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Cardiac disease in young adult patients with end-stage renal disease since childhood: A Dutch cohort study

Mariken P. Gruppen, Jaap W. Groothoff, Martin Prins, Poll van der Wouw, Martin Offringa, Willem Jan Bos, Jean Claude Davin, and Hugo S.A. Heymans

Department of Pediatrics, Emma Children's Hospital AMC, Department of Clinical Epidemiology and Biostatistics AMC, Department of Cardiology, Onze Lieve Vrouwen Gasthuis, Amsterdam; and St. Antonius Ziekenhuis, Nieuwegein, The Netherlands

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Background. Cardiovascular disease is the most important cause of death in patients with pediatric end-stage renal disease (ESRD). Yet, few data exist on cardiac function in these patients. We assessed the extent of cardiac abnormality and analyzed its association with potential determinants in young adult patients with pediatric ESRD in a long-term follow-up study.

Methods. All Dutch living adult patients with ESRD onset at age of 0 to 14 years between 1972 and 1992 were invited for echocardiography and blood pressure assessment. Special attention was paid to evidence of left ventricular hypertrophy (LVH), diastolic dysfunction, and aortic valve calcification. We collected data on determinants by review of all medical charts.

Results. Of all the 187 living patients, 140 participated in the study. Of those, 110 patients had received a transplant and 30 patients were on dialysis. Mean age was 29.2 (20.7 to 41.8) years. Left ventricular mass index (LVMI) exceeded 150 g/m^2 in 47% of all male patients and 120 g/m^2 in 39% of all female patients, both consistent with LVH. Diastolic dysfunction, defined as an early over atrial transmitral blood flow velocity (E/A ratio) <1, was found in 18 (13%) patients; 27 (19%) had aortic valve calcification. Multiple regression analysis revealed the following: a high LVMI was associated with a current high blood pressure ($\beta = 0.46$, $P < 0.001$) and male gender ($\beta = 0.21$, $P = 0.009$), a low E/A ratio with aging ($\beta = -0.28$, $P < 0.001$) and a glomerular filtration rate (GFR) <25 mL/min/1.73 m^2 ($\beta = -0.29$, $P < 0.001$), and aortic valve calcification with prolonged peritoneal dialysis ($\beta = 0.36$, $P < 0.001$).

Conclusion. Young adult patients with pediatric ESRD are at risk for LVH caused by hypertension and for aortic valve calcification. Diastolic function decreases with age and is enhanced by a current low GFR. Prolonged peritoneal dialysis may enhance aortic valve calcification.

As life expectancy has increased in children with end-stage renal disease (ESRD), concern has arisen about its late sequelae. Improvement in dialysis technique and supportive therapy over the last two decades, such as the introduction of bicarbonate buffer or peritoneal dialysis and the use of recombinant erythropoietin (EPO), have been associated with a decrease in morbidity and mortality [1–3]. Nevertheless, detailed information of long-term outcomes of renal replacement therapy (RRT) in children is lacking.

In adults, cardiovascular disease has been recognized as the most important cause of death in patients with ESRD [4–8]. Left ventricular hypertrophy (LVH) is the most frequently observed alteration in these patients and has been directly associated with acute death [5, 7]. Chronic pressure and volume overload, as a result of water and salt retention and hypertension, and the use of cyclosporine in transplantation have been regarded as potential risk factors in the development of LVH in older adult patients with ESRD [6, 9]. Enhanced calcification of the aortic valve as a result of chronic volume overload and a high serum calcium-phosphate product has recently been recognized as another independent risk factor for acute death in adult patients with ESRD [10, 11].

To date, few data exist on cardiac disease in young adults with ESRD since childhood. There are concerns that, as in patients with adult onset of ESRD, these patients are at risk for cardiovascular death at a very young age. We conducted a national long-term follow-up study to evaluate late effects of renal insufficiency in children (LERIC). The cohort consisted of all Dutch adult patients that commenced RRT between 1972 and 1992 at age 0 to 14 years. Recently, we reported on mortality and causes of death [3]. Cardiovascular disease was found to be the cause of death in more than 40% of all deceased patients. In this paper, we report on the prevalence and extent of LVH, systolic and diastolic dysfunction, and cardiac valve abnormalities, and the relation between these abnormalities and potential risk factors in those patients of the cohort who are still alive.

