Diastolic dysfunction in paediatric patients on peritoneal dialysis and after renal transplantation

Arend Derk Jan Ten Harkel1, Karlien Cransberg2, Magdalena Van Osch-Gevers1 and Jeroen Nauta2

1Department of Pediatric Cardiology and 2Department of Pediatric Nephrology, Erasmus MC-Sophia, Rotterdam, The Netherlands

Correspondence and offprint requests to: Arend Derk Jan Ten Harkel; E-mail: A.D.I.Ten_Harkel@lumc.nl

Abstract

Background. Cardiovascular disease is the leading cause of death in children with end-stage renal disease. We investigated the presence of cardiac systolic and diastolic dysfunction in patients on peritoneal dialysis or after renal transplantation.

Methods and results. Fourteen patients on peritoneal dialysis for a mean of 1.4 years (range 0.1–5.3) and 39 patients with a functioning kidney transplant for a median time of 3.3 years (range 1.2–14.5) were studied. These patients were compared to 153 age-matched healthy controls. As assessed by echocardiography, both dialysis and transplant patients showed left ventricular dysfunction. Systolic tissue Doppler values were lower as compared to controls. Mitral E/A ratios were significantly lower as well, indicating diastolic dysfunction (transplant 1.82 ± 0.58 versus 2.15 ± 0.63, P < 0.01; dialysis patients 1.57 ± 0.73 versus 2.31 ± 0.52, P < 0.01). Also, tissue Doppler values were different, showing an increased E′/E ratio in the patients, indicating diastolic dysfunction (transplant 9.49 ± 1.71 versus 7.50 ± 1.60, P < 0.01; dialysis patients 11.90 ± 2.11 versus 8.10 ± 1.24, P < 0.01). The left ventricular mass index was increased in the transplant patients (controls 25 ± 7 g/m²2.7; transplant 59 ± 64 g/m²2.7; P < 0.01), as well as in the dialysis patients (controls 28 ± 7 g/m²2.7; dialysis 43 ± 11 g/m²2.7; P < 0.01) and was associated with systolic hypertension (R = 0.46, P < 0.05). High parathyroid hormone (PTH) levels, more prevalent in dialysis patients, were associated with abnormal E/A and E′/E ratios.

Conclusions. Abnormalities in diastolic function are present in both peritoneal dialysis and renal transplanted patients. In the dialysis group, abnormalities in calcium–phosphate metabolism are associated with diastolic dysfunction. Cardiac hypertrophy was noted in both patient groups and was associated with systolic hypertension.

Keywords: diastolic dysfunction; peritoneal dialysis; renal transplantation

Introduction

Cardiovascular disease is the leading cause of death in patients who started renal replacement therapy in childhood [1–3]. This includes cerebrovascular accident, cardiomyopathy, arrhythmias and cardiac arrest of unknown origin. Early signs of cardiac disease include hypertrophy and diastolic dysfunction of the left ventricle. These abnormalities develop in children already at the time of mild-to-moderate chronic renal insufficiency and progress as renal function deteriorates [4,5]. They have been described in patients on chronic dialysis as well as after renal transplantation. Hypertension and prolonged dialysis are predictors for cardiovascular mortality. Other risk factors for cardiovascular disease in children include abnormalities in calcium–phosphate metabolism, nephrotic syndrome, anaemia and long-term use of immunosuppressive agents, such as corticosteroids and calcineurin inhibitors [1,6]. Many of these factors improve after transplantation. There exists, however, conflicting evidence about improvements in cardiac function after renal transplantation. We therefore investigated children on chronic peritoneal dialysis or after renal transplantation. All patients underwent both conventional echocardiography and measurement of tissue Doppler variables, and were compared with the results obtained in normal children. These may help to determine early onset diastolic dysfunction.

We hypothesized that the cardiovascular abnormalities in transplanted patients may be less prominent compared to patients on dialysis and that diastolic dysfunction is associated with left ventricular hypertrophy.

Methods

This is a cross-sectional study of dialysis and transplanted patients in a tertiary paediatric nephrology department in a single university hospital in Rotterdam, The Netherlands. Transplant patients and dialysis patients were compared to age-matched controls (N = 112 and N = 41, respectively).

The patients were followed up by the outpatient nephrology clinic, and all underwent yearly echocardiography as part of their medical follow-up. The controls underwent echocardiography and were healthy school children without any medication or illness known to influence renal or cardiac function. The institutional review board of the Erasmus Medical Center, Rotterdam, The Netherlands, approved the study, and written informed consent was obtained from all controls and their parents. The need for individual consent of the patients was waived. Patients' medical records were reviewed for age, cause of renal failure, duration of peritoneal dialysis or time after renal transplantation and biochemical parameters. Calcium–phosphate disturbances were restricted by the use of dialysate with a physiologic calcium concentration (1.25 mmol/l), a protein-restricted diet, phosphate binding medication with the meals...
(usually sevelamer) and alphacalcidol as vitamin D analogue. In transplanted patients, 24-h ambulatory blood pressure monitoring was performed at the same occasion as the cardiac evaluation, by using an oscilometric device (SpaceLabs monitor, 90207; SpaceLabs Medical Inc., Redmond, WA, USA). Measurements were performed every 30 min during daytime and every hour during the night. Bedtime of the child was used as nighttime. Hypertension was scored as mean daily and nightly systolic and diastolic blood pressure above the 95th percentile for height and sex [7]. In the dialysis patients, 24-h ambulatory blood pressure monitoring has not been performed, and their casual blood pressure was taken as the average of three consecutive measurements as taken just before echocardiography, and compared to normal reference values [8].

Each patient had serum creatinine (normal reference 21–75 µmol/l), urea (normal reference 3–7 mmol/l), calcium (normal reference 1.9–2.7 mmol/l), phosphorous (normal reference 1.0–2.4 mmol/l), intact parathyroid hormone (iPTH) and haemoglobin (normal reference 8.2–12 mmol/l) determined at the time of echocardiography. Glomerular filtration rate (GFR) was estimated using the Schwartz formula, modified to conform with local laboratory practice [9,10].

Echocardiography was performed using a commercially available machine (Philips Sonos 5500, Andover, MA, USA). Echo studies included the M-mode measurement of left ventricular wall and septum, mitral inflow parameters and pulsed tissue Doppler estimates of the basal part of the left ventricle.

Echocardiograms were performed using standard techniques. Left ventricular mass (LVM) was measured by two-dimensional directed M-mode echocardiography according to the American Society of Echocardiography criteria [11]. The LVM index [mass divided by height raised to a power of 2.7 (g/m^2.73)] was used to evaluate LVM accounting for body size, as described elsewhere [12]. LV systolic performance was assessed by calculation of shortening fraction (SF) and heart rate-corrected velocity of circumferential shortening (VCF).

Transmitral flow was obtained with pulsed wave Doppler at the leaflet tips; early diastolic inflow velocity (E), velocity during active atrial contraction (A), E to A wave (E/A) ratio and deceleration time (D) were measured [13]. In the early stages of diastolic dysfunction, impaired relaxation of the left ventricle predominates, and this decreases early diastolic filling (E), increases filling at atrial contraction (A) and thus decreases the E/A ratio [13].

Pulsed wave Doppler tissue velocities were obtained at the cardiac base in the apical four-chamber orientation from three locations: the lateral mitral annulus, the interventricular septum and the lateral tricuspid annulus. Tissue Doppler measurements from each of these myocardial wall segments included peak systolic annular velocity (S), peak early diastolic annular velocity (E') and peak late diastolic annular velocity (A) waves. The ratio of early mitral inflow measured by Doppler to peak early diastolic annular velocity (E/E') was calculated as well. An increase in this ratio is correlated with the presence of diastolic dysfunction [14]. More specifically, this value is most closely related to the increased left ventricular pressure as present in patients with diastolic dysfunction [15]. In various studies, the prognostic significance of an increased E/E' ratio has been established [16,17].

Statistics

Statistical analysis was performed with SPSS 11.5 (SPSS, Inc., Chicago, IL, USA). Values are presented as mean ± SD unless stated otherwise. A two-sample t-test was used to compare the means of continuous variables with a normal distribution and the Mann–Whitney test for continuous variables without normal distribution. Categorical values were compared using the chi-square test or Fisher exact test. The correlations between blood pressure, parameters of calcium–phosphate metabolism, haemoglobin and urea levels and LVM index and E/A and E/E' ratios as assessed by echocardiography were assessed by Spearman correlation analysis. A P value < 0.05 was considered statistically significant.

Results

Patient characteristics (Table 1)

The study population consisted of 53 patients with a median time on renal replacement therapy of 4.3 years (range 0.1–16.0). Thirty-nine patients had a functioning kidney transplant for a median time of 3.3 years (range 1.2–14.5), and 14 patients were on peritoneal dialysis for a median of 1.4 years (range 0.1–5.3). The median time of end-stage renal disease (ESRD) was 1.7 years (0.1–8.3) in the dialysis patients and 5.4 years (1.2–16) in the transplanted patients. The peritoneal dialysis patients were significantly younger than the transplant patients. Also length and weight were therefore lower.

