow were present only in patients with radiocephalic fistula.

Cardiovascular risk assessment using QRISK2 – 2014

We evaluated a link between cardiovascular risk estimated by QRISK2 and various cardiovascular risk factors present in patients with end-stage CKD, using Pearson correlation coefficient. The data obtained are shown in Table 5.

Table 5. Cardiovascular risk assessment using QRISK2

Factor	r	p
Hb	0.234	0.189
Vârsta	0.702	**<0.0001**
Col/HDL	0.829	**<0.0001**
iPTH	0.321	**0.053**
uree post-dializă	0.415	**0.016**
LVMi	-0.153	0.392
LVVi	-0.029	0.871
E/A	-0.365	**0.036**
TAS	0.416	**0.016**
TAD	0.227	0.202
Debit cardiac	0.359	**0.040**
Fvol venă	-0.097	0.590
Fvol arteră	0.013	0.942

2.2.4. Discussion

Overall prevalence of LVH at baseline was 55%. The concentric type of LVH was predominent (43%), but there was a fairly large group of patients with eccentric LVH (12%), so we can say that both pressure overload and volume overload are present in the study group. According to Middelton et al. in patients with CKD on hemodialysis is better to estimate LVH by LV volume index (LVVi) and not using relative wall thickness (RWT) because it turned out that this can be estimated in a higher risk of cardiovascular morbidity and mortality [21]. LV dilation expressed as the LVVi >90 g/m^2 was present in 18% of patients at baseline.

There are several mechanisms associated with LVH, which contribute to increased cardiovascular risk in patients with CKD. LVH is associated with myocardial fibrosis and diastolic dysfunction, as a major factor in the development of heart failure. In our study, diastolic dysfunction was present in 58% of patients at baseline and heart failure at 36% of patients. Patients with heart failure had a fistula flow significantly higher than in patients without heart failure. Fistula threshold value output for heart failure is 1170 ml/min. In dialysis patients may appear high output cariac failure due to increased flow of vascular access. Thus, a significant amount of arterial blood passes through the fistula into venous circulation and increases the preload, wich increases cardiac output. As result, in time, volume overload produces cardiac hypertrophy, and on a heart with diastolic dysfunction, heart failure [22].

Currently, most of the literature argues that LVH in dialysis patient is irreversible, and any increase in LVMi is associated with increased risk of cardiovascular events in these patients [23]. However, in recent years, different studies showed a regress of LVH in dialysis over the years, through adequate control of anemia, prevention or control of hyperphosphatemia, hyperhydration and in patients after a transplant was performed [24, 25].

In our study LVMi decreased over time, but this did not reach statistical significance.

A positive outcome in our study was the improvement of the ejection fraction and shortening fraction of LV, although not reaching statistical significance, the numerical differences are obvious. Probably a long period of follow-up would definitely be inclined to a positive balance.

Cardiac output decreases during the 6 months of follow-up, but was higher in patients with FAV brahiocephalic and radio-ephalic fistulas, than those with brahiobasilic fistula. The results suggest that the reduction in cardiac output after hemodialysis is related to the redistribution of blood volume away from the heart. Performing a correlation analysis between cardiac output and venous flow through the fistula, showed no statistically significant correlations were identified. Statistically

significant correlations between cardiac output and arterial flow were present only in patients with radio-cephalic fistula.

Throughout the study fistula's vein diameter and area were significantly lower in patients with radiocephalic fistula to brahiobasilic and brahiocephalic fistulas. This together with the fact that the average flow for radiocephalic fistula was significantly lower than that of veins flows for brahiobasilic and brahiocephalic, betrays that vascular bed level 0 is smaller in size. However there is no difference between the flow rate or the blood pulse wave parameters.

We evaluated a link between cardiovascular risk estimated by QRISK2 and various cardiovascular risk factors present in patients with end-stage CKD. The age and the cholesterol/HDL-cholesterol ratio are strongly correlated with QRISK2. The value of iPTH, post-dialysis urea, SBP and cardiac output correlates directly proportional to cardiovascular risk, while E/A correlated inversely with QRISK2.

Unfortunately there was no evidence of a correlation between arteriovenous fistula flow and cardiovascular risk, betraying this complex pathophysiology behind fistula's hemodynamics, and the need to assess in real-time, the risk of cardiovascular morbidity and mortality.

2.2.5. Conclusions

- Left ventricular hypertrophy has a high prevalence in dialysis patients and increased LV mass index is a major cardiovascular risk factor

- Concentric and eccentric ventricular hypertrophy are present simultaneously in hemodialysis patients

- LVH regression is possible, but requires an interventional approach on cardiovascular risk factors (anemia, blood pressure, secondary hyperparathyroidism) in hemodialysis patients

- Patients on dialysis with a higher fistula flow, over 1170 ml/min have heart failure, and the fistula's constant increased flow is a risk factor for heart failure with a high flow.

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