36. Tsukaguchi H, Sudhakar A, Le TC *et al.* NPHS2 mutations in late-onset focal segmental glomerulosclerosis: R229Q is a common disease-associated allele. J Clin Invest 2002; 110: 1659–1666
37. Machuca E, Hummel A, Nevo F *et al.* Clinical and epidemiological assessment of steroid-resistant nephrotic syndrome associated with the NPHS2 R229Q variant. Kidney Int 2009; 75: 727–735
38. Santin S, Tazon-Vega B, Silva I *et al.* Clinical value of NPHS2 analysis in early- and adult-onset steroid-resistant nephrotic syndrome. Clin J Am Soc Nephrol 2011; 6: 344–354
39. Li MX, Kwan JS, Bao SY *et al.* Predicting mendelian disease-causing non-synonymous single nucleotide variants in exome sequencing studies. PLoS Genet 2013; 9: e1003143
40. Hicks S, Wheeler DA, Plon SE *et al.* Prediction of missense mutation functionality depends on both the algorithm and sequence alignment employed. Hum Mutat 2011; 32: 661–668
41. Chan PA, Duraisamy S, Miller PJ *et al.* Interpreting missense variants: comparing computational methods in human disease genes CDKN2A, MLH1, MSH2, MECP2, and tyrosinase (TYR). Hum Mutat 2007; 28: 683–693
42. Kopp JB, Nelson GW, Sampath K *et al.* APOL1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy. J Am Soc Nephrol 2011; 22: 2129–2137
43. Foster MC, Coresh J, Fornage M *et al.* APOL1 variants associate with increased risk of CKD among African Americans. J Am Soc Nephrol 2013; 24: 1484–1491
44. O'Seaghdha CM, Parekh RS, Hwang SJ *et al.* The MYH9/APOL1 region and chronic kidney disease in European-Americans. Hum Mol Genet 2011; 20: 2450–2456
45. Genovese G, Friedman DJ, Ross MD *et al.* Association of trypanolytic ApoL1 variants with kidney disease in African Americans. Science 2010; 329: 841–845
46. Papeta N, Kiryluk K, Patel A *et al.* APOL1 variants increase risk for FSGS and HIVAN but not IgA nephropathy. J Am Soc Nephrol 2011; 22: 1991–1996
47. Madhavan SM, O'Toole JF, Konieczkowski M *et al.* APOL1 localization in normal kidney and nondiabetic kidney disease. J Am Soc Nephrol 2011; 22: 2119–2128
48. Larsen CP, Beggs ML, Saeed M *et al.* Apolipoprotein L1 risk variants associate with systemic lupus erythematosus-associated collapsing glomerulopathy. J Am Soc Nephrol 2013; 24: 722–725
49. McCarthy HJ, Bierzynska A, Wherlock M *et al.* Simultaneous sequencing of 24 genes associated with steroid-resistant nephrotic syndrome. Clin J Am Soc Nephrol 2013; 8: 637–648
50. Buscher AK, Kranz B, Buscher R *et al.* Immunosuppression and renal outcome in congenital and pediatric steroid-resistant nephrotic syndrome. Clin J Am Soc Nephrol 2010; 5: 2075–2084

Received for publication: 11.6.2013; Accepted in revised form: 24.12.2013

Nephrol Dial Transplant (2014) 29: 2069–2074
doi: 10.1093/ndt/gfu199
Advance Access publication 10 June 2014

ORIGINAL ARTICLE

The association between glomerular filtration rate and left ventricular function in two independent community-based cohorts of elderly

Elisabet Nerpin[1,2], Erik Ingelsson[3], Ulf Risérus[4], Johan Sundström[5], Bertil Andren[5], Elisabeth Jobs[1,2], Anders Larsson[5], Lind Lars[5] and Johan Ärnlöv[1,2]

[1]Department of Public Health and Caring Sciences/Geriatrics, Uppsala Science Park, Uppsala, Sweden, [2]Department of Health and Social Sciences, Högskolan Dalarna, Falun, Sweden, [3]Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden, [4]Department of Public Health and Caring Sciences/Section of Clinical Nutrition and Metabolism, Uppsala Science Park, Uppsala, Sweden and [5]Department of Medical Sciences, Uppsala University, Uppsala, Sweden

Correspondence and offprint requests to: Elisabet Nerpin; E-mail: ene@du.se

ABSTRACT

Background. The cardiorenal syndrome, the detrimental bi-directional interplay between symptomatic heart failure and chronic kidney disease, is a major clinical challenge. Nonetheless, it is unknown if this interplay begins already at an asymptomatic stage. Therefore we investigated whether the glomerular filtration rate (GFR) is associated with left ventricular function in participants free from clinical heart failure and with a left ventricular ejection fraction (LVEF) >40% and with pre-specified sub-group analyses in individuals with a GFR >60 mL/min/m^2.

Methods. Two independent community-based cohorts were used; the Prospective Investigation of the Vasculature in

Uppsala Seniors (PIVUS; $n = 911$; 50% women; mean age: 70 years) and the Uppsala Longitudinal Study of Adult Men (ULSAM; $n = 538$; mean age: 71 years). We investigated cross-sectional association between cystatin C-based GFR (estimated glomerular function [eGFR]) and systolic (LVEF), diastolic- (isovolumic relaxation time [IVRT]) and global left ventricular function (myocardial performance index [MPI]) determined by echocardiography.

Results. In both PIVUS and ULSAM, higher eGFR was significantly associated with higher LVEF (P = 0.004 [PIVUS] and P = 0.005 [ULSAM]). In PIVUS, higher eGFR was significantly associated with lower IVRT (P = 0.001) and MPI (P = 0.006), in age- and sex-adjusted models. After further adjustment for cardiovascular risk factors, the association between higher eGFR and higher LVEF was still statistically significant (P = 0.008 [PIVUS] and P = 0.02 [ULSAM]). In PIVUS, the age- and sex-adjusted association between eGFR and left ventricular function was similar in participants with eGFR >60 mL/min/m^2.

Conclusions. Our data suggest that the interplay between kidney and heart function begins prior to the development of symptomatic heart failure and kidney disease.

Keywords: chronic kidney disease, cystatin C, glomerular filtration rate, left ventricular dysfunction, heart failure

INTRODUCTION

Chronic kidney disease (CKD) is recognized as a global public health problem and is known to be an independent risk factor for cardiovascular disease (CVD) including heart failure [1]. It is also known that worsening heart failure or acute decompensated heart failure can accelerate deterioration of renal function or vice versa—often referred to as the cardiorenal syndrome [2, 3]. Anomalies of left ventricular function have been shown to be very prevalent among CKD patients in stages 3–5 (estimated glomerular function rate [eGFR] <60 mL/min/1.73 m^2) [3, 4]. However, whether eGFR is associated with left ventricular function in the community is less studied.

We are aware of a few previous community-based studies that have reported the association between impaired kidney function and left ventricular function. However, these studies have included patients with CKD [5–7] or patients with clinical heart failure at baseline [7] making it difficult to fully evaluate whether the association between eGFR and anomalies of left ventricular function is present prior to the development of symptomatic heart failure and CKD.

Based on previous data, we hypothesized that the interplay between impaired kidney function and left ventricular function begins already at the asymptomatic stages of heart failure and with eGFR >60 mL/min/1.73 m^2. Accordingly, we investigated cross-sectional associations between eGFR and ventricular function in two community-based samples of elderly free from a clinical heart failure and with a left ventricular ejection function (LVEF) >40%. In secondary analyses, we also investigated associations between eGFR and ventricular function in pre-specified sub-groups of the cohorts with eGFR >60 mL/min/1.73 m^2.

MATERIALS AND METHODS

Study samples

Prospective Investigation of the Vasculature in Uppsala Seniors. All 70-year-old residents of Uppsala County (Sweden), between April 2001 and June 2004, were invited to participate in the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study, described in detail elsewhere [8]. Of 2025 subjects invited, 1016 were examined within 1 month of their 70th birthday. For this study, we excluded 49 participants who had not undergone the echocardiography examination, 8 participants with LVEF <40%, 33 participants with a previous diagnosis of heart failure, 14 participants with missing data on cystatin C and 1 participant with eGFR >270 mL/min/1.73 m^2. After these exclusions, 911 individuals aged 70 (50.6% women) were eligible. Of these individuals, 785 had valid measurement of LVEF, 850 isovolumic relaxation time (IVRT) and 732 global ventricular function (myocardial performance index, MPI).

Uppsala Longitudinal Study of Adult Men. The Uppsala Longitudinal Study of Adult Men (ULSAM) is a community-based study aimed at identifying risk factors for CVD. All men born in 1920–24 and living in Uppsala were invited to participate in a health survey in between 1970 and 1973, of the 2841 invited subjects, 2322 participated (82%). At a re-investigation after approximately 20 years, 1221 men (mean age 71 years) were investigated. At this re-investigation, an echocardiographic Doppler examination was performed on the first consecutive 583 participants. We excluded 15 participants where it was not possible to obtain reliable data from the echocardiographic examination, 14 participants with LVEF <40%, 4 participants who had previously been hospitalized for heart failure and 12 participants for missing data on cystatin C. After these exclusions, 538 individuals aged 70 were eligible. Of these individuals, 407 had valid measurement of LVEF, 494 IVRT and 424 MPI.

All participants gave written informed consent and the Ethics Committee of Uppsala University approved the study protocols.

Clinical and biochemical evaluation

The investigations in PIVUS and ULSAM were performed using the same standardized methods, which included anthropometrical measurements, blood pressure, fasting blood and a questionnaire regarding their medical history, smoking habits and regular medication.

All participants were investigated in the morning after an overnight fast, with no medication or smoking allowed after midnight. Venous blood samples were drawn in the morning after an overnight fast and stored at −70°C.

Body mass index (BMI) was calculated as the ratio of the weight to the height squared (kg/m^2). Blood pressure was measured by a calibrated mercury sphygmomanometer to the nearest even mmHg after at least 10 min of rest and the average of three (PIVUS) or two (ULSAM) recordings were used. Lipid variables and fasting blood glucose were measured by standard laboratory techniques.

Use of diabetes medication was ascertained through self-report questionnaires. Diabetes was defined as a fasting plasma glucose ≥7.0 mmol/L or use of insulin or oral hypoglycaemic agents. Hypertension was defined as ≥140 mmHg systolic blood pressure, ≥90 mmHg diastolic blood pressure or treatment for hypertension.

Estimations of glomerular filtration rate (eGFR) were measured from serum cystatin C performed by Gentian (Moss, Norway) using an Architect Ci8200 (Abbott Park, IL, USA), with the corresponding formula eGFR = 79.901 × cystatin $C^{-1.4389}$ (PIVUS), and latex enhanced reagents from Dade Behring (Deerfield, IL, USA) using a Behring BN ProSpec analyzer (Dade Behring) with the formula: eGFR = 77.24 * cystatin $C^{-1.2623}$ (ULSAM) and which both have been shown to be closely correlated with iohexol clearance [9, 10].

Information about hospitalization due to myocardial infarction, angina pectoris, ischaemic stroke and heart failure was obtained from the Swedish Hospital Discharge Register (ULSAM). The validity of myocardial infarction and stroke in the Swedish Hospital Discharge Register has been demonstrated to be high [11]. In PIVUS, information on prior CVD was collected from a questionnaire.

Echocardiography. A 2–5 MHz transducer was used for two-dimensional and Doppler echocardiography and was performed with an Acuson XP124 cardiac unit (Acuson, CA) in PIVUS and a Hewlett-Packard Sonos 1500 cardiac ultrasound unit (Hewlett-Packard, Andover, MA) in ULSAM.

Left ventricular dimensions were measured with M-mode. Left ventricular volumes (LVEDV, LVESV) were calculated according to the Teichholz M-mode formula; volume = $7D^3/(2.4 + D)$, D = diameter LVEF, reflecting left ventricular systolic function, was calculated as left ventricular diastolic volume – left ventricular systolic volume/left ventricular diastolic volume. Impaired LVEF was defined as LVEF <40% [12]. Ventricular diastolic function was measured with isovolumic relaxation time as the interval between aortic valve closure and the onset of mitral flow, using the Doppler signal from the area between the LV outflow tract and mitral flow. MPI, reflecting global left ventricular function, was calculated as isovolumic contraction time + isovolumic relaxation time/left ventricular ejection time. Examinations and readings of the images were performed by two experienced physicians (Dr Lind, PIVUS and Dr Andrén, ULSAM) who were unaware of the other data of the subjects.

Statistical analysis

Variables with a skewed distribution (NT-proBNP and glucose) were logarithmically transformed to achieve normal distribution, and these transformed variables were used in all analyses. Missing data on covariates were handled via multiple imputation techniques to deal with the loss of information on covariates in the data set. Two-tailed 95% confidence intervals (CIs) and significance values were given, with a value of $P < 0.05$ regarded as significant.

Linear regression analyses were used to assess the cross-sectional associations of eGFR (independent variable) with LVEF, IVRT and MPI (dependent variables in separate models).

We used the directed acyclic graph (DAG) approach to establish a parsimonious model with minimized confounding of the effect estimates in the statistical model B.

The following models were performed:

- Model A: adjusted for age (continuous) and sex (binary [PIVUS]).
- Model B: DAG-adjusted; adjusted for age (continuous), sex (binary [PIVUS]), systolic and diastolic blood pressure (continuous), BMI (continuous), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) (continuous), smoking (binary), diabetes (binary).

In our analysis, we modelled eGFR, LVEF, IVRT and MPI as continuous variables (expressed as a 1 SD increase). In secondary models we also added to the whole cohort and to participants with eGFR >60 mL/min/1.73 m^2, the use of angiotensin converting enzyme (ACE) inhibitors, beta-blockers, Ca-antagonist or diuretics to multivariable model B. To gain additional insights into the potential nonlinearity of the associations, we examined the regression models using splines.

We also performed the above analyses in a pre-specified sub-group with normal eGFR (>60 mL/min/1.73 m^2), PIVUS: n = 743/802/688 for LVEF/IVRT/MPI analyses, respectively; ULSAM: n = 224/268/243 analyses, respectively. Moreover, we also investigated the association between creatinine-based eGFR (Chronic Kidney Disease Epidemiology Collaboration formula [CKD-EPI]) [13] and LVEF.

In secondary analyses, we performed tests for effect modification by gender by including a multiplicative interaction term in multivariable model B.

RESULTS

Baseline characteristics for the whole cohort in PIVUS and ULSAM are shown in Table 1.

In both PIVUS and ULSAM, higher eGFR was significantly associated with higher LVEF, adjusted for age and sex (model A, Table 2). Further, higher eGFR was significantly associated with lower IVRT and MPI (reflecting better ventricular function) in PIVUS. After further adjustment of systolic and diastolic blood pressure, BMI, diabetes, LDL- and HDL-cholesterol and smoking, a significant association was seen between eGFR and LVEF (model B, Table 2) in both cohorts. Further, in sub-group analyses of participants with eGFR >60 mL/min/1.73 m^2 a significant association between eGFR and LVEF, IVRT and MPI was seen in PIVUS but not in ULSAM after adjustment for age and sex (model A, supplementary data, Table S1). These associations were similar when the use of ACE inhibitors, beta-blockers, Ca-antagonist or diuretics was added to multivariable model B in the whole cohort and in sub-group analyses of participants with eGFR >60 mL/min/1.73 m^2 (data not shown).

The association between creatinine-based eGFR with LVEF in PIVUS and ULSAM was similar to cystatin C-based eGFR adjusted for age and sex but of borderline significance

Table 1. Baseline characteristics of two cohorts

Variable	PIVUS Whole sample (n = 911)	ULSAM Whole sample (n = 538)
Age (year)	70.2 ± 0.2	71.2 ± 0.5
Females no (%)	461 (50.6)	NA
LVEF (%)	67 ± 7	65 ± 8
IVRT	121 ± 21	123 ± 22
MPI	0.60 ± 0.16	0.69 ± 0.16
Cystatin C (mg/L)	0.90 ± 0.17	1.24 ± 0.25
eGFR (mL/min/1.73 m^2)	93 ± 22	62 ± 14
$eGFR_{CKD\text{-}EPI}$ (mL/min/1.73 m^2)	79 ± 14	72 ± 11
Systolic blood pressure (mmHg)	150 ± 23	149 ± 19
Diastolic blood pressure (mmHg)	79 ± 10	85 ± 9
BMI (kg/m^2)	27 ± 4	26 ± 3
HDL-cholesterol (mmol/L)	1.5 ± 0.4	1.3 ± 0.3
LDL-cholesterol (mmol/L)	3.4 ± 0.9	3.9 ± 0.9
Diabetes mellitus, no. (%)	101 (11.1)	76 (14.1)
Diabetes medication, no. (%)	61 (6.7)	26 (4.8)
Smoking, no. (%)	95 (10.4)	113 (21.0)
Dyslipidaemia, no (%)	699 (76.7)	475 (88.3)
Lipid-lowering treatment, no. (%)	138 (15.1)	39 (7.3)
Cardiovascular disease, no. (%)	117 (12.8)	183 (34.0)
Hypertension, no. (%)	655 (71.9)	407 (75.7)
Anti-hypertensive treatment, no. (%)	270 (29.6)	185 (34.4)
Beta-blocker, no. (%)	181 (19.9)	103 (19.1)
Calcium channel blockers, no. (%)	99 (10.9)	64 (11.9)
Diuretic, no. (%)	93 (10.2)	64 (11.9)
ACE-antagonist, no. (%)	67 (7.4)	28 (5.2)
A-1 antagonist, no. (%)	75 (8.2)	NA

Date are mean ± SD for continuous variables and no (%) for dichotomous variables.
BMI, body mass index; LVEF, left ventricular ejection fraction; IVRT, isovolumic relaxation time; MPI, myocardial performance index; NA, not available.

Table 2. Cross-sectional associations between cystatin C-based glomerular filtration rate (eGFR) and LVEF, IVRT or MPI at age 70 in PIVUS and ULSAM: multivariable regression, whole cohort with LVEF >40%

Estimated glomerular filtration rate (eGFR) Whole cohort	β-coefficient (95% CI)	P-value
PIVUS		
Model A; sex and age		
LVEF	0.11 (0.03 to 0.18)	0.004
IVRT	−0.12 (−0.18 to −0.05)	0.001
MPI	−0.10 (−0.17 to −0.03)	0.006
Model B; DAG-adjusted		
LVEF	0.10 (0.03 to 0.17)	0.008
IVRT	−0.07 (−0.14 to −0.01)	0.02
MPI	−0.07 (−0.14 to 0.0001)	0.051
ULSAM		
Model A; sex and age		
LVEF	0.14 (0.04 to 0.23)	0.005
IVRT	−0.05 (−0.14 to 0.04)	0.24
MPI	−0.09 (−0.18 to 0.01)	0.08
Model B; DAG-adjusted		
LVEF	0.11 (0.02 to 0.21)	0.02
IVRT	−0.03 (−0.12 to 0.06)	0.50
MPI	−0.06 (−0.15 to 0.04)	0.25

Data are regression coefficients for a 1-SD higher eGFR.
LVEF, left ventricular ejection fraction; IVRT, isovolumic relaxation time; MPI, myocardial performance index.
Model A: adjusted age, sex. Model B: DAG-adjusted; age, sex, systolic and diastolic blood pressure, BMI, diabetes, LDL-cholesterol and smoking. Whole cohort PIVUS: LVEF (n = 785), IVRT (n = 850), MPI (n = 732); ULSAM: LVEF (n = 407), IVRT (n = 494), MPI (n = 424).

(multivariable regression coefficient for 1 SD increase of LVEF 0.07 [95% CI −0.07 to 0.14, P = 0.08] in PIVUS and 0.09 [95% CI −0.01 to 0.19, P = 0.08] in ULSAM).

No evidence of effect modification by gender on the association between eGFR and LVEF was observed in PIVUS. Examination of regression splines suggests no obvious deviation from linearity in the association between eGFR and the different indices of left ventricular function (LVEF, IVRT and MPI, data not shown).

DISCUSSION

In two independent community-based cohorts of elderly individuals free from clinical heart failure and with LVEF >40%, we found a positive association between eGFR and different echocardiographic indices of left ventricular systolic, diastolic and global function. However, after adjustment for cardiovascular risk factors only the association between eGFR and left ventricular systolic function (LVEF) was statistically significant in the two cohorts. Interestingly, an association between eGFR and systolic function was seen also in participants with eGFR >60 mL/min/m^2 in the PIVUS cohort. Our data suggest that the interplay between the kidney and heart may be evident already prior to the development of symptomatic heart failure and CKD.

Comparison with the literature

Clinical studies have indicated that impaired left ventricular function is observed among individuals with moderate-to-severe kidney function in patients with hypertension [14, 15], heart failure [16–19], chronic glomerulonephritis [20], diabetes [21] and anaemia [22]. However, previous community-based data are scarce and inconsistent [5–7].

Our findings are in accordance with one previous community-based study [6] measuring LV function with echocardiography in 818, 60–70-year-old participants with coronary heart disease, but free from heart failure. Circulating cystatin C was associated with both diastolic and systolic dysfunction in both crude and multivariable models.

In contrast, the Multi-Ethnic Study of Atherosclerosis by Agarwal *et al.* [5], an analysis of 4970 participants age 44–80 years, demonstrated no significant association between mild-to-moderate reduction in kidney function measured with cystatin C and LVEF using cardiac magnetic resonance imaging. Similarly, in the Dallas Heart Study [7] a cohort of 2548 individuals aged 30–65 years showed no significant associations between cystatin C and LVEF. Perhaps differences in clinical characteristics, such as age and prevalence of CVD and CKD, could explain these discrepant results between the studies. The participants of the previous negative studies were younger, healthier and with less CVD and CKD comorbidities. We are not aware of any previous study that have reported the association between glomerular filtration rate and left

ventricular function in individuals free from clinical heart failure and GFR >60 mL/min/1.73 m^2.

Possible mechanisms for the observed associations

The mechanisms of association between impaired kidney function and CVD are not fully understood:

A chronic activation of the renin–angiotensin system (RAAS) is a hallmark of CKD. RAAS activation leads to sodium retention and increased extracellular fluid volume which may further exacerbate LV function. A persistent activation of RAAS also has direct damaging effects on cardiac function and contributes to the progression of heart failure via promotion of cardiac remodelling and myocardial fibrosis [2]. An experimental study by Martin *et al.* [23] demonstrated that mild renal insufficiency in rats resulted in an early cardiac fibrosis and impaired diastolic function, which progresses to more global LV remodelling and dysfunction and further on to heart failure.

CKD often coexists with cardiovascular risk factors, such as dyslipidaemia, hypertension, smoking and diabetes [24], all of which have been shown to be important risk factors for heart failure [25]. In this study, the association between renal function and ventricular function was attenuated after adjustment for cardiovascular risk factors (in particular the association between eGFR and diastolic or global ventricular function), which could indicate that these factors are deleterious for both the heart and the kidney and provide a common pathophysiologic link. Elevated cardiovascular risk factors contribute to accelerated atherosclerosis in these patients through increased production of reactive oxygen species, which then could lead to increased incidence of heart failure in the general population [26].

Clinical implications

Cardiorenal syndrome is a major clinical challenge and early diagnosis by assessing biomarkers of cardiac and renal injury may be critical for timely therapeutic intervention. A better understanding of the cardiorenal interplay in the early stages of the disease may in the long term improve the patients' outcome, delaying not only early renal disease but also the progression of heart failure. Studies have shown that therapeutic interventions introduced before the presence of left ventricular dysfunction or symptoms can reduce the population morbidity and mortality of heart failure [27, 28].

In our study, the cross-sectional regression coefficients suggest that the magnitude of the association between eGFR and left ventricular heart function appears modest even though it was statistically significant. Yet, no firm conclusions on effect size should be drawn from observational data, additional intervention trials are needed to properly investigate this issue.

Strengths and limitations

The strengths of our investigation include the use of two independent community-based study samples with longitudinal data and the detailed characterization regarding cardiovascular risk factors, which allowed adjustment for many potential confounders.

Some limitations are also worth noting. The study design was cross-sectional; thus, we cannot assess causality between eGFR and left ventricular function. The present sample consisted of individuals of Northern European descent and 70 years of age, so generalizability to other ethnic and age groups is unknown. The PIVUS cohort had a moderate participation rate. However, an analysis of non-participants showed the present sample to be fairly representative of the total population in terms of most cardiovascular disorders and medication [8]. Cystatin C is an indirect approximation for eGFR, and direct measures of eGFR through the gold standard method (exogenous clearance measurements) were unavailable. Yet, exogenous clearance measurements are seldom used in epidemiological research as it is a time-consuming and costly procedure. In this study, we used a cystatin C-based eGFR formula, which has been shown to be closely correlated with eGFR assessed by isotope clearance measurements also in the normal range of eGFR [9, 10]. We did not use the CKD-EPI formula that incorporates both creatinine and cystatin C as this formula is based on standardized cystatin C or creatinine measurements and these were not available at the baseline of this study.

CONCLUSION

Among elderly individuals in two independent community-based cohorts, lower levels of eGFR were independently associated with decreased left ventricular function. Our data suggest that the detrimental interplay between the kidney and the heart begins at the early stages of left ventricular dysfunction, prior to the development of symptomatic heart failure and CKD.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

ACKNOWLEDGEMENTS

This study was supported by The Swedish Research Council (2006-6555), Swedish Heart-Lung foundation, Marianne and Marcus Wallenberg Foundation, the Thuréus Foundation, Dalarna University and Uppsala University and Swedish Society of Medical Research.

CONFLICT OF INTEREST STATEMENT

The results presented in this paper have previously been published in Elisabet Nerpin's thesis.

(See related article by Campese. Left ventricular function and chronic kidney disease: how soon does it start? *Nephrol Dial Transplant* 2014; 29: 1989–1991.)

ORIGINAL ARTICLE

REFERENCES

1. Tonelli M, Wiebe N, Culleton B *et al.* Chronic kidney disease and mortality risk: a systematic review. J Am Soc Nephrol 2006; 17: 2034–2047
2. Sun Y. The renin–angiotensin–aldosterone system and vascular remodeling. Congest Heart Fail 2002; 8: 11–16
3. House AA. Cardio-renal syndrome type 4: epidemiology, pathophysiology and treatment. Semin Nephrol 2012; 32: 40–48
4. Foley RN, Parfrey PS, Harnett JD *et al.* Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. Kidney Int 1995; 47: 186–192
5. Agarwal S, Thohan V, Shlipak MG *et al.* Association between cystatin C and MRI measures of left ventricular structure and function: multi-ethnic study of atherosclerosis. Int J Nephrol 2011; 2011: 153868
6. Ix JH, Shlipak MG, Chertow GM *et al.* Cystatin C, left ventricular hypertrophy, and diastolic dysfunction: data from the Heart and Soul Study. J Card Fail 2006; 12: 601–607
7. Patel PC, Ayers CR, Murphy SA *et al.* Association of cystatin C with left ventricular structure and function: the Dallas Heart Study. Circ Heart Fail 2009; 2: 98–104
8. Lind L, Fors N, Hall J *et al.* A comparison of three different methods to evaluate endothelium-dependent vasodilation in the elderly: the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. Arterioscler Thromb Vasc Biol 2005; 25: 2368–2375
9. Flodin M, Jonsson AS, Hansson LO *et al.* Evaluation of gentian cystatin C reagent on Abbott Ci8200 and calculation of glomerular filtration rate expressed in mL/min/1.73 m(2) from the cystatin C values in mg/L. Scand J Clin Lab Invest 2007; 67: 560–567
10. Larsson A, Malm J, Grubb A *et al.* Calculation of glomerular filtration rate expressed in mL/min from plasma cystatin C values in mg/L. Scand J Clin Lab Invest 2004; 64: 25–30
11. Merlo J, Lindblad U, Pessah-Rasmussen H *et al.* Comparison of different procedures to identify probable cases of myocardial infarction and stroke in two Swedish prospective cohort studies using local and national routine registers. Eur J Epidemiol 2000; 16: 235–243.
12. Paulus WJ, van Ballegoij JJ. Treatment of heart failure with normal ejection fraction: an inconvenient truth! J Am Coll Cardiol 2010; 55: 526–537
13. Levey AS, Coresh J, Greene T *et al.* Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006; 145: 247–254
14. Shah AM, Lam CS, Cheng S *et al.* The relationship between renal impairment and left ventricular structure, function, and ventricular–arterial interaction in hypertension. J Hypertens 2011; 29: 1829–1836
15. Nardi E, Palermo A, Mule G *et al.* Left ventricular hypertrophy and geometry in hypertensive patients with chronic kidney disease. J Hypertens 2009; 27: 633–641
16. Khan NA, Ma I, Thompson CR *et al.* Kidney function and mortality among patients with left ventricular systolic dysfunction. J Am Soc Nephrol 2006; 17: 244–253
17. Dini FL, Demmer RT, Simioniuc A *et al.* Right ventricular dysfunction is associated with chronic kidney disease and predicts survival in patients with chronic systolic heart failure. Eur J Heart Fail 2012; 14: 287–294
18. Hillege HL, Nitsch D, Pfeffer MA *et al.* Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation 2006; 113: 671–678
19. Mathew J, Katz R, St John Sutton M *et al.* Chronic kidney disease and cardiac remodelling in patients with mild heart failure: results from the REsynchronization reVErses Remodeling in Systolic Left vEntricular Dysfunction (REVERSE) study. Eur J Heart Fail 2012; 14: 1420–1428.
20. Schroeder AP, Kristensen BO, Nielsen CB *et al.* Heart function in patients with chronic glomerulonephritis and mildly to moderately impaired renal function. An Echocardiographic Study. Blood Press 1997; 6: 286–293
21. Chen SC, Chang JM, Liu WC *et al.* Stepwise increases in left ventricular mass index and decreases in left ventricular ejection fraction correspond with the stages of chronic kidney disease in diabetes patients. Exp Diabetes Res 2012; 2012: 789325
22. Astor BC, Arnett DK, Brown A *et al.* Association of kidney function and hemoglobin with left ventricular morphology among African Americans: the Atherosclerosis Risk in Communities (ARIC) study. Am J Kidney Dis 2004; 43: 836–845
23. Martin FL, McKie PM, Cataliotti A *et al.* Experimental mild renal insufficiency mediates early cardiac apoptosis, fibrosis, and diastolic dysfunction: a kidney-heart connection. Am J Physiol Regul Integr Comp Physiol 2012; 302: R292–R299
24. Kasiske BL. The kidney in cardiovascular disease. Ann Intern Med 2001; 134: 707–709
25. Chen YT, Vaccarino V, Williams CS *et al.* Risk factors for heart failure in the elderly: a prospective community-based study. Am J Med 1999; 106: 605–612
26. Shlipak MG, Fried LF, Cushman M *et al.* Cardiovascular mortality risk in chronic kidney disease: comparison of traditional and novel risk factors. JAMA 2005; 293: 1737–1745
27. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigators. N Engl J Med 1992; 327: 685–691
28. Hunt SA, Abraham WT, Chin MH *et al.* ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. Circulation 2005; 112: e154–e235

Received for publication: 6.2.2014; Accepted in revised form: 18.4.2014