Cardiovascular remodelling and extracellular fluid excess in early stages of chronic kidney disease

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Abstract

Background. Patients with a mild to moderate decrease of glomerular filtration rate (GFR) are at risk of cardiovascular (CV) events and CV remodelling has been demonstrated in patients with advanced chronic kidney disease (CKD). However, early stages of CKD and the mechanisms involved in these modifications have not been studied.

Methods. A total of 104 patients with early CKD (mean GFR 60 ± 21 ml/min/1.73 m²) had cardiac and vascular ultrasound study and measurement of extracellular fluid by multifrequency spectroscopic bioimpedance.

Results. GFR decline was associated with left ventricular (LV) remodelling or hypertrophy in 58 and 68% of DOQI-2 and DOQI-3 patients, respectively and impaired LV diastolic function. GFR decrease was also associated with common carotid remodelling and increased aorta stiffness. Cardiac and vascular remodelling were significantly associated with an excess of extracellular fluid (ECFe) evidenced as early as DOQI-2 stage. In multivariate analysis with adjustment for GFR, ECFe, age and systolic blood pressure (sBP), GFR was no longer independently associated with cardiac and vascular remodelling, whereas ECFe was an independent determinant of LV hypertrophy, left atrium enlargement, common carotid diameter and intima media thickness.

Conclusion. This study shows that CV remodelling and ECF excess occurred at a very early stage of CKD. The independent association between ECF excess and cardiac and vascular remodelling and hypertrophy may be instrumental in the increased cardiovascular risk in CKD patients. Early therapeutic control of ECF may reduce CV events in CKD patients.

Keywords: cardiovascular remodelling; chronic kidney disease; extracellular fluid; hypervolaemia

Introduction

Chronic kidney disease (CKD) has been recently recognized as an independent cardiovascular risk factor. The involvement of mild to moderate renal failure in the occurrence of cardiovascular complications was found in two large epidemiological studies. The National Health and Nutrition Examination Study II reported a 1.68-fold increase in the risk of cardiovascular death in patients with mild renal failure [1], while the Atherosclerosis Risk in Communities Study indicated a continuum of the effect of renal failure with a 10 ml/min decrease in glomerular filtration rate (GFR) linked to a 7% increase in the risk of de novo atherosclerosis and cardiovascular disease [2]. Furthermore, the cardiovascular risk rose as the GFR dropped below 60 ml/min/1.73 m². This increase in cardiovascular risk was not accounted for by classical risk factors, such as age, hypertension or diabetes. Hypervolaemia, activation of the autonomic nervous system and of the renin-angiotensin pathway, oxidative stress, malnutrition and inflammation status have been advocated [3] but not directly demonstrated. Cardiovascular remodelling has been demonstrated in end-stage kidney disease and haemodialysis [4–6] and recently, Briet et al. [7], reported that GFR was independently related to carotid enlargement and increased aortic stiffness in patients with advanced
CKD (mean population GFR 36 ml/min/1.73 m²). However, the issue of cardiac and vascular remodelling has not been clarified at the earliest stages of CKD, i.e. in patients with kidney disease but normal or mild to moderate decrease in GFR (GFR >30 ml/min/1.73 m²).

One main characteristic of end-stage renal disease is the modification of body water compartments, and especially of extracellular fluid (ECF) [8]. In dialysed patients, volume overload was shown to contribute to an increase in blood pressure and arterial stiffness, as shown by an increased pulse wave velocity (PWV) [9]. However, the occurrence of alterations of ECF in patients with early stages of CKD and cardiovascular alterations has not been evaluated.

We took advantage of a cross-sectional analysis of a cohort of patients entering a 5-year longitudinal follow-up programme to focus on cardiac and body composition alterations in patients with mild to moderate decrease in GFR, and to analyse the links between these alterations, GFR and ECFe.

**Subjects and methods**

**Patients**

From September 2002 to December 2005, all ambulatory patients aged 18 to 75 years with body mass index below 35 kg/m², referred to the Nephrology Department with mild to moderate renal disease, defined according to the Dialysis Outcome Quality Initiative (DOQI) and (K-DIGO) classifications (DOQI-1: kidney disease without renal function impairment i.e. GFR ≥90 ml/min/1.73 m² BSA, DOQI-2: mild renal failure i.e. GFR 90–60 ml/min/1.73 m² BSA and DOQI-3: moderate renal failure i.e. GFR 60–30 ml/min/1.73 m² BSA) were proposed to enter a 5-year follow-up study, with measurement of GFR, body composition analysis by dual-X-ray absorptiometry and bioimpedance spectroscopy, cardiac and vascular ultrasound study. One hundred and four patients were included in the study. All parameters analysed in the study were routinely performed in the follow-up of subjects with renal disease in our department.

