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Is echocardiography mandatory for patients with chronic kidney disease?

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Abstract
This study aims at evaluating the prevalence of left ventricular diastolic dysfunction in a group of 319 hypertensive patients with stage 3b–4–5 chronic kidney disease (according to Kidney Disease Improving Global Outcomes classification), compared with 216 patients with essential hypertension and normal renal function. All patients underwent echocardiographic examination. Patients on stage 1–2–3a chronic kidney disease, dialysis treatment, or with previous manifestations of heart failure or other cardiovascular diseases were excluded. Patients with renal disease had significantly worse diastolic function (both considering trans-mitral flow and tissue Doppler imaging parameters). Diastolic dysfunction is found in 70.5% of the CKD group and in 41.6% of hypertensive patients ($p < 0.0001$). Multiple regression analysis shows an association between renal function and diastolic function (β 0.223; $p < 0.0001$), independent of potential confounders. Our study shows that diastolic dysfunction is highly prevalent in patients with advanced chronic kidney disease; we posit that in this population, the risk of diastolic heart failure is very high. We think that patients with a marked decrease of glomerular filtration rate (GFR) must be considered at high risk for diastolic heart failure and should have an echocardiographic examination performed, even if asymptomatic and in the absence of evident cardiovascular disease.

Keywords Chronic kidney disease · Hypertension · Heart failure · Diastolic function

Introduction

CKD is associated with increased cardiovascular risk and mortality [1] and increased incidence of heart failure (HF) [2]; some studies have shown an association between kidney function and HF risk across a wide spectrum of disease stages from preclinical kidney disease to advanced CKD [3–5].

The pathogenesis of HF in patients with CKD is not very clear, but likely relates to a combination of cardiac structural abnormalities and alterations of volume handling [3]. Moreover, the diagnosis of HF can be difficult because many of the symptoms of HF are non-discriminating, and, therefore, of limited diagnostic value [6–10]. Many of the signs of HF result from sodium and water retention, conditions very frequent in advanced CKD. Demonstration of an underlying cardiac cause is therefore central to the diagnosis of HF [11].

In patients with clinical HF, studies estimate that the prevalence of HF due to diastolic dysfunction (HF with preserved ejection fraction—HFpEF) is approximately 50% (range 40–71%) [12].

The diagnosis of HFpEF is more difficult than the diagnosis of HF with reduced ejection fraction (HFrEF) because it is largely based on exclusion criteria. Usually, these patients do not have a dilated heart, and many have an increase in left ventricular (LV) wall thickness and increased left atrial (LA) size. Most have evidence of diastolic dysfunction, which is generally accepted as the likely cause of HF in these patients [13]. It is reasonable to hypothesize that in patients with CKD, the prevalence of HFPEF is very high.

We designed the present study to investigate the prevalence of diastolic dysfunction in patients with CKD and hypertension; we posit that the identification of these patients may contribute to select a population at very high risk of HFpEF.

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Methods

In accordance with the Declaration of Helsinki and institutional guidelines, the protocol was approved by the local ethics committee and subjects were aware of the investigational nature of the study and agreed to participate after informed consent.

Study population

We enrolled 319 Caucasian subjects with CKD and hypertension (male/female 181/138; mean age 61.3 ± 10.6 years) referred to our ambulatory clinic for CKD between 2010 and 2014. Study subjects underwent a detailed review of their medical history and routine laboratory measurements.

Exclusion criteria were: age < 30 or > 79 years, history of cardiovascular diseases (previous coronary artery disease, history of angina or myocardial infarction, abnormalities of cardiac rhythm, heart failure, ejection faction < 55%, moderate or severe valvular diseases, previous transient ischemic attack or stroke), current or previous dialysis treatment, previous renal transplantation and other major non-cardiovascular (CV) diseases.

After the application of the exclusion criteria, patients were defined as hypertensives according to the European Society of Hypertension/European Society of Cardiology (ESH/ESC) Guidelines [14]. Clinic blood pressure (BP) was considered as the average of three consecutive measurements using a mercury sphygmomanometer after the subjects had been supine for 5 min.

Eighty-nine patients (30.4%) were also diabetics. Diabetes was diagnosed according to ADA recommendations [15].

GFR was estimated by Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation [16].

CKD patients were stratified using the National Kidney Foundation (NKF)—Kidney Disease Improving Global Outcomes (KDIGO 2012) classification [16]: G1 (kidney damage with normal or increased GFR): GFR ≥ 90 ml/min/1.73 m^2; G2 (mildly decreased GFR): GFR 89–60 ml/min/1.73 m^2; G3a (mildly to moderate decreased GFR): GFR 59–45 ml/min/1.73 m^2; G3b (moderately to severely decreased GFR): GFR = 30–44 ml/min/1.73 m^2; G4 (severely decreased GFR): GFR = 29–15 ml/min/1.73 m^2; G5 (kidney failure): GFR < 15 ml/min/1.73 m^2.

Patients on stage 3b, 4 and 5 (not on dialysis treatment) were included in the study.

Enrolled patients were divided as follows: 91 patients (28.5%) were in stage 3b CKD, 118 (37%) in stage 4 and 110 (34.5%) in stage 5. Mean GFR for the whole group was 21.9±11.2 ml/min/1.73 m^2.

The etiology of CKD was determined by chart review: hypertension or diabetes (75%), chronic glomerulonephritis (7%), autosomal dominant polycystic kidney disease (3%), unknown (15%).

After analyzing the 319 CKD patients, we compared them with 216 Caucasian subjects (male/female: 117/99) with essential hypertension (EH) and normal renal function, referred to our ambulatory clinic for hypertension between 2010 and 2014 (Table 1); 65 of them (30.1%) were also diabetics.

In the EH group, secondary forms of hypertension were ruled out by clinical examination, determination of serum creatinine and GFR, serum and urinary electrolytes, plasma catecholamines, aldosterone and renin activity, renal echography and color Doppler of the main renal arteries.

All patients were pharmacologically treated. For CKD patients, the antihypertensive treatment was as follows: 32% angiotensin-converting enzyme (ACE) inhibitors (alone or in combination with a diuretic); 31% angiotensin II type 1 (AT_1) receptor blockers (alone and in combination with a diuretic); 6% β-blockers or α-β-blockers; 1% α-blockers; 10% calcium-channel blockers (CCB); 2% diuretic alone; 18% a combination of two or more of these drugs.

24% of patients were on current recombinant human erythropoietin treatment.

In the EH group, the antihypertensive treatment was based on ACE inhibitors (alone or in combination with a

Table 1 CKD and EH patients' clinical data

	CKD patients (N = 319)	Hypertensive patients (N = 216)	P
Age, years	61.3 ± 10.6	60.3 ± 10.6	0.285
Males/females	181/138	117/99	0.713
Body mass index (kg/m^2)	26.6 ± 3.7	27.4 ± 2.7	0.007
Serum creatinine (mg/l)	3.46 ± 1.9	0.94 ± 0.11	< 0.0001
GFR (ml/min/1.73 m^2)	21.9 ± 11.2	79.4 ± 12	< 0.0001
Hemoglobin (g/dl)	12.4 ± 1.3	13.1 ± 0.99	< 0.0001
Systolic blood pressure (mmHg)	145 ± 20	145 ± 18	1
Diastolic blood pressure (mmHg)	82 ± 12	85 ± 11	0.003
Pulse pressure (mmHg)	63 ± 18	60 ± 16	0.049

diuretic) (32%), AT_1 receptor blockers (alone or in combination with a diuretic) (28%), β-blockers or α–β-blockers (12%), α-blockers (2%), CCB (13%) or a combination of two or more of these drugs (13%). Diuretic therapy was mainly based on furosemide in CKD patients and on thiazides in the EH group.

Laboratory methods

Determination of routine biochemical parameters was performed with standard techniques using an auto-analyzer.

Echocardiographic methods

The echocardiographic examination was performed using an Acuson Sequoia 512 system (Siemens, Mountain View, CA, USA). Images were taken in the left lateral decubitus position. M-mode echocardiography was performed to evaluate the left ventricular end-diastolic diameter (LVEDD), end-systolic diameter (LVESD), interventricular septum thickness (IVST), posterior wall thickness (PWT), and left atrial volume index (LAVI) according to the American Society of Echocardiography (ASE) recommendations [17].

Left ventricular mass (LVM) was determined using the ASE-corrected cube formula [18] and was indexed by body surface area (LVMI). Relative wall thickness (RWT) was calculated as the ratio of 2PWT/LVEDD. Left ventricular hypertrophy (LVH) was defined as suggested by the 2018 ESH/ESC Guidelines (LVMI > 115 g/m^2 in men and > 95 g/m^2 in women) [14].

Left ventricular ejection fraction (EF) was assessed by 2D-echo using modified Simpson's rule [19]. Only those frames with optimal visualization of interfaces and showing simultaneous visualization of septum, left ventricular diameters and posterior wall were used for readings.

Diastolic function was evaluated using both mitral inflow and tissue Doppler echocardiography, performed according to the ASE recommendations [20]. Mitral inflow was assessed in the apical four-chamber view, using pulsed-wave Doppler echocardiography, with the Doppler beam aligned parallel to the direction of flow and the sample volume at the leaflet tips. From the mitral inflow profile, the E-wave (E) and A-wave (A) peak velocities, E/A ratio and E-deceleration time (DT) were measured. Isovolumic relaxation time (IVRT) was calculated between aortic valve closure and the start of E-wave.

Tissue Doppler imaging (TDI) of the mitral annulus was obtained from the apical four-chamber view, using a 1- to 2-mm sample volume placed in the lateral mitral valve annulus to evaluate early diastolic myocardial velocity (e'). The E/e' ratio was also calculated.

We decided to evaluate the presence of diastolic dysfunction principally by means of TDI, since parameters measured by TDI are more preload independent than those measured by mitral inflow [21]; further, e' is inversely related to myocardial fibrosis [22]. E/e' is considered a good predictor of elevated LV filling pressure [23].

We considered LV diastolic dysfunction patients with e' values (lateral mitral annulus) < 0.1 m/s [11]. Echocardiographic data are expressed as the average of five consecutive cardiac cycles. Images were read by a single cardiologist, who was blinded to the patient's clinical characteristics.

In our laboratory, the mean intra-observer variability for LVM and diastolic function parameters was 8.6%.

Statistics

Data for continuous variables are given as mean ± standard deviation.

Differences between groups were evaluated, where appropriate, using ANOVA and Tukey post hoc test for multiple comparisons for continuous variables and the Chi square (χ^2) test, with Yates' correction, for the categorical variables.

In CKD patients, univariate associations between the variables were assessed by the Pearson correlation coefficients.

To investigate the independent correlates of diastolic dysfunction, we performed multiple linear and logistic regression analyses, considering the e' value, respectively, as continuous and as dichotomous (> 0.1 m/s = 0; < 0.1 m/s = 1) dependent variables. The strength of the associations between the variables was expressed, respectively, by the standardized multiple regression coefficients (β) and by the odd ratios and their 95% confidence limits. The covariates included in the multivariate models as potential explanatory variables were: age, gender (men = 1; women = 0), diabetes (yes = 1; no = 0), blood pressures, GFR, hemoglobin (Hb), treatment with a renin–angiotensin system blocker with or without the combination with a diuretic (yes = 1; no = 0), treatment with a calcium antagonist (yes = 1; no = 1), treatment with a β-blocker or an α–β blocker (yes = 1; no = 0) and association with two or more of these or other antihypertensive drugs (yes = 1; no = 0), LVMI (or RWT). The null hypothesis was rejected at a two-tailed $p \leq 0.05$.

The statistical analyses were performed using the SYSTAT DATA software package, version 13 (Systat, Chicago, IL, USA).

Results

Table 1 shows the clinical data of the CKD patients in comparison with the EH patients.

There were no differences in age and distribution of gender. Body mass index was lower in the CKD group ($p = 0.007$). As expected, CKD patients had lower hemoglobin concentration ($p = 0.0001$). With regard to BP,

CKD patients had lower diastolic blood pressure value ($p=0.003$) and higher pulse pressure ($p=0.049$).

The main echocardiographic findings are reported in Table 2. Compared with the EH patients, CKD patients have higher LVEDD, LVESD, IVST and PWT; these changes determine the values of LVMI, left ventricular mass indexed by height elevated by a power of 2.7 ($LVMH^{2.7}$) and RWT considerably higher in the CKD group ($p<0.0001$ for all parameters).

Ejection fraction, although in the normal range, was lower in the CKD group ($p<0.0001$).

In CKD patients, the prevalence of LVH is 80.6% ($N=257/319$), significantly higher than that in the EH group (44.4%, $N=96/216$; $p<0.0001$).

Patients with renal disease had worse diastolic function (lower E/A, higher DT, IVRT and LAVI); TDI confirmed this trend with lower e' and higher E/e' values ($p<0.0001$ for all parameters).

Diastolic dysfunction, considered as an e' value < 0.1 m/s [11], was found in 70.5% of the CKD group and in 41.6% of hypertensive patients ($p<0.0001$) (Table 3 and Fig. 1).

In Table 4, the significant univariate correlations of e' are presented: in subjects with CKD e' significantly correlates with

Table 2 Main echocardiographic findings in patients with CKD and essential hypertension

	CKD patients ($N=319$)	Hypertensive patients ($N=216$)	$P <$
Left ventricular end-diastolic diameter (mm)	51.4 ± 5.5	48.3 ± 4.8	0.0001
Left ventricular end-systolic diameter (mm)	32.9 ± 4.7	29.6 ± 3.6	0.0001
Ejection fraction, %	64.3 ± 4.6	66.0 ± 3.7	0.0001
Interventricular septum thickness (mm)	11.7 ± 2	11.0 ± 1.8	0.0001
Posterior wall thickness, mm	11.4 ± 2	10.2 ± 1.8	0.0001
LVMI (g/m^2)	135.7 ± 43	103.9 ± 27.3	0.0001
$LVMH^{2.7}$ ($g/m^{2.7}$)	63.8 ± 21	48.7 ± 12.6	0.0001
Relative wall thickness	0.446 ± 0.08	0.428 ± 0.08	0.0001
LAVI (ml/m^2)	33.26 ± 15.8	26.53 ± 8.7	0.0001
E/A	0.8 ± 0.34	1.04 ± 0.3	0.0001
DT (m/s)	302 ± 86	238.2 ± 55	0.0001
IVRT (m/s)	116.3 ± 24.7	98.8 ± 19	0.0001
e' (m/s)	0.086 ± 0.028	0.107 ± 0.026	0.0001
E/e'	8.01 ± 3.3	7.05 ± 2.2	0.0001

CKD chronic kidney disease, *LVMI* left ventricular mass index, *LVMI* left ventricular mass indexed by height elevated by a power of 2.7, *LAVI* left atrial volume index, *E* E-wave peak velocity, *A* A-wave peak velocity, *DT* E-deceleration time, *IVRT* isovolumic relaxation time, *e′* early diastolic myocardial velocity

Table 3 Main indices in patients with ($e'<0.1$ m/s) and without ($e'>0.1$ m/s) diastolic dysfunction

	$e'<0.1$ m/s ($N=225$)	$e'>0.1$ m/s ($N=94$)	$P <$
Age, years	63.4 ± 9.3	56.5 ± 12	0.0001
Sex (males/females)	131/94	50/44	0.457
GFR ($ml/min/1.73\ m^2$)	19.48 ± 10.9	27.7 ± 10.5	0.0001
Ejection fraction (%)	64.5 ± 4.6	67.0 ± 4	0.0001
LVMI (g/m^2)	144.5 ± 44.8	114.8 ± 29.9	0.0001
$LVMH^{2.7}$ ($g/m^{2.7}$)	63.8 ± 21	53 ± 15	0.0001
RWT	0.458 ± 0.08	0.415 ± 0.05	0.0001
LAVI (ml/m^2)	34.86 ± 16.2	29.46 ± 14.1	0.0001
E/A	0.72 ± 0.25	1 ± 0.43	0.0001
DT (m/s)	322 ± 87	255 ± 65	0.0001
IVRT (m/s)	121.9 ± 23.8	103 ± 21.8	0.0001
e' (m/s)	0.072 ± 0.016	0.12 ± 0.01	0.0001
E/e'	8.84 ± 3.4	6 ± 1.95	0.0001

GFR glomerular filtration rate, *LVMI* left ventricular mass index, *LVMH* left ventricular mass indexed by height elevated by a power of 2.7, *RTW* relative wall thickness, *LAVI* left atrial volume index, *E* E-wave peak velocity, *A* A-wave peak velocity, *DT* E-deceleration time, *IVRT* isovolumic relaxation time, *e′* early diastolic myocardial velocity

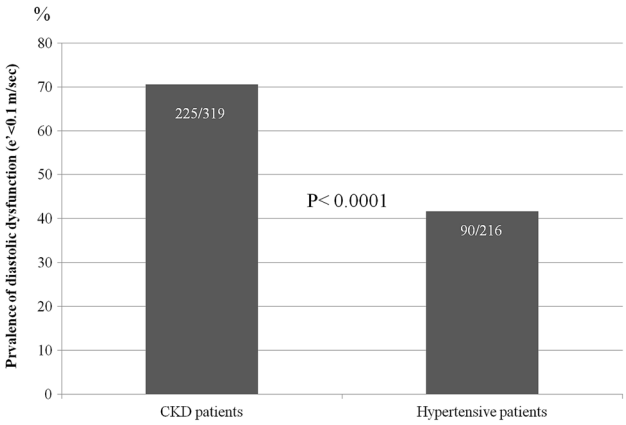

Fig. 1 Multivariate correlates of early diastolic myocardial velocity in the whole study population of 319 hypertensive patients with CKD

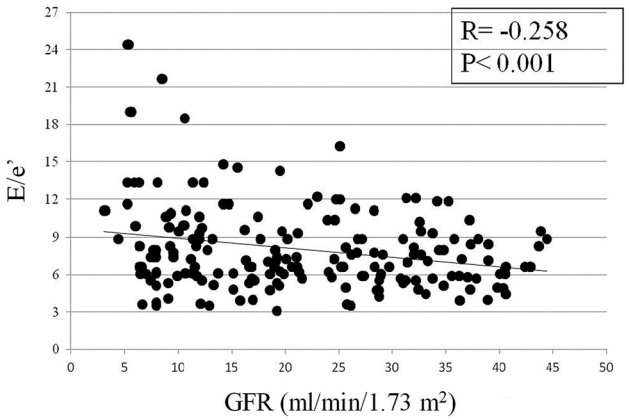

Fig. 2 Correlation between a parameter of diastolic function (*e′*) and GFR in the whole study population of 319 hypertensive patients with CKD

Table 4 Univariate correlations between a parameter of diastolic function (*e′*) and some studied variables in the whole study population of 319 hypertensive patients with CKD

	R	*P* <
Age	− 0.360	0.0001
BMI	− 0.102	NS
SBP (mmHg)	− 0.038	NS
DBP (mmHg)	− 0.019	NS
PP (mmHg)	− 0.056	NS
Hemoglobin (g/dL)	0.287	NS
Diabetes	− 0.034	NS
GFR (ml/min/1.73 m^2)	0.384	0.0001
LVMI (g/m^2)	− 0.442	0.0001
Relative wall thickness	− 0.389	0.0001

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *PP* pulse pressure, *GFR* glomerular filtration rate, *LVMI* left ventricular mass index

age ($p < 0.0001$), GFR ($p < 0.0001$), LVMI ($p < 0.0001$) and RWT ($p < 0.0001$).

The association of estimated GFR with *e′* value (Fig. 2) holds in multiple linear regression analysis after adjustment for various confounding factors ($\beta = 0.223$; $p < 0.0001$). This is true even when *e′* value is considered as a dichotomous outcome variable (> 0.1 m/s = 0; < 0.1 m/s = 1) in logistic regression analyses (Table 5) where the variables independently associated with diastolic dysfunction are age ($p < 0.0001$), GFR ($p < 0.0001$) and LVMI ($p < 0.0001$). Similar results were obtained when RWT replaced LVMI in the multivariate model.

Discussion

CKD is a major risk factor for the development of HF [24, 25]; the very high prevalence of LVH [26–29] in these patients, in large part responsible for diastolic dysfunction, plays a fundamental role in the development of HFpEF. The diagnosis of HFpEF is more difficult than the diagnosis of HFrEF because it is based on exclusion criteria. The classical signs and symptoms of HF result from sodium and water retention, conditions also very frequent in advanced CKD. Moreover, circulating brain natriuretic peptide (BNP), which is a widely used marker for the evaluation of HFpEF, has limited usefulness in patients with deteriorated kidney function, because levels of BNP are basically increased in these subjects.

The presence of diastolic dysfunction may be considered a critical precursor of HF, because CKD patients are more likely to develop HF with normal ejection fraction [3, 18].

Demonstration of an underlying diastolic dysfunction is therefore central to the diagnosis of HFpEF [11] and may contribute to identifying patients at high risk of heart failure in the absence of symptoms.

In a population of hypertensive patients with CKD and without evidence or symptoms of cardiovascular disease, we found a very high prevalence of diastolic dysfunction (70.5%, Fig. 1), and all parameters of diastolic function (E/A, DT, IVRT, *e′*, *E*/*e′* and LAVI) were significantly worse in comparison to a population of hypertensive patients with normal renal function (Table 2).

Moreover, there is an association between kidney function (GFR value) and diastolic dysfunction (*e′* value) independent of potential confounders (age, hemoglobin, LVMI or RWT).

In our study, patients with CKD have significantly higher LV diameters, interventricular septum and

Table 5 Logistic regression analyses considering e' as dichotomous outcome variable (> 0.1 m/s = 0; < 0.1 m/s = 1)

	Odds ratio	$P <$
Age (for 1 year increase)	1050 (1027–1082)	0.0001
GFR (ml/min/1.73 m^2), (for 1 ml/min increase)	0.944 (0.919–0.969)	0.0001
LVMI (g/m^2), (for 1 g/m^2 increase)	1.017 (1008–1026)	0.0001

GFR Glomerular filtration rate, *LVMI* Left ventricular mass index

posterior wall thickness, and consequently higher LVMI and $LVMH^{2.7}$ values responsible, in large part, for diastolic dysfunction.

The found prevalence of LVH is very high (80 vs. 44% in the control group; $p < 0.0001$). In a study by Park et al. [3], a high prevalence of LVH is found (75% in patients with GFR < 30 ml/min per 1.73 m^2), but only a minimal association between kidney function and diastolic dysfunction is observed.

Due to the cross-sectional design of the study, we cannot provide information on the mechanisms linking reduced kidney function with the impairment of myocardial lusitropic properties. However, the pathophysiology of LVH and diastolic dysfunction in CKD patients who are not yet on dialysis seems to be related to the interaction of multiple factors including hemodynamic and non-hemodynamic ones [30]: hypertension, chronic volume overload, anemia, arterial stiffness as well as inflammation [31, 32], oxidative stress [32], activation of the renin–angiotensin–aldosterone system [30, 33], activation of the sympathetic nervous system, abnormalities in bone and mineral metabolism [30]. In the past few years, a great deal of interest has been given to fibroblast growth factor 23, a hormone secreted by osteoblasts/osteocytes that acts on the kidney to regulate phosphate and active 1,25-di-hydroxyvitamin D [34]. More recently, it has been shown that indoxyl sulfate, a uremic toxin, may exert profibrotic and prohypertrophic effects on cardiac cells and has been associated with diastolic dysfunction in CKD subjects [35].

In conclusion, our data highlight a very high prevalence of LVH and diastolic dysfunction in CKD patients without signs or symptoms of heart failure or other cardiovascular diseases.

The difficulty in diagnosing HFpEF probably leads to an underestimation of this condition, above all in these patients (advanced CKD) characterized by an overlap of pathological conditions.

We think that in all patients with advanced CKD (GFR < 45 ml/min/1.73 m^2), even if asymptomatic and in the absence of anamnestic evidence of cardiovascular disease, an echocardiographic examination with a complete study of diastolic function, preferably including TDI, should be carried out, to obtain a better prognostic definition and to begin early treatment that could lead to a better prognosis.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Statement of human and animal rights The article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Our study is retrospective and formal consent is not required.

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