Cardiovascular Complications in Chronic Kidney Disease

Ph.D. theses

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Pécs

2012.

1. Introduction

Patients with chronic kidney disease (CKD) generally die of cardiovascular disease (CVD), before even requiring renal replacement therapy. Although we know that any degree of decreased renal function or any proteinuria increases cardiovascular (CV) risk the mechanism linking CKD and CVD are not fully explained. Beyond tradicional risk factors like hypertension, diabetes, obesity and lipid abnormality nontradicional risk factors are referred as subclinical target organ damage as well like arterial stiffness, dysfunction of the vegetative nervous system, microalbuminuria, or chronic kidney disease.

1.1 Arterial stiffness

The arterial system has two interrelated haemodynamic function: to deliver an adequate blood supply from the heart to the peripheral tissues (the conduit function) and to dampen blood flow and pressure oscillation caused by the intermittent character of the left ventricle (LV) ejection ensuring peripheral organ perfusion at steady flow (the dampen function). About 50 % of stroke volume would be stored during systole in the aorta and large elastic arteries stretching the arterial walls. During diastole the accumulated energy recoils the aorta squeezing the stored blood forward ensuring a continuous flow. The ability of arteries to accommodate the volume ejected by the LV instantaneously can be described as arterial compliance or stiffness. Every heart cycle raises a pressure wave transmission along the arterial system. In the case of increasing arterial rigidity this pressure wave travels more quickly. This traveling can be characterized by the pulse wave velocity (PWV).

We focused our attention on damaged vascular function as one of the nontradicional mechanisms responsible for disproportionate CVD burden in CKD patients. Longitudinal epidemiologic studies have demonstrated the independent predictive value of arterial stiffness on cardiovascular outcome in hypertension, diabetes and in patients with with end-stage renal disease. However, the relationship between arterial stiffness and kidney function in nonuremic patients with homogenous chronic renal diseases is unclear.

1.2. The autonomic nervous system

Autonomic nervous system (ANS) regulates multiple physiological processes including heart rate, blood pressure and CV responses to physical or mental stress. Autonomic imbalance with increased sympathetic activity and decreased parasympathetic tone, have been shown to be a risk factor for CV morbidity and mortality. Recently has been published data about the increased sympathetic activity in end-stage renal disease. It has been described many non-invasive measures which represent the function of the ANS like resting heart rate, hart rate variability, baroreflex sensitivity or heart rate recovery (HRR). During graded exercise test the heart rate increases as a result of withdrawal of the parasympathetic tone and increased sympathetic activity. After the peak during recovery the heart rate decreases depending to the reactivation of the parasympathetic tone and the decrease of the sympathetic activity. Earlier studies have evaluated the prognostic significance of HRR in patients with different cardiac diseases. Attenuated HRR has been described as a predictor of total mortality and sudden cardiac death in coronary artery disease, heart failure, left ventricular dysfunction, and after coronary artery revascularization. Cardiovascular risk is

increased with any decrease in kidney function. However, any relationship between HRR and renal function is unexplored.

1.3. The investigated types of kidney diseases

1.3.1. IgA nephropathy

IgA nephropathy (IgAN) is the most common, nondiabetic immunologically mediated glomerular renal disease in the world. The disease generally progresses slowly over 20 years and thus is very suitable for longitudinal cardiovascular risk assessment of blood pressure, lipid value, smoking and proteinuria severity.

1.3.2. Polycystic kidney disease

Polycystic kidney disease (PKD) is the most common inherited renal disease and occurs in 1 of 400-1000 individuals. In most of cases it shows an autosomal dominant inheritance and two genes (polycystin gene 1 and 2) are implicated in its development. The clinical picture is characterized by cystic involvement of the kidneys with slow progression to ESRD and by some extrarenal cardiovascular manifestations e.g. intra- et extracranial aneurysms, and cardiac valvular defect. It is accepted that cardiovascular complications are the main cause of death also in PKD.