Key words: cardiac function, end-stage renal disease, children, follow-up.

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METHODS

Study design

The study was designed as a cohort study and consisted of a cross-sectional and a retrospective part. The aim of the cross-sectional study was to assess current cardiac abnormality by ultrasound, to assess blood pressure, and to assess current glomerular filtration rate (GFR) in transplanted patients. The aim of the retrospective part of the study was to evaluate the influence of a set of predefined determinants on cardiac outcome parameters. The study covered the total period of RRT for each patient. The end of the study was marked by the day of the examination for participants and the day of last chart review for eventual nonparticipants in the cross-sectional part of the study. The medical ethical committees of all participating centers approved the study.

Formation of the cohort

The LERIC cohort comprises all Dutch patients who had begun chronic RRT at age 0 to 14 years between 1972 and 1992, and who were born before 1979. Patients in whom renal function recovered within 4 months after commencing dialysis were excluded. Pre-emptively transplanted patients were included. A list of patients, based on these criteria, was submitted by the National Dutch Registry of patients on RRT [Registratie Nierfunctievervanging Nederland (RENINE), Rotterdam, The Netherlands]. RENINE, founded in 1985, is the Dutch source of the European Dialysis and Transplantation Association. The completeness of these database approaches 100% as registration is compulsory for reimbursement of RRT.

The completeness of retrospective registration of patients with RRT starting before 1985 was checked by comparing RENINE data with the databases of all Dutch centers for pediatric dialysis and kidney transplantation, as well as the databases of all centers for adult dialysis and transplantation. The procedure of cohort formation was as follows: the list submitted by RENINE consisted of only registry numbers of patients, treatment modality, and the name of the last physician and hospital of treatment. All nephrologists in The Netherlands received a list of those cohort patients who were under their treatment or had been under their treatment at the time of death. The LERIC team contacted all the physicians and asked them if the list sent by RENINE was consistent with their registry database. Patients were contacted by their own physicians and invited to take part in this study.

Data collection of determinants

Between November 1998 and August 2000, members of the LERIC team visited 37 hospitals in The Netherlands. Data were collected on total duration of hemodialysis, peritoneal dialysis and transplantation, primary renal disease, age at initiation of first RRT, the burden of hypertension, the burden of anemia, the use of recombinant human erythropoietin (EPO), and the use and duration of prescription of cyclosporine of all patients of the cohort. The observation period for all variable determinants lasted from the first day of RRT until the day of chart review or examination at our hospital. All eventful periods since onset of RRT over which data could not be obtained were excluded from evaluation and recorded as missing patient-years. The total duration of RRT, hemodialysis, peritoneal dialysis, and transplantation was expressed in years. The total duration of hypertension was scored as follows: the mean blood pressure per 3 months was calculated from all documented blood pressures and recorded on file. In hemodialysis patients, the mean of pre- and post-dialysis blood pressures was used to calculate the 3-month period mean. Over periods of uneventful follow-up after transplantation, in which patients were less frequently controlled than once per 3 months, the mean value of two subsequently recorded blood pressures was presumed to represent the mean blood pressure of the intervening 3-month period. Hypertension was defined as both systolic and diastolic blood pressure values above the 95th percentile for age and gender, in accordance with the Task Force on Blood Pressure in Children [12]. The total number of periods of hypertension and normal blood pressure was recorded. The total "burden of hypertension" was defined per patient as the cumulative period with hypertension, expressed in years. The burden of anemia was expressed as the total duration of a hemoglobin level below 5 mmol/L (8 g/dL).

