RAS Inhibition in Haemodialysis Patients
Impact on mortality

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Patients with chronic kidney disease (CKD) represent a special category of risk. As part of the renal and cardiovascular continuum from risk factors to end stage diseases, they develop clinical syndromes with potentially severe prognosis. Patients on dialysis have severe cardiac risk, have a peculiar hyperlipemic profile with intense atherogenic effect, phosphocalcic metabolic alterations and thus a higher rate of development of atheroma and degenerative valve diseases. They have higher cardiovascular mortality and morbidity being potential candidates for aggressive reduction of risk factors. Dialysate patients are exposed to higher risk of ischemic and arrhythmic events. Echocardiographic assessment of these patients is extremely important in risk stratification and treatment strategy in order to improve prognosis. Drugs proved to improve cardiac remodeling, reduce hypertrophy and LV mass and enhance ejection fraction, improved prognosis.

Keywords: chronic kidney disease, hemodialysis, cardiovascular risk

Cardiovascular continuum established more than 20 years ago proved to be extremely actual and the medical effort is focused on breaking this continuum in any of its part: risk factor control, control of comorbidities, slowing progression of the cardiac disease, developing strategies in order to reduce sudden cardiac death, cardiac failure or major adverse cardiac events (MACE). Chronic kidney disease with or without albuminuria represents a risk factor for cardiac disease [1-3].

In the special situation of a haemodialysed patient, his cardiac and vascular condition might be at risk and the disease growth rapidly because his metabolic condition , acidotic milieu, the entire enzimatic mechanism favoring the atherogenesis and oxidative stress [4-7, 9]. The angiogenesis develops slower than hypertrophy so oxigen diffusion is prolonged at least 25%. Even mild renal failure is associated with reduced coronary flow reserve in patients with non-obstructive coronary artery disease and this reserve decreases ones more in hypertensive dialysed patients [10-12]. Microvascular remodeling determins capillary number reduction, increased ration wall/lumen, reduction of vascular lumen, functional occlusion and vascular rarefaction. High blood pressure precipitates left ventricular hypertrophy which also represent a high risk for sudden cardiac death due to arrhythmic and ischaemic events. Together with vascular changes due to chronic kidney disease, metabolic changes of the disease itself - albumin to creatinine ratio (A/CR) is positively related to plaque initiation and plaque growth. This relationship is substantially modified by fibrinogen in previously plaque free subjects. eGFR <60 mL/min/1.73 m² and A/Cr >1.1 mg/mmol (10 mg/g) are independent predictors of CV mortality risk in the general population. Lipidemic profile with small and dense LDL cholesterol, low HDL cholesterol is highly atherogenic. phosphocalcic metabolic alterations expose to a higher rate of development of atheroma and degenerative valve diseases. All these changes are well established before the initialization of dialysis. Treatment of high blood pressure in the predialysis phase changes in dosage and strategy during hemodialysis.

The aim of this study is to investigate the impact of blood pressure control with ACE inhibitors or AT1 receptor blockers known to be efficient in reducing left ventricular hypertrophy and the best strategy in order to improve prognosis.

Experimental part

Material and methods

We studied 1200 dialysed patients with mean follow-up of 3 years. Mean age 57.8±2.3 years old, 52% men, being on dialyses treatment of the average duration of 6.5±2.3 years.

In all patients we performed clinical exam, standard electrocardiography (ECG), transthoracic echocardiography in M mode, 2D, color and spectral flow Doppler parameters, to assess morphology and cardiac performance. The ECG and ECO evaluation were performed during hemodialysis procedure.

In a pilot group we evaluate eco parameters before and after dialysis and we noticed significant changes in left atrial dimension, LV EDD - left ventricular end diastolic diameter and diastolic filling according to mitral flow pattern. These parameters are highly influenced by fluid retention and varies in different moments of dialysis, being then of low interest in long term prognostic assessment and mimicking other clinical situation of fluid retention [8,9]. In order to keep the evaluation simple we assess left ventricular dimensions and hypertrophy, left ventricular mass, left ventricular ejection fraction (EF), endomyocardial calcification, valvular changes, presence of pericardial effusion table 1.

Statistical analysis

Two-group comparisons were performed using t-test and Fisher test, correlation has been evaluated with Pearson test. Statistical significance was considered if $p < 0.05$.

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Table 1
ECHOCARDIOGRAPHIC DATA

Ecocardiographyc changes	Changes prevalence%
Normal	11
Left ventricular hypertrophy	74
Dilatation	43
Degenerative valvular changes	41
Ischaemic valvular changes	18
EF	Atention associated valvulopathy
Pericardial effussion	28
Endomiocardial calciffication	19
Pulmonary hypertension	28
Ecocardiographyc changes before and after dialysis	
Left atrial dimension	
end diastolioc diameter	
Diastolic filling	

Results and discussions

In our studied population we find only 11% of patients with normal eco parameters, the rest have left ventricular hypertrophy in 74%, dilatation 43%, degenerative valvular changes 41%, valvular incompetence associated with ischemia 18%. Regarding the efficacy of dialyses we assess pericardial effusion, endomyocardial calcification 19% and pulmonary hypertension - assessed on tricuspid flow.

We measured LV morphologic parameters: EDD - end diastolic diameter, ESD - end systolic diameter, IVS-interventricular septum, LV mass calculated with Devereux formula, and functional parameters and their dynamic: ejection fraction EF, diastolic filling through Appleton pattern. At the same time we assess endomyocardial calcification and degenerative valvular involvement. All data assimilate EF as the most powerful prognostic parameter. But ones have to discriminate between real improvement in EF because positive remodeling and changes in EF due to hemodynamic changes in pressure or, most frequently, volume overload in valvular involvement. We compare all parameters at the beginning of the study and after 3 years on dialysis for the survival and deceased patients. There are significant differences between the two groups ($p=0.00034$) in all morphologic parameters and also EF as shown in figure1.

Patients who survive have rather normal LV dimensions, EF in normal range and varying in years also in normal range over 50%. On the other hand, deceased patients have significant higher EDD and ESD, *thicker* hearts with IVS 15 ± 2.8 and impaired EF $41\pm3.7\%$.

We assessed the impact of different medications on survival. Those which had the most important impact were also those which proved to induce positive remodeling [13]. Blood pressure control with RAS inhibitors – ACE inhibitors or *sartans* (in case of cough), had the best prognosis. In figure 2 the difference after 3 years of treatment in patients with and without RAS inhibitors is shown, taking into account that we compare patients with the same characteristics (etiology, age, comorbidities, duration of dialysis treatment), and in whom we achieved blood pressure control.

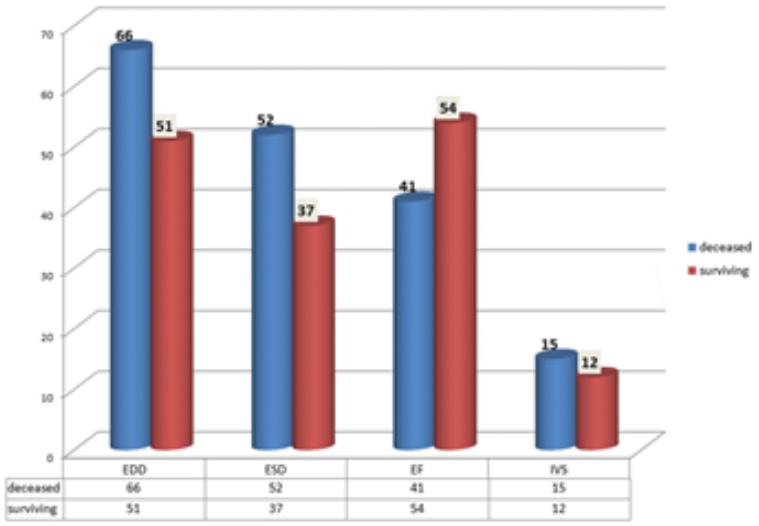

Fig. 1. Eco parameters in surviving and deceased patients

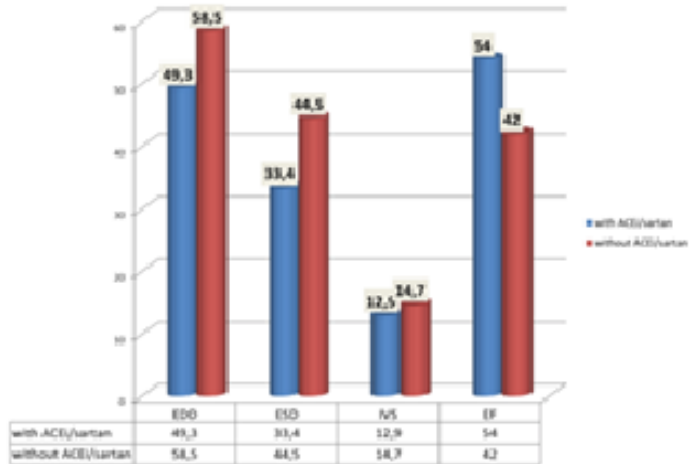

Fig. 2. Changes in eco parameters in patients treated with ACEi or sartans

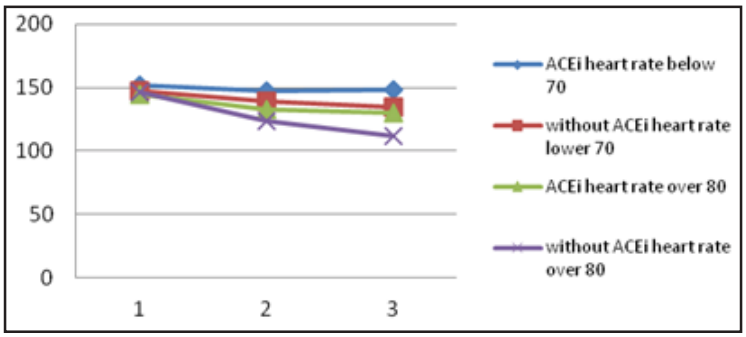

Fig. 3. Kaplan Mayer survival curves according to treatment and heart rate

Heart rate was another strong factor that influenced prognosis. It is common knowledge now (after Beautiful and Shift trials) that target heart rate is 62 b/min in patients without anemia. Survival curves showed that best prognosis was achieved in patients treated with RAS inhibition with near normal morphologic parameters and with heart rate below 70 b/min as showed in figure 3.

The principal causes of death in dialysis patients are cardiovascular events and infections. We have to control blood pressure, ischemia but also factors that can precipitate MACE such as diselectrolitemia and anemia.

Conclusions

Efficient hemodialysis procedure is an important step in order to control high blood pressure but LV hypertrophy of hypertensive dialysed patient (DP) has some peculiarities like higher risk of ischemic and arrhythmic events.

ACE inhibitors and betablockers at the highest tolerated dose decreased cardiovascular morbidity and mortality and improved quality of life. Small doses of these drugs proved to be effective even in patients where hemodialysis alone was enough to control blood pressure. ACE inhibitors reduced hypertrophy and improved diastolic filling.

Antiischemic treatment, active surveillance of arrhythmias, control of blood pressure and electrolytes are of paramount importance. Changes in treatment according to guidelines improved blood pressure control, echo parameters and dialysis flow. All of these are main contributors for better prognosis.

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