2. Aims of the studies

- To assess the arterial stiffness in a type of homogenous chronic renal disease, in IgAN, and determine the possible confounding factors influencing the arterial stiffening.
- To investigate the arterial stiffness and compare it in two ethiologically different homogenous chronic renal disease, in IgAN and PKD.
- To asses the HRR in IgAN and analyse its connection with the kidney function and other CV risk factors.

3. Clinical investigations

3.1. Arterial stiffness in chronic kidney disease

3.1.1. Arterial stiffness in IgA nephropathy. The role of the metabolic parameters

We investigated 107 IgAN patients (68 male, 37 female, 45±11 years of age). The tradicional CV risk factors (age, gender, hypertension, diabetes, obesity, lipid abnormality, smoking habit, and the complete metabolic syndrome-MetS) were analyzed. We performed 24 hour-ambulatory blood pressure monitoring (ABPM) at every patient. An estimated glomerular filtration rate (eGFR) was given calculated by the Cockroft-Gault method. The control group contained 35 patients they were free from any renal disease. The renal patients were divided into three groups according there kidney function. Group 1 (eGFR ≥ 90 ml/min - CKD1 stage, n=45); Group 2 (eGFR 60-89 ml/min, CKD 2 stage, n=37); and Group 3 (eGFR 15-59 ml/min, CKD 3-4 stage, n=23).

Several methods are available for the determination of pulse wave velocity (PWV), including carotid-femoral or brachial-ankle PWV, applanation tonometry, and echo tracking. All reflect the stiffness of the great arteries A simple and validated method for the estimation of PWV is finger photoplethysmography. The method enables determining the stiffness index (SI), which can be derived from the digital volume pulse (DVP) and is reflected as SI_{DVP}. We used the Pulse Trace system (Micro Medical Ltd. Rochester, UK) for the estimation of arterial stiffness. A finger clip containing an infrared-light emitting diode and a receiver was applied to the index finger of the dominant hand. DVP comprises two distinct waves within one cardiac cycle, an early systolic peak arising from pressure wave propagating from the heart along the arterial tree to the finger followed by a delayed second peak caused by pressure wave reflected backward mainly from the aortic bifurcation. The time between the first peak and the inflection point in the waveforms was determined (ΔT_{DVP}). SI_{DVP} was calculated by the following equation: SI(m/s) = body height/ΔT_{DVP} . A single waveform was obtained by averaging DVP contours during a period of 30 sec. To enhance the accuracy of the investigation of SI_{DVP} five period samples were taken and the upper and lower merit of DVP was deleted. The remaining three merits were averaged and used in further analysis.

3.1.1.1. Results

SI_{DVP} of the CKD 3-4 and CKD 2 patients was significantly higher, than SI_{DVP} of the control group (11.11 m/s vs. 8.71 m/s; $p < 0.001$), and (10.36 m/s vs. 8.71; $p = 0.013$, respectively). We did not find any difference in SI_{DVP} between control group and CKD 1 group (8.71 m/s vs. 9.27 m/s, p = NS, **Fig. 1**). It was found a significant negative correlation between eGFR and SI_{DVP} : r = -0,304; p = 0,002**; Fig. 2**).