**Cardiac and vascular ultrasound studies**

Ultrasound studies were conducted in a temperature-controlled room after a 15-min rest, with a Toshiba Power vision 6000, SSA 370A device equipped with a 7.5–11 MHz linear probe for high resolution vascular echography and a 2–4.2 MHz phase array probe for cardiac study.

Standard cardiac ultrasound examination was performed. Left ventricle (LV) dimension measurements were made according to the recommendations of the American Society of Echocardiography [10]. Apical view was used for pulse wave (PW) Doppler measurement of LV mitral inflow and septal mitral annulus motion (PW tissue Doppler). Left atrium (LA) volume was measured from a four-chamber apical view by the method of the discs [11]. LV mass was calculated according to Penn convention [12]. Relative wall thickness (RWT) was computed as posterior plus septal wall thickness/LV diastolic diameter (LVEDD).

Concentric remodelling was defined as RWT >0.42 and normal LV mass; concentric LV hypertrophy as LV mass/m² increase (>115 g/m² for men and >95 g/m² for women) and RWT >0.42; eccentric hypertrophy as LV mass increase and RWT ≤0.42 [13].

Right and left common carotid arteries (CCA) were imaged. Intima media thickness (IMT) was measured offline from B mode diastolic images, as gated on ECG R wave, with IodDP station (IodDP, France) [14]. Right and left values were averaged for each patient. CCA diameter was measured within 1 cm proximal to the carotid bifurcation. B mode image was obtained and an M-line was then placed at the measurement site for measurement of CCA diameter at end diastole, as gated on ECG R wave. Blood pressure was simultaneously measured on the left arm and averaged from three measurements. Pulse pressure (PP) was computed as systolic minus diastolic pressure. PWV was measured by the carotid to femoral method [15]. The time delay between ECG R wave and the Doppler flow onset was measured at right CCA and common femoral artery and the difference computed (t). D is the body surface distance between the two measurement points minus the distance from the suprasternal notch to the carotid measurement point; PWV was computed as D/t. To take into account the relationship between artery size and body size, CCA diameter was normalized to the squared height. Reference vascular values were obtained from a group of 73 healthy individuals without known renal or cardiovascular disease, who were 40.8 ± 12.6 [range 21–64]-year old (control group).

**Extracellular fluid analysis**

ECF was measured in the fasting patient by multifrequency spectroscopic bioimpedance (Analycor XF: Spengler, Cachan, France). The Hanai equation was used for computation [16]. Multifrequency spectroscopic bioimpedance record and the use of Hanai modelization allows the precise measurement of extracellular water, as demonstrated by comparison with the gold standard bromide sodium dilution measurements by De Lorenzo [17]. It has also been demonstrated by Gudivaka et al. [18] to predict more accurately changes in extracellular water than the usual single-frequency, 50-kHz models. Measurements were performed in a standard manner by the same technician. Briefly, four skin electrodes (Control Graphic) were placed on the dorsal surface of the right hand and left foot. Measurements were made after supine rest of at least 15 min. Twenty frequencies were measured ranging from 1 to 300 kHz. Data were collected and analysed with software IMP BO4 (Spengler). The variability of resistance and reactance measurements was below 1 and 2%, respectively. Reference ranges, as established from a French normal population, and adjusted for gender, age, and height, was supplied by the manufacturer. For each patient, the difference between the measured fluid volume and the upper limit (mean ± 2SD) of the reference range was computed as ECF excess (ECFe). ECFe was found to be independent of body height (P = 0.24, R² = 0.014).

**Glomerular filtration rate and biochemistry**

GFR was measured with the plasma clearance of unlabelled iohexol. Plasma concentration of iohexol was determined by
Cardiac remodelling, extracellular fluid excess and early CKD

high performance chromatography [19]. The plasma profile was analysed with the exponential slope and intercept method in the slow clearance phase with six samples between 90 and 240 min after injection, and corrected by the Brochner Mortensen’s formula [20].

Plasma albumin, haemoglobin, homocystein, C-reactive protein, total, HDL and LDL cholesterol, triglycerides, parathyroid hormone, daily proteinuria and natriuresis were determined using standard laboratory methods.

Statistical analysis

Data are expressed as mean±SD. The differences for cardiac and vascular ultrasound parameters and ECFe across DOQI-1, DOQI-2 and DOQI-3 groups were evaluated by ANOVA with a Tukey–Kramer test for pairwise comparisons if the global test was significant.

Relationships between LV hypertrophy and remodelling and vascular ultrasound parameters were tested by regression adjusted for PWV, IMT and systolic blood pressure (sBP). The association between ECFe and cardiovascular ultrasound parameters was studied with Pearson’s correlation coefficient test. The independent role of GFR and ECFe on cardiovascular ultrasound parameters was studied by regressions adjusted for PWV, IMT and systolic blood pressure (sBP).

Treatment comparisons if the global test was significant.

Results

Population characteristics

Thirty-three women and 71 men were studied and their characteristics are displayed in Table 1. Eleven patients were staged DOQI-1, 36 DOQI-2 and 57 DOQI-3. Thirty-one patients had glomerulonephritis, 10 had diabetic glomerulosclerosis, 11 had chronic nephrectomy because of malignancy or urolithiasis. Patients with diabetic nephropathy or nephroangiosclerosis were older (58±12 vs 45±13 year, P=0.003) and had lower GFR (49±13 vs 65±23 ml/min/1.73m², P=0.0002) than others. Thirty-three patients received diuretics. Renin angiotensin system (RAS) blockers were given to 70 patients and statins to 31 patients (Table 1).

In the CKD population, cholesterol, glycaemia, homocystein level and CRP were in the normal range (Table 2). However, there was a significant increase in homocystein and PTH across the three DOQI groups. BMI was slightly increased in DOQI-2 and DOQI-3 groups indicating a slightly overweight condition without, however, overt obesity (Table 1). PP and sBP increased significantly with CKD, whereas diastolic blood pressure (DBP) was not different across the three DOQI groups (Table 1).

Cardiac and vascular alterations at early stages of CKD

A significant increase in LV mass but no significant LV enlargement was evidenced across DOQI groups (Table 3). As assessed by RWT and LV mass, LV geometry tended toward concentric remodelling and hypertrophy across the DOQI groups (Table 3).

Table 1. Characteristics of the patients

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>DOQI-1</th>
<th>DOQI-2</th>
<th>DOQI-3</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>74</td>
<td>11</td>
<td>36</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>F/M</td>
<td>39/35</td>
<td>8/3</td>
<td>11/25</td>
<td>14/43</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>40.5±12</td>
<td>38±13</td>
<td>49±14*</td>
<td>55±14*</td>
<td>0.0017</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.6±2.4</td>
<td>23±4</td>
<td>26±4</td>
<td>26±4</td>
<td>NS</td>
</tr>
<tr>
<td>Waist circ. (cm)</td>
<td>89±6.6</td>
<td>87±11</td>
<td>94±11</td>
<td>96±11</td>
<td>NS</td>
</tr>
<tr>
<td>GFR (ml/min/1.73m²)</td>
<td>ND</td>
<td>106±10</td>
<td>70±8*</td>
<td>45±8*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>65±9</td>
<td>67±12</td>
<td>64±9</td>
<td>64±12</td>
<td>NS</td>
</tr>
<tr>
<td>sBP (mmHg)</td>
<td>124±12.8</td>
<td>123±22</td>
<td>134±17</td>
<td>138±18*</td>
<td>0.04</td>
</tr>
<tr>
<td>dBP (mmHg)</td>
<td>72±10.1</td>
<td>72±17</td>
<td>76±12</td>
<td>76±12</td>
<td>NS</td>
</tr>
<tr>
<td>PP (mmHg)</td>
<td>51±8</td>
<td>51±17</td>
<td>58±10</td>
<td>62±15*</td>
<td>0.04</td>
</tr>
<tr>
<td>Treatment</td>
<td>RAS blocker</td>
<td>5 (45%)</td>
<td>22 (61%)</td>
<td>43 (74%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diuretic</td>
<td>1 (9%)</td>
<td>6 (17%)</td>
<td>27 (47%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Statin</td>
<td>3 (27%)</td>
<td>8 (22%)</td>
<td>20 (35%)</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD.
P, P-values of global ANOVA analysis; NS, not significant.
*P<0.05 vs DOQI-1, **P<0.05 vs DOQI-2 of the pairwise comparisons if the global test was significant.

Table 2. Biological data of the patients

<table>
<thead>
<tr>
<th></th>
<th>DOQI-1</th>
<th>DOQI-2</th>
<th>DOQI-3</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>12.3±1.9</td>
<td>13.6±1.7*</td>
<td>13.1±1.7#</td>
<td>NS</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>40.4±5.3</td>
<td>40.4±4.0</td>
<td>40.1±5.8</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.7±1.2</td>
<td>5.0±1.1</td>
<td>4.8±1.2</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.6±0.45</td>
<td>1.4±0.4</td>
<td>1.5±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>3.1±1.7</td>
<td>3.0±1.1</td>
<td>2.7±0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Triglyceride (mmol/l)</td>
<td>1.4±1.0</td>
<td>1.4±0.8</td>
<td>1.6±1.2</td>
<td>NS</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.7±1.3</td>
<td>5.7±0.98</td>
<td>5.9±1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Glycaemia (mmol/l)</td>
<td>5.0±1.9</td>
<td>4.9±1.5</td>
<td>5.1±1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Homocystein (mmol/l)</td>
<td>11±7</td>
<td>12±5</td>
<td>16±6**</td>
<td>0.009</td>
</tr>
<tr>
<td>C-reactive protein (mg/l)</td>
<td>8.0±1.45</td>
<td>4.4±27</td>
<td>4.9±7.8</td>
<td>NS</td>
</tr>
<tr>
<td>Parathyroid hormone (pg/ml)</td>
<td>32±18</td>
<td>61±35</td>
<td>69±36*</td>
<td>0.015</td>
</tr>
<tr>
<td>Daily proteinuria (g/day)</td>
<td>1.2±2.84</td>
<td>0.3±0.6</td>
<td>1.4±3</td>
<td>NS</td>
</tr>
<tr>
<td>Daily natriuresis (mmol/day)</td>
<td>136±63</td>
<td>148±66</td>
<td>109±59**</td>
<td>0.028</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD.
P, P-values of global ANOVA analysis; NS, not significant.
*P<0.05 vs DOQI-1, **P<0.05 vs DOQI-2 of the pairwise comparisons if the global test was significant.
At DOQI-2 stage, only 42% of the patient had normal LV geometry. LV hypertrophy progressively increased with the decline of GFR and was observed in 13/36 (36%) in the DOQI-2 group and in 29/57 (50%) in the DOQI-3 group (Figure 1).

In DOQI-3 patients, an alteration of LV diastolic function was found, with a significantly lower septal mitral annulus wave (Ea), an increase in deceleration time and isovolumic relaxation time (Table 3). E/Ea tended to increase and was above 10 in the DOQI-3 group. LV systolic function was unaltered, as depicted by ejection fraction and S wave of the mitral annulus (Table 3). LA volume tended to increase across the DOQI groups and 66% of the patients had an LA volume above 32 ml/m².

Patients with early CKD also exhibited vascular remodelling and stiffness with a significant increase in CCA diameter (Figure 2A), PWV (Figure 2B) and IMT (Figure 2C) across the control and the DOQI groups. The significant increase in CCA diameter, PWV and IMT was also observed in the subgroup of patients without diabetes or nephroangiosclerosis ($P < 0.0001$, $P = 0.0002$ and $P < 0.0001$ for CCAd, PWV and IMT, respectively).

<table>
<thead>
<tr>
<th></th>
<th>DOQI-1</th>
<th>DOQI-2</th>
<th>DOQI-3</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left atrial volume (ml/m²)</td>
<td>40 ± 14</td>
<td>37 ± 8</td>
<td>42 ± 19</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDV (ml/m²)</td>
<td>67 ± 11</td>
<td>61 ± 12</td>
<td>64 ± 17</td>
<td>NS</td>
</tr>
<tr>
<td>LV mass (g/m²)</td>
<td>94 ± 28</td>
<td>101 ± 28</td>
<td>118 ± 39*</td>
<td>0.025</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>71 ± 7</td>
<td>71 ± 7</td>
<td>69 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>Sa wave (cm/s)</td>
<td>7.1 ± 1.0</td>
<td>7.1 ± 1.5</td>
<td>6.8 ± 1.6</td>
<td>NS</td>
</tr>
<tr>
<td>Deceleration time (ms)</td>
<td>180 ± 48</td>
<td>205 ± 56*</td>
<td>257 ± 56*</td>
<td>0.026</td>
</tr>
<tr>
<td>Isovolumic relaxation time (ms)</td>
<td>95 ± 18</td>
<td>104 ± 20</td>
<td>114 ± 28</td>
<td>0.042</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD.

LVEDV, left ventricular end-diastolic volume; LV, left ventricle; RWT, relative wall thickness; Sa and Ea, septal systolic (Sa) and diastolic (Ea) mitral annulus TDI wave velocity; PAP, pulmonary artery pressure; CCAd/h², common carotid artery end-diastolic diameter to squared body height ratio; PWV, aortic pulse wave velocity; IMT, intima media thickness; $P$: $P$-values of global ANOVA analysis, NS, not significant. *$P < 0.05$ vs DOQI-1, of the pairwise comparisons if the global test was significant.

**Figure 1.** LV remodelling and hypertrophy in very early CKD: LV remodelling and hypertrophy across the DOQI groups: normal LV geometry (open square); concentric remodelling (light shaded square); concentric hypertrophy (dark shaded square); eccentric hypertrophy (filled square).

**Figure 2.** Vascular alterations in early CKD. (A) CCAd: Common carotid artery diameter. (B) PWV: Pulse wave velocity. (C) IMT: Intima media thickness.
The influence of the different arterial components on LV geometry and function was assessed in simple and multivariate analysis. LV mass and RWT were significantly related to PWV ($P = 0.005$ and $P < 0.0001$ for LV mass and RWT, respectively), IMT ($P < 0.0001$ for both) and sBP ($P < 0.0001$ for both). In multiple regression taking into account PWV, IMT and sBP, LV mass and RWT were independently associated with sBP ($P < 0.005$ for both). LV mass was significantly associated with IMT but not with PWV ($P = 0.01$ and 0.9, respectively). On the contrary, RWT was significantly associated with PWV but not with IMT ($P = 0.05$ and 0.06, respectively).

Extracellular fluid and cardiovascular alterations in early chronic kidney disease

Patients with CKD showed a progressive increase in ECFe across the DOQI groups (Figure 3A). ECFe was significantly related to the decline in GFR (Figure 3B), and to the daily natriuresis (Figure 3C) accounting for 8 and 6% of the change of ECFe, respectively.

In univariate analysis, ECFe was related to both LV concentric remodelling and LV hypertrophy (Figure 4A and B) and to LV diastolic dysfunction, as depicted by Ea and E/Ea (Figure 4C, D). ECFe accounted for 23% of the observed LV hypertrophy and 14% of the LV diastolic dysfunction. LA enlargement was also strongly associated with ECFe (Figure 4E), which accounted for 27% of LA change. ECFe was also significantly associated with vascular remodelling and stiffness, as depicted by CCA diameter, PWV and IMT (Figure 5A–C).

Determinants of cardiovascular alterations in early chronic kidney disease

Since the cardiac and vascular alterations described with CKD resemble that associated with ageing and hypertension, multivariate analysis was performed with adjustment for GFR, ECFe, age and mBP, to analyse the independent role of GFR and ECFe in cardiac and vascular remodelling. Whereas GFR was not independently associated with cardiac and vascular remodelling, ECFe was an independent determinant of LV hypertrophy, LA enlargement and vascular remodelling as depicted by CCA diameter and IMT (Table 4). Artery stiffness was mostly dependent on mBP and ageing and not on GFR or ECFe.

Since there is a close association between parathyroid hormone and left ventricular function and structure in end-stage renal failure and in primary hyperparathyroidism, we assessed the relationship between PTH and cardiac and vascular remodelling in the regression adjusted for age, GFR, mBP and ECFe. We did not find any significant relationship between PTH and LA volume, LV mass, RWT, Ea wave, CCA diameter or PWV. IMT was the only parameter significantly related to PTH level ($P = 0.02$).

Discussion

In this study, we observed that cardiac and vascular remodelling were present at the very early stages of CKD and that ECFe was a major determinant of cardiac and vascular alterations.

We found that structural and functional cardiac alterations occurred very early in the course of CKD, as early as DOQI-2 stage (GFR 60–90 ml/min/1.73 m²), and paralleled the magnitude of GFR decline. LV remodelling and/or hypertrophy was present in 58% of the patients at DOQI-2 stage. This highlighted...
how early CKD alters cardiac status. The increase in LV mass was consistent with previous studies in patients with more advanced CKD in whom renal function was estimated with Cockcroft or MDRD formula [5,21,22]. It is worth noting that the accuracy of these formulas was the highest in patients with moderate to severe CKD but decreased when renal function was better preserved, as in our population [23]. As we used the reference technique of Iohexol clearance to measure GFR, precise and reliable relationships were found between cardiac and renal status, even in patients with modest decline in GFR.

We also observed an increase in LA volume in the early course of CKD. The increase in LA volume has been demonstrated to predict the risk of stroke or other cardiovascular events, independently of age, diabetes, myocardial infarction or hyperlipidaemia [24]. In our study, 66% of the patients displayed an LA volume above 32 ml/m², the threshold value associated with increased mortality [24].

In addition to cardiac remodelling, we showed alterations in structural and mechanical properties of large arteries with enlargement of common carotid artery and increased aortic stiffness in the early course of CKD. These results are in line with those recently reported by Briet et al [7] in a population of older patients (mean age 58 years) and with more severe renal disease (mean GFR 36 ml/min/1.73 m²) since our patients were middle age (mean age 47 years) and had an early kidney disease (mean GFR
In the present study, the relationship between vascular alterations and GFR was also observed in the subpopulation of patients without diabetes or nephroangiosclerosis who may be more prone to vascular disease. Although IMT is significantly increased in CKD patients, as compared with the control group, it did not progress between the DOQI-2 and DOQI-3 group. This might result from the high number of patients receiving statins and/or RAS blockers in DOQI-3 patients (Table 1), since statins have been demonstrated to reduce IMT in early carotid atherosclerosis [25–27].
Contrary to Wang et al. [28] who found GFR an independent determinant of PWV during the course of CKD, our relationship between GFR and PWV were no longer significant after adjustment for age, blood pressure and ECFe. Kimoto et al. [29] recently observed that, after adjustment for age, BP and other confounding factors, decreased GFR was not associated with PWV of heart-carotid, heart-brachial and femoral-ankle arterial segments. Furthermore, the association between GFR and heart-to-femoral PWV was no longer significant when age, sBP, diabetes, lipids and medication were added to the model. In our study, we used the carotid to femoral artery which is close to that of the heart to femoral artery segment and thus could have a weaker association that would have the heart-to-femoral PWV. Of interest, in a statistical model taking into account medications as done by Kimoto et al. (RAS blockers and Statins), ECFe became an independent factor of PWV (P = 0.0016), beside age and BP. Altogether, these results suggested that numerous factors are involved in the increased artery stiffness during the course of CKD, among them the most important are age and blood pressure.

Of major interest was evidencing that ECFe, which increased when GFR declined, was an independent factor in the structural cardiac and vascular changes during the course of CKD. Indeed, we showed that a major determinant of cardiac hypertrophy and vascular remodelling was not GFR per se but the change in extracellular body fluid content, along with the well-documented effects of age and sBP. It could have been expected that LV enlarged with increasing ECFe. However, in most patients we observed LV concentric hypertrophy or LV concentric remodelling. One explanation could be that LV distensibility and compliance decreased with hypertrophy and remodelling. In accordance with this hypothesis, we showed a progressive alteration of LV diastolic parameters. In the same way, the increase in LA volume that we observed, resulted probably from the increase in LV filling pressure, as described by E/Ea ratio. This result is in agreement with that observed in other situations with predominant LV diastolic alterations such as ageing, or infiltrative heart disease, such as cardiac sarcoidosis, in which LA dilation is one of the earliest echocardiographic findings. We demonstrated that LA volume was also strongly associated with ECFe. For bedside clinical practice, evaluation of ECFe in CKD patients is an important point that could be drawn from our study. Indeed physical examination is poorly efficient for detection of small increases in ECFe, as expected at early stages of CKD, because ECFe increase is spread all over the body. From our study and other large scale study [30], it could be proposed to look for small increases in ECFe in CKD patients either by ECFe measurement with spectroscopic bioimpedance or by evaluation of the cardiac-associated alteration with LA volume and LV remodelling measurement with echocardiography. Since, LA volume is also a strong determinant of the occurrence of atrial fibrillation [30], which is a known complication in end-stage renal disease and dialysis, the link that we observed between LA volume and ECFe suggested that ECFe could be instrumental in the frequent occurrence of atrial arrhythmias in CKD patients. The low cost and availability of bioimpedance measurement is in favour of this technique for first line ECFe evaluation in a large population.

An increase in ECF is a hallmark of end-stage kidney disease; however whether ECFe occurs early in the course of CKD has remained under debate. In this study, we demonstrated the presence of an increase in ECF very early in the course of CKD. This modest, albeit significant, 8% increase in ECF may easily be underestimated by clinical examination and can only be proved by accurate measurement of body water volume, as with multifrequency spectroscopic bioimpedance. Although progressive chronic kidney failure is typified by an adaptive increase in sodium excretion rate per nephron as the total GFR declines, the increase in sodium excretion rate by nephron may not succeed to excrete a high sodium intake, which is a characteristic of the western diet. This increase in sodium excretion per nephron is caused by a decreased expression of sodium transporters along the proximal tubule [31] and the effect of various natriuretic factors whose release are increased with volume expansion and kidney disease. We showed an increase in Na excretion across DOQI-1 and DOQI-2 groups but a surprising decrease across DOQI-2 and DOQI3 groups. At steady state, whatever be the presence of diuretics, Na excretion is the strict reflection of Na intake. Natriuresis decrease at DOQI-3 stage could thus result from a decrease in Na intake, associated with nutritional counsels that are more frequently given to more advanced CKD patients. However, despite the decrease in Na excretion, the fact that DOQI-3 patients displayed an increase in ECFe could result from a previous disequilibrium between Na intake and Na excretion due to the progressive fall in GFR. Indeed, an Na balance disequilibrium resulting in a gain of 0.5 mmol of Na per day in DOQI-1-3 would lead, despite subsequent reduction in Na intake, to a gain of about 185 mmoles per year which would correspond to a gain of 11 of ECF. This value is close to the measured difference in ECF between DOQI-3 and DOQI-1. The relationship between daily natriuresis, as a reflection of sodium intake at equilibrium, and the excess of ECF, that we observed suggested that a decrease in sodium intake could reduce ECFe in CKD patients. According to the relationships between ECFe and cardiovascular alterations, the control of sodium balance very early in the course of the disease, even in the absence of hypertension, might participate in decreasing the risk of cardiovascular events. The latter point is of major importance as ECF can be controlled with diet advice and diuretic use. This should be considered early in CKD, in combination with other renoprotective treatments such as RAS blockers. However, further studies with intervention on sodium intake should be done to confirm this hypothesis.
We acknowledged that many of the cardiac and vascular data show a high degree of scatter when related to ECFe. However the involvement of bioimpedance to explain this scattering seems unlikely. Indeed, the variability of resistance and resistivity coefficient, as measured by bioimpedance, is 1%. Since ECF is calculated using resistance and resistivity measure, variability of ECF measure should be close to 1%

One explanation of the scatter could be the number of independent factors associated with cardiac and vascular remodelling that is modified during the course of CKD. This study aimed to specifically address the role of ECF excess but we agree that the role of other factors was not studied. However, the relationship between ECF excess and cardiovascular parameters after adjustment on age, GFR and blood pressure was a strong argument supporting the role of ECFe by itself in the alterations of heart and vessel observed during the course of CKD

In conclusion, by evaluation of patients with early CKD, this study gave insight into genesis and pathophysiology of cardiac and vascular remodelling, which are highly frequent in this population. Although limited by the observational design of the study, the association between GFR, ECF excess and cardiac and vascular alterations suggested a pathophysiological link. This does not preclude the occurrence of other mechanisms, such as anaemia, hyperhomocystaemia, inflammation or toxic effects of uraemia per se [4,7,32–34]. Although markers associated with these abnormalities were not present in our population, we cannot rule out that unidentified confounding variables might also affect cardiovascular remodelling. A prospective evaluation will thus be mandatory to establish the benefit of ECF control in CKD patients with regard to cardiovascular events.

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