The main causes of ESRD in the transplanted patients were congenital anatomic abnormalities (N = 16, 43%) and glomerulonephritis (N = 14, 38%). In the dialysis patients, the main causes were congenital anatomic abnormalities (N = 5, 36%), glomerulonephritis (N = 4, 29%) and congenital nephrotic syndrome (N = 4, 29%). Phosphate and iPTH levels were significantly higher in dialysis patients as compared to transplant patients, as were urea and creatinine levels. The glomerular filtration rate in the transplanted patients had a mean value of 54 ml/min/1.73 m² (range 16–107).

Blood pressure registration

In 37 transplanted patients, 24-h blood pressure monitoring was performed. Blood pressure above the 95th percentile was present in 8 (22%) for daytime systolic blood pressure, in 8 (22%) for daytime diastolic blood pressure, in 16 (44%) for nighttime systolic blood pressure and in 15 (40%) for nighttime diastolic blood pressure. In 11 patients, mean systolic and diastolic blood pressure during both day

| Table 1. Patients’ basic characteristics and laboratory values |
|----------------|----------------|----------------|----------------|
|               | Controls 1 (N = 41) | PD (N = 14) | Controls 2 (N = 112) | Transplant (N = 39) |
| Age            | 9 ± 1            | 8 ± 6         | 14 ± 2          | 14 ± 4^a             |
| Length         | 138 ± 5^a       | 113 ± 32      | 165 ± 12^a      | 147 ± 25^a            |
| Weight         | 32 ± 4^a        | 24 ± 15       | 53 ± 13         | 49 ± 19^a            |
| Sex (M/F)      | 21/20            | 7/7           | 52/60           | 20/19                |
| Ethnicity (%)  | 40 (90%)        | 12 (86%)      | 110 (98%)       | 36 (97%)             |
| Hb (mmol/l)    | 7.2 ± 1.0       | 7.5 ± 1.1     |                |                      |
| Ht (%)         | 0.33 ± 0.05     | 0.35 ± 0.05   |                |                      |
| Urea (mmol/l)  | 14.7 ± 6.0      | 9.9 ± 3.2     |                |                      |
| Creatinine (µmol/l) | 692 ± 367     | 126 ± 60^a    |                |                      |
| Phosphate (mmol/l) | 1.69 ± 0.48   | 1.39 ± 0.25^a|                |                      |
| Calcium (mmol/l) | 2.45 ± 0.15    | 2.47 ± 0.13   |                |                      |
| CaPO₄ product (mmol²) | 4.17 ± 1.40  | 3.42 ± 0.57^a|                |                      |
| iPTH (mmol/l)  | 36.7 ± 35.9     | 13.0 ± 9.2^a  |                |                      |

Sex (M/F), number of males and females; Ethnicity (C), number of Caucasians; Hb, haemoglobin; Ht, haematocrit; CaPO₄ product, calcium* phosphate; iPTH, parathyroid hormone.

^P < 0.01 for the difference between age-matched controls and PD patients or transplanted patients.

^*P < 0.01 for the difference between PD patients and transplanted patients.
Table 2. M-mode values of left ventricular function

<table>
<thead>
<tr>
<th></th>
<th>Controls 1</th>
<th>PD</th>
<th>Controls 2</th>
<th>Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVSd (mm)</td>
<td>6.2 ± 1.3</td>
<td>7.3 ± 2.1</td>
<td>7.4 ± 1.9*</td>
<td>10.4 ± 2.3*</td>
</tr>
<tr>
<td>LV PWd (mm)</td>
<td>5.8 ± 1.2</td>
<td>6.7 ± 2.1</td>
<td>6.0 ± 1.5*</td>
<td>9.0 ± 2.0*</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>28 ± 7*</td>
<td>43 ± 11</td>
<td>25 ± 7*</td>
<td>59 ± 64</td>
</tr>
<tr>
<td>SF</td>
<td>0.37 ± 0.05</td>
<td>0.36 ± 0.11</td>
<td>0.37 ± 0.05</td>
<td>0.38 ± 0.12</td>
</tr>
<tr>
<td>LV E/D</td>
<td>41 ± 3*</td>
<td>33 ± 9</td>
<td>47 ± 4</td>
<td>45 ± 5*</td>
</tr>
<tr>
<td>LV E/S</td>
<td>26 ± 3*</td>
<td>20 ± 6</td>
<td>29 ± 4</td>
<td>27 ± 4*</td>
</tr>
<tr>
<td>VCFC</td>
<td>1.16 ± 0.20</td>
<td>1.25 ± 0.29</td>
<td>1.16 ± 0.20</td>
<td>1.21 ± 0.22</td>
</tr>
</tbody>
</table>