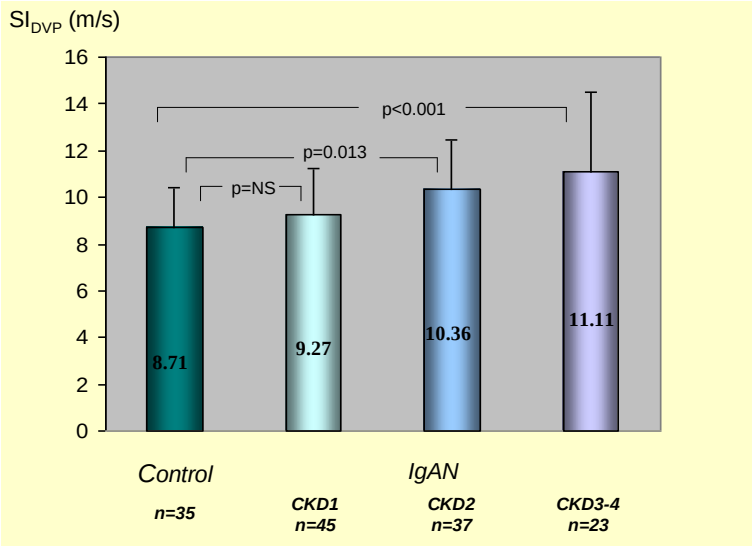


Fig. 1. SI_{DVP} across the different groups

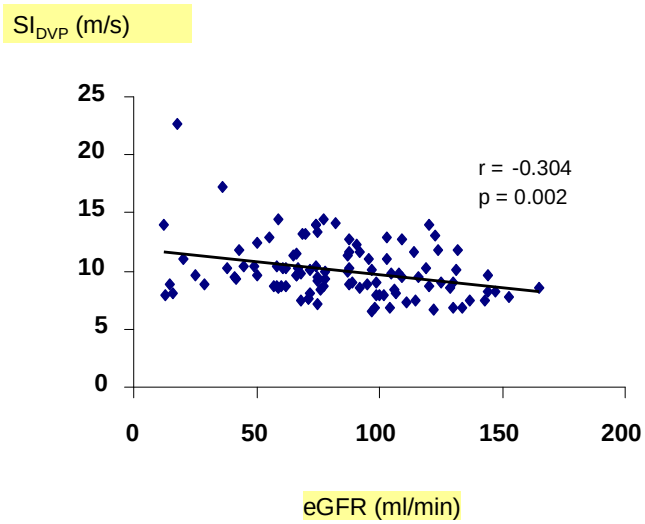


Fig 2. Correlation between SI_{DVP} and eGFR

Twenty nine from the investigated 105 IgAN patients had MetS. Theirs SI_{DVP} was slightly higher, than the patients without MetS, but the difference was not significant (10.65 m/s vs. 9.83 m/s, p = NS). Patients having at least two or more metabolic risk factors had higher SI_{DVP} than patients with one or zero risk factor (10.43 m/s, vs. 9.12 m/s; p = 0.006).

Univariate and multivariate analysis was performed to investigate the influence of 11 confounding factor on arterial stiffness. In univariate model age, hypertension, eGFR and dyslipidemia was in connection with SI_{DVP}, while in multivariate analysis only age and hypertension had an independent effect on SI_{DVP}.

Patients with uncontrolled blood pressure (on ABPM more than 130/80 mm Hg) had significantly higher SI_{DVP} than patients with well controlled blood pressure (on ABPM ≤ 130/80 mm Hg), or patients without hypertension (**Fig. 3**).

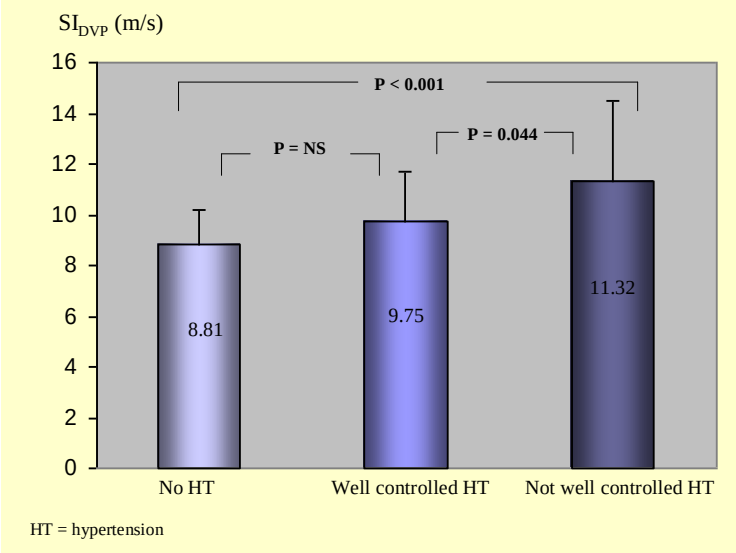


Fig 3. SI_{DVP} depending on blood pressure control

3.1.2. Different effect on arterial stiffness of IgA nephrpathy and polycystic kidney disease

In a cross-sectional study 120 CKD (60 with IgAN and 60 with PKD) and 50 control patients were investigated. Their arterial stiffness was compared. To asses the arterial stiffness we used the photoplethysmographic method, and the SI_{DVP} was determined. The method of the measuring is detailed above.