Cross-sectional data

All living patients were contacted by their current nephrologist and were invited to participate in the study. Written informed consent was obtained from all participants. Data were collected on the current body weight, height, current use of cyclosporine, current modality of RRT, and the GFR in transplanted patients. The GFR was based on the last measured serum creatinine, using the Cockcroft-Gault formula [13]. A value below 25 mL/min/1.73 m^2 was defined as a low GFR. Blood pressure was assessed every 5 minutes during 30 minutes using an Omron 705CP automated oscillatory blood presure device (Omron Matsusaka Co., Ltd., Tokyo, Japan). The Omron 705CP has been validated according to guidelines of the British Hypertension Society and the United States Association for the Advancement of Medical Instruments for clinical and research purposes [14, 15].

Echocardiograph assessment

Echocardiographic studies were performed using a HDI 3000 (Philips ATL, Bothell, WA, USA) or a CFM800 (GE Vingmed, Horten, Norway) equipped with 2 to 4 MHz probes allowing M-mode, two-dimensional,

and pulsed Doppler measurements. One and the same experienced cardiac sonographer performed the measurements. Echocardiography was performed according to the guidelines of American Society of Echocardiography [16]. Left ventricular end diastolic diameter (LVEDD), interventricular wall thickness during diastole (IVST), and posterior wall thickness during diastole (PWT) were measured by M-mode. From these measurements, the left ventricular mass (LVM) and left ventricular mass index (LVMI) were calculated according to the Devereux formula as follows: LVM = [LVEDD/10 + IVST/10 + posterior wall thickness (PWT)/$10^3 \times 1.04$] − (LVEDD/10)^3 −13.6, and LVMI = LVM/$\sqrt{}$(weight × length/3600) [17]. We used reference values for the LVMI to define LVH as in the Framingham study: in male patients, LVH was defined as LVMI >150 g/m^2, and in female patients as LVMI >120 g/m^2 [18]. We decided to use the LVMI and not the LVM as a reference for LVH, since most of our patients were severely growth retarded. The presence or absence of cardiac valve calcification was noted. Diastolic dysfunction was defined as an early transmitral peak blood flow velocity divided by the atrial transmitral peak blood flow (E/A ratio) <1. Systolic function was assessed by calculation of the shortening fraction, which was defined by the ratio of the difference between the end-diastolic and end-systolic dimensions to the end-diastolic dimension (i.e., shortening fraction = (end diastolic diameter − end systolic diameter/end diastolic diameter). Systolic dysfunction was defined as a shortening fraction of less than 28%.

Analysis

A comparison of nominal variables on clinical parameters of participants and nonparticipants of the cross-sectional study was performed using the chi-squared test. Mean values, or prevalence of outcomes measures, were calculated for all patients, for male and female patients apart, and for the following four therapeutic subgroups of patients: (*1*) transplanted patients with a GFR >25 mL/min/1.73 m^2, (*2*) transplanted patients with a GFR <25 mL/min/1.73 m^2, (*3*) all transplanted patients, and (*4*) all patients currently on dialysis. Mean values of continuous variables in the therapeutic subgroups were compared using the Mann-Whitney test. The prevalence of aortic valve calcification in all therapeutic subgroups was compared using the chi-squared test. Pearson's correlation was assessed between E/A ratio and intraventricular dimensions for all patients, transplanted patients and dialysis patients, in order to analyze the relation between diastolic function and change in ventricular anatomy. Pearson's correlation was also assessed for all patients between LVMI, E/A ratio, aortic valve calcification and the following potential determinants: gender, modality of RRT at time of investigation, total duration of RRT, total duration of living with a renal graft, total duration of hemodialysis, total duration of peritoneal dialysis, age at onset of RRT, blood pressure at time of investigation, total burden of hypertension, a GFR <25 mL/min/1.73 m^2 (including dialysis status), and total years of cyclosporine prescription. The relationship of all significant determinants (set at $P < 0.2$) identified from these univariate analyses with LVH, E/A ratio, and aortic valve calcification were studied with a linear stepwise multiple regression using the F statistic with $P = 0.05$ as criterion for selection.