IVSd, thickness of the interventricular septum in diastole (mm); LV PWd, thickness of the left ventricular posterior wall in diastole (mm); LV mass, left ventricular mass index (g/m²); SF, shortening fraction (%); LV E/D, left ventricular end-diastolic dimension (mm); LV E/S, left ventricular end-systolic dimension (mm); VCFC, velocity of circumferential fibre shortening, corrected for heart rate.

*P < 0.01 for the difference between age-matched controls and PD patients or transplanted patients.

and night were below P95, and in 6 all these values were above P95. In the dialysis patients, one had a casual blood pressure above the 95th percentile, while the others had normal casual blood pressure.

Left ventricular mass (Table 2)

The LVM index was increased in both the dialysis and the transplanted patients. LV mass above the 95th percentile of our reference population of healthy school children was present in 8/14 PD patients (57%) and 29/39 transplanted patients (74%) (NS). Systolic function as assessed by shortening fraction and velocity of circumferential fibre shortening, corrected for heart rate (VCFC), was similar between patients and controls. In the transplanted patients, there was a significant correlation between mean 24-h systolic blood pressure and LV mass index (R = 0.46; P < 0.05) (Figure 1).

Table 3. Mitral inflow parameters

<table>
<thead>
<tr>
<th></th>
<th>Controls 1</th>
<th>PD</th>
<th>Controls 2</th>
<th>Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV-E (m/s)</td>
<td>1.05 ± 0.14</td>
<td>0.97 ± 0.24</td>
<td>0.97 ± 0.16</td>
<td>0.98 ± 0.17</td>
</tr>
<tr>
<td>MV-A (m/s)</td>
<td>0.47 ± 0.11*</td>
<td>0.69 ± 0.28</td>
<td>0.48 ± 0.14*</td>
<td>0.57 ± 0.14</td>
</tr>
<tr>
<td>MV E/A</td>
<td>2.31 ± 0.52*</td>
<td>1.57 ± 0.73</td>
<td>2.15 ± 0.63*</td>
<td>1.82 ± 0.58</td>
</tr>
<tr>
<td>Dec time (ms)</td>
<td>0.15 ± 0.03</td>
<td>0.18 ± 0.04</td>
<td>0.18 ± 0.03</td>
<td>0.17 ± 0.04</td>
</tr>
</tbody>
</table>

MV-E, early mitral inflow (m/s); MV-A, active mitral inflow (m/s); MV E/A, ratio of early mitral inflow to active mitral inflow; Dec time, deceleration time (ms).

*P < 0.01 for the difference between age-matched controls and PD patients or transplanted patients.

Tissue Doppler velocities (Table 4)

Tissue Doppler variables indicating systolic function (S) and diastolic function (E’) were smaller in the patients, both at the basal part of the left ventricular posterior wall and at the basal part of the interventricular septum. Especially, a lower E wave and an increase in the E/E’ ratio were seen in the patients, indicating diastolic dysfunction. Also for the tissue Doppler values, differences from controls were more prominent in the dialysis patients. A E/E’ ratio of the basal part of the interventricular septum above +2 SD
of the normal values was found in 11/14 (79%) of the dialysis patients and in 17/39 (44%) of the transplanted patients. In contrast, tissue Doppler values at the basal part of the right ventricle were similar between patients and normal controls. The E/E′ ratio was significantly higher in patients with blood pressure above the 95th percentile (P < 0.01) (Figure 2). The significance was reached for both systolic and diastolic blood pressure during daytime as well as during nighttime.

Discussion

The main findings of the present study are a small decrease in systolic function as assessed by tissue Doppler measurements in both patient groups, an increase in the LVM index in the transplant patients as well as in the dialysis patients and diastolic dysfunction of the left ventricle in all patients, but more prominent in the dialysis patients. Correlations were found between systolic blood pressure and LVM index and between increased iPTH and diastolic dysfunction. An increased E/E′ ratio was found predominantly in patients with hypertension, indicating an association between an increased blood pressure and diastolic dysfunction.

Among patients on renal replacement therapy the cardiovascular-related mortality is significant. In a follow-up study on patients who started renal replacement therapy in childhood, a mortality rate of 25% before the age of 30 was registered. Forty percent of these cases died of cardiovascular disease [1,2]. Risk factors for the development of cardiovascular disease are already present in ESRD before the onset of dialysis. It is therefore important to identify risk factors for the development of cardiovascular morbidity and mortality at an early stage. The most prominent risk factor for the development of cardiovascular disease is the presence of hypertension. The high prevalence of hypertension among transplant patients as measured by 24-h ambulatory blood pressure may be partially due to the toxic effects of immunosuppressive agents. We also found a high prevalence of hypertension, being 50% of the transplanted patients. In contrast, nearly all our dialysis patients were normotensive. This may be explained by the predominant use of peritoneal dialysis in the present study, contrasting to most studies in children where haemodialysis was the most prominent renal replacement therapy. In four reports, the contribution of PD patients to the dialysis population was only 25% (16/61) [3,4,18,19]. More difficult blood pressure regulation has been found in haemodialysis patients [20]. Another explanation is that we have underestimated the incidence of hypertension in our dialysis patients by the use of casual blood pressure measurements instead of 24-h ambulatory blood pressure [21].

The amount of left ventricular hypertrophy in the present study is comparable to the values presented in previous investigations [3,5,6] The LVM has been reported to increase gradually before and during the time on chronic dialysis treatment [4,5]. During this period, LVM is especially related to the presence of systolic hypertension [5]. There is conflicting evidence about the changes that occur after renal transplantation. Some authors report a gradual decline of the LVM, although the prevalence of left ventricular hypertrophy remained unchanged [22], while others did not find any change in left ventricular hypertrophy or diastolic dysfunction after renal transplantation [2,23]. In the present study, we found a more severe left ventricular hypertrophy in the transplanted patients (59 ± 64 g/m²³ versus 43 ± 11 g/m²³). This finding may be due to the longer period of ESRD in the transplanted patients (5.4 versus 1.7 years), the higher prevalence of hypertension in the transplanted patients or the use of immunosuppressive agents.

In the present study, we found lower systolic tissue Doppler values in the patients. This contrasts to earlier findings of an increased contractility in paediatric patients with ESRD [3]. However, in the present study we evaluated dialysis patients, who probably have a more advanced state of cardiovascular dysfunction as compared to patients who are predominantly in the pre-dialysis phase [3]. Both dialysis and transplanted patients showed signs of diastolic dysfunction. The mechanism of this diastolic dysfunction is as yet not completely elucidated. Mechanisms that may be involved are disturbed calcium–phosphate metabolism, anaemia, hypertension, dyslipidaemia and hyperhomocysteinaemia. In the present study, both hypertension and increased iPTH levels were identified to be associated with diastolic dysfunction.

The increased PTH secretion, hyperphosphataemia and hypercalcaemia contribute to cardiovascular morbidity and mortality by vascular calcification [18,24]. In dialysed patients, a strong correlation exists between disturbed calcium–phosphate metabolism and diastolic dysfunction [18,19]. The effect of calcium–phosphate metabolism on cardiovascular morbidity may be mediated by increased arterial stiffness, which is known to be correlated with poor diastolic function, as studied in children in all phases of chronic kidney disease [18]. Since calcium–phosphate metabolism normalizes with renal function after kidney transplantation, new vascular calcifications are not expected to develop. Nevertheless, existing calcified vascular lesions are not expected to diminish considerably. Further longitudinal studies are necessary to unravel these mechanisms, and to give insight into the cardiovascular...
changes that occur when a dialysis patient receives a kidney transplantation.

Limitations of the study

Since the present investigation is a cross-sectional study, differences between dialysis and transplant patients may be due to differences in patients’ characteristics. Only long-term follow-up studies can answer the question whether subsequent transplantation in dialysis patients will improve left ventricular diastolic dysfunction. In the present study, 24-h blood pressure measurements were not obtained in the dialysis patients. It was therefore not possible to compare blood pressure levels between the two patient groups. We used the LVM index for determining the presence of LVH. However, this measure is dependent on the body size of the patient, potentially resulting in overdiagnosis of LVH in small children [25]. This could partly explain the LVH in the patients, since they were smaller as compared to the healthy controls.

Conclusions

Abnormalities in left ventricular diastolic function are present in both peritoneal dialysis and renal transplant patients. The most important risk factor associated with these abnormalities in dialysis patients is an increased iPTH level. In the transplant group, an increased LVM index is prominent, probably related to arterial hypertension and toxicity of immunosuppressive agents.

Conflict of interest statement. None declared.

References


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