3.1.2.1. Results

Arterial SI values were as follows: Controls: 8.87 m/s, IgAN group: 9.66 m/s, PKD group: 11.14 m/s. The SI_{DVP} of PKD group was significantly higher than SI_{DVP} of IgAN patients and controls ($p<0.001$ in both relation) while there was no significant difference in SI_{DVP} values between IgAN group and controls (**Fig. 4*).***

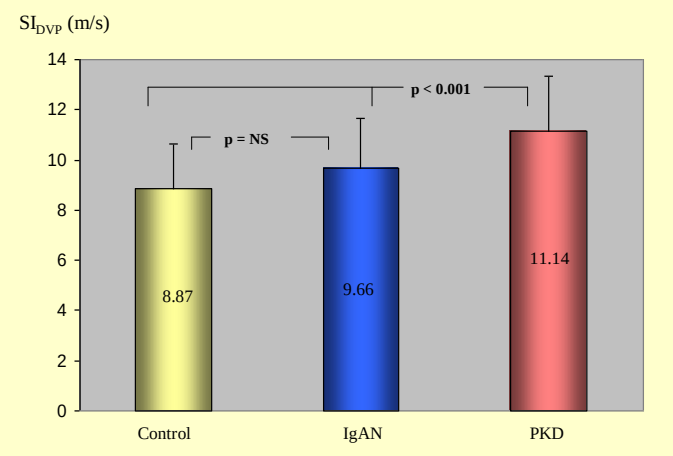


Fig. 4. SI_{DVP} in the CKD and control groups

The two groups of renal patients were matched according to their eGFR. There were 24 patients in CKD 3-4 (eGFR 15-59 ml/min) and 36 patients in CKD 1-2 stage (eGFR ≥ 60 ml/min), in both IgAN and PKD groups. We found that SI_{DVP} of CKD 3-4 IgAN patients was significantly higher, than controls (10.43 m/s vs. 8.87 m/s, $p<0.05$) while SI_{DVP} of CKD 1-2 IgAN patients (9.15± m/s) did not differed significantly from controls **(Fig. 5).**

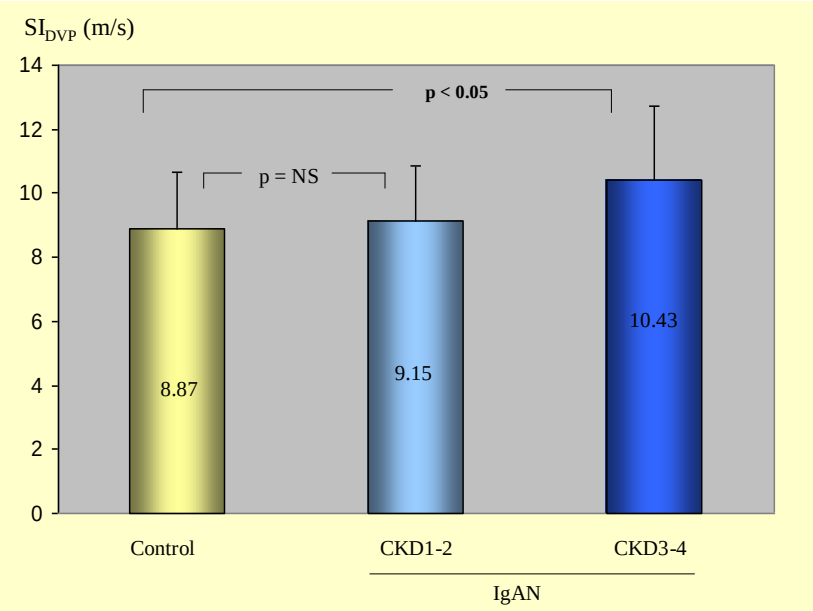


Fig. 5. SI_{DVP} in the IgAN subgroups

There was a not significant increase in the stiffening of the CKD 3-4 patients compared to the CKD 1-2 IgAN patients. In PKD patients the SI_{DVP} in both groups (CKD3-4

and of CKD1-2 patients) was significantly higher, than in controls (11.41 m/s and 10.95 m/s vs. 8.87 m/s, p<0.001, respectively, (**Fig. 6)**.

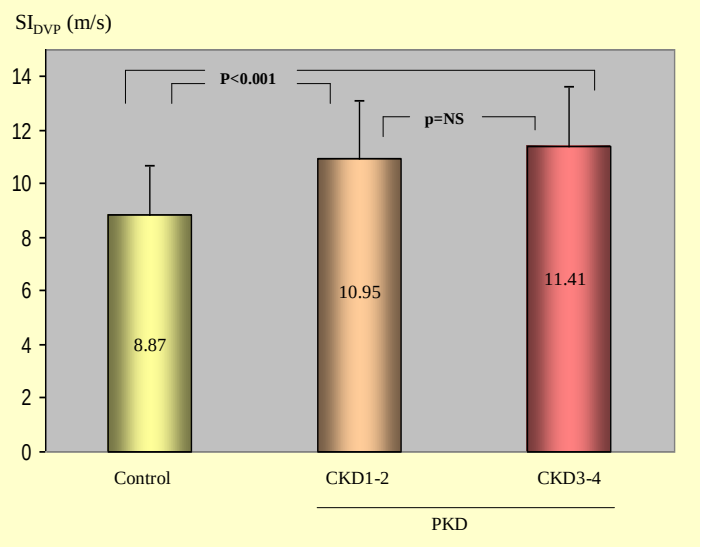
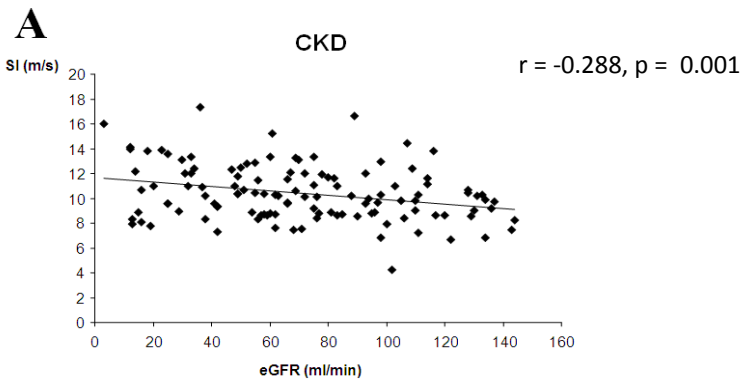


Fig. 6. SI_{DVP} in the PKD subgroups

There was an inverse significant correlation between SI_{DVP} and GFR in the whole CKD group, (IgA+PKD) and in IgAN patients (r = -0.288, p = 0.001 and r=0.368, p<0.01, respectively, but in PKD patients there was not **(Fig. 7 a-c).**



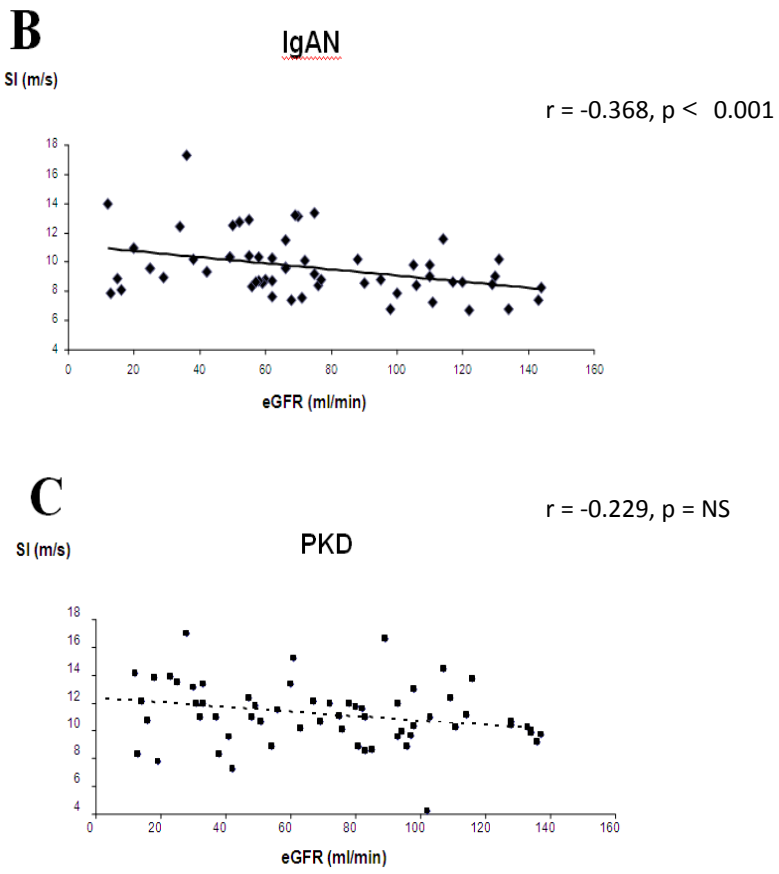


Fig. 7. The correlation between SI_{DVP} and eGFR in the different groups: **a.** all CKD patients; **b.** IgAN patients; **c.** PKD patients

Univariate linear regression analyses were performed in both renal groups to assess the confounding factors affecting SI_{DVP}: age, gender, 24-hour systolic, diastolic blood pressure and theirs diurnal indeces, mean arterial pressure, pulse pressure, CH metabolic disorder (diabetes, IGT or IFG), hypertension in history, dyslipidemia, BMI, hyperuricaemia, eGFR. We found that age, diastolic diurnal index and eGFR have significant impact on SI_{DVP} in IgANP, while age, eGFR and hypertension were significantly related to SI_{DVP} in PKD. However, in a multivariate model only age associated independently with SI_{DVP} in both renal groups.

It is well known that arterial stiffness increases with age. Using an estimated regression model to compare the increase of SI_{DVP} during aging in the three groups (PKD, IgAN and controls) we found that SI_{DVP} of both PKD and IgAN patients increased significantly faster with age, than SI_{DVP} of controls (PKD vs. controls: 0.091-0.073>0, beta: 0.814, 95% CI: 1.682-3.028, p<0.001; IgAN vs. controls: 0.089-0.073>0, beta: 0.313, 95% CI: 1.059-1.764, p<0.05, respectively) (**Fig. 8).**

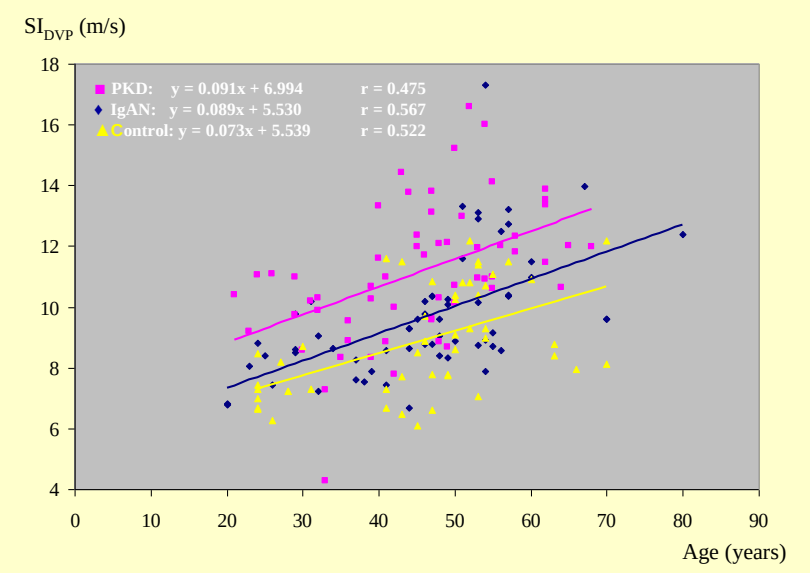


Fig. 8. Changing of the SI_{DVP} depending on the age, across the IgAN, PKD and control group.

3.1.3. Summary

We identified an increased vascular stiffness in IgAN patients, compared to controls. The metabolic syndrome and the presence of metabolic factors may cause a harmful effect on arterial stiffness. We confirmed first that chronic kidney diseases of different origin may have a distinct influence on SI_{DVP}. In PKD the arterial stiffness is often increased even before the worsening of the glomerular function. However, the progression of the arterial stiffening is more pronounced in CKD patient, than in controls without any renal disease.

3.2. The importance of the heart rate recovery in IgA nephropathy

3.2.1. Patients and Methods

We studied 107 IgAN patients, who did not have known heart failure, although treated coronary artery disease (CAD) was accepted. Left bundle branch block on ECG was an exclusion criterion. Patients with manifest symptoms of heart failure (NYHA III-IV) were also excluded, as well as patients with atrial fibrillation or severe hypertension (≥180/110 mm Hg). All patients that we included were able to perform exercise testing. The cohort included 71 men and 36 women aged 45±11 years. Written informed consent was obtained in all participants after the University ethical committee had approved the study. As is routine in our department, the patients had been counseled in a low-sodium diet (100 mmol/day), protein

reduction to 0.6-0.8 g/kg/day, they had been advised not to smoke and to exercise regularly.). The tradicional CV risk factors (age, gender, hypertension, diabetes, obesity, lipid abnormality, smoking habit), and the actual medical therapy were analyzed.

To asses the left ventricular systolic condition we performed echocardiography at every patient before the stress test. Left ventricular systolic function was characterized by ejection fraction (LVEF). The patients underwent a symptom-limited graded exercise treadmill test according to the standard Bruce protocol with a goal of achieving the maximum predicted heart rate (220 minus age). Beta-blockers and nitrates were stopped at least for 48 hours before the examination. Continuous 12-lead ECG monitoring was performed throughout testing. ECG samples were recorded and printed every minute during the examination including the whole recovery. Exercise capacity was expressed in seconds and was measured from the zero second of the first step to the termination moment at peak exercise. The termination was followed by at least one-minute cool-down period with a treadmill speed of 1.6 km per hour. The value for HRR was defined as the difference between the heart rate from peak exercise to 1 min after the peak. Analyses were performed off-line on printed formats. Diagnosis of CAD was established if horizontal or down-sloping ST depression of $\geq$ 1 mm was found for at least 1 minute in two or more coherent leads.

Twenty nine patients with normal renal function and without any renal disease formed the control group. The indication of cardiac stress test at all patients was to assess the exercise capacity and the suspected diagnosis of CAD.

3.2.2. Results

HRR reduction showed significant correlation with decreased eGFR ($r=0.422$ $p<0.001$; Fig 9).

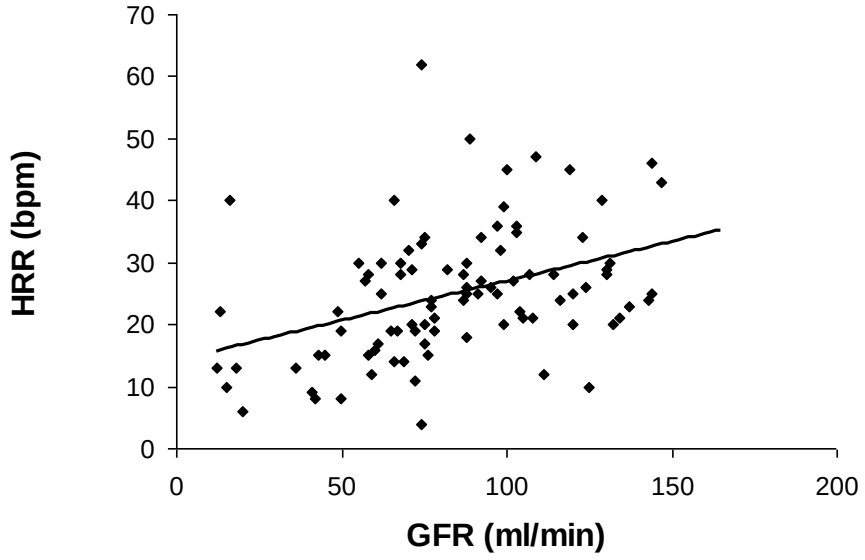


Fig. 9. Correlation between HRR and eGFR.

HRR values in CKD 3-4 group (16.3 bpm) were significantly lower compared to the patients of CKD 2 group (24.5 bpm, p=0.015), or the CKD 1 group (27.8 bpm, p<0.001) and the control group (29.9 bpm, p<0.001), respectively ***(Fig 10).*** There was no difference in HRR between the control group, the CKD 1 and CKD 2 groups. HRR reduction

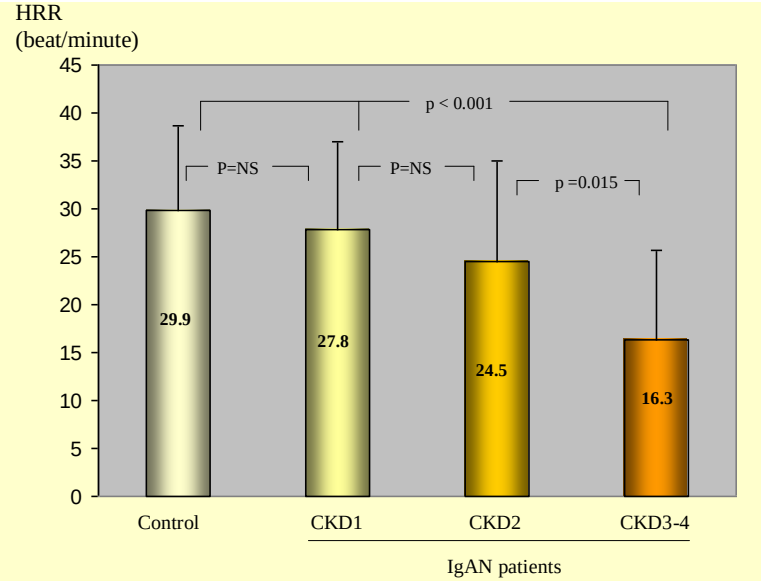


Fig. 10. Heart rate recovery in the different groups

Univariate linear regression analysis was performed in renal patients including 23 confounding variables: gender, age, exercise capacity, CAD, metabolic syndrome, hypertension in history, systolic and diastolic BP, systolic and diastolic diurnal index on ABPM, pulse pressure, heart rate, BMI, dyslipidemia, carbohydrate metabolic disorder, LVEF, smoking habit, hemoglobin level, eGFR, and medical treatment (ACEi/ARB, Ca-antagonists, beta-blockers and statins) . We found that factors associated with HRR were age, systolic 24 hour BP, pulse pressure, systolic diurnal index on ABPM, BMI, dyslipidemia, CH metabolic disorder (IFG, IGT or DM), metabolic syndrome, eGFR, ACEI/ARB and statin therapy. Only eGFR was independently associated with decreased HRR by multivariate linear regression analysis.

3.2.3. Summary

Our data suggest that IgA nephropathy patients with decreased renal function (CKD 3-4) have autonomic imbalance. Furthermore, the effect of kidney damage on increased sympathetic activity seems to be more important than other classic cardiovascular risk factors. We considered many factors that may have influence on the cardiovascular status of IgA nephropathy patients. Our finding suggests the more important role of decreased GFR in the development of sympathetic hyperactivity in IgA nephropathy patients than diabetes or other established CV risk factors.