RESULTS

The cohort

The RENINE database produced a list of 251 patients, who fulfilled the inclusion criteria. Checking with the local databases of all participating centers revealed that one patient was mentioned twice and three patients did not meet the inclusion criteria. Reviewing the databases of all dialysis and transplantation centers produced two additional eligible patients. Thus, the cohort consisted of 249 patients. Of these, 62 patients (25.3%) had died at time of cross-sectional study. The average follow-up time was 15.5 years. We recorded a total of 3870 patient years of all LERIC patients, covering the whole period from the onset of RRT until August 2000 or the time of death, with 81 patient-years (2.1%) missing. No patients were lost to follow-up. Of two patients (0.8%), who both died in 1974, no clinical data could be found.

The main characteristics of all the patients are listed in Table 1. Of 187 patients alive, 47 (25.1%) declined to participate in the cross-sectional study, leaving 140 subjects. No significant differences were found in age, gender, age of onset of RRT, and therapy characteristics between participants and nonparticipants of the cross-sectional study. Antihypertensive drugs were used by 70 out of 130 patients (53.8%), of whom 26 (20%) used angiotensin-converting enzyme (ACE) inhibitors, 35 (26.9%) calcium channel blockers, and 45 (34.6%) beta blockers. In 43 (30.7%) participants, the onset of RRT was before the age of 10 years.

Cross-sectional data

Mean age of all participants was 29.2 years (range, 20.9 to 41 years). Of all 140 patients, 110 were living with a functioning renal graft, 19 were on hemodialysis, and 11 on peritoneal dialysis. Mean LVMI of all 75 male patients was 150 g/m^2, of all female patients 119 g/m^2. Of all male patients, 47% had a LVMI exceeding 150 g/m^2, and of all female patients 39% had a LVMI exceeding 120 g/m^2, both consistent with LVH. An E/A ratio <1.0 was found in 18 (13%) patients, and calcification of the aortic valve in 27 (19%) patients. We found a normal systolic function in all but one patient (Table 2).

Table 1. Demographic and clinical characteristics at the time of echocardiography

Parameters	Participants $N = 140$	Non-participants $N = 47$
Mean age at time of investigation *years* (range)	29.2 (20.7–41.8)	29.9 (21.3–41.6)
Male gender *number* (range)[a]	75/140 (54%)	27/45 (60%)
Weight *kg* (range)	61.5 (38–122)	No data
Height *cm* (range)	161 (139–186)	No data
Treatment at time of investigation *number*[a]	111/140 (79.3%)	38/47 (80%)
Hemodialysis at time of investigation *number*[a]	18/140 (12.9%)	5/47 (11%)
Peritoneal dialysis at time of investigation *number*[a]	11/140 (7.9%)	4/47 (8.5%)
Mean duration of renal replacement therapy >18 years	83/140 (59%)	29/47 (62%)
Age at onset of renal replacement therapy *years* (range)	10.9 (1.9–15)	10.8 (2.7–14.9)
Mean duration of renal replacement therapy *years* (range)	18.3 (6–30)	18.9 (10.5–27.5)
Mean duration of hemodialysis *years* (range)	3.6 (0–25.7)	2.4 (0.2–10.4)
Mean duration of peritoneal dialysis *years* (range)	0.9 (0–12.3)	1.2 (0–14.7)
Mean duration of renal transplant *years* (range)	13.5 (0–28.9)	15.3 (2.8–26.9)

[a] Number of patients

Table 2. Blood pressure, height, weight, and echocardiographic measurements in male and female patients

	Male patients ($N = 75$)	Female patients ($N = 65$)
Weight *kg*	64 (range 38 to 98)	58 (range 39 to 85)
Height *cm*	165 (range 140 to 186)	156 (range 39 to 174)
Body surface kg/m^2	1.7 (range 1.2 to 2.1)	1.6 (range 1.3 to 2.0)
Mean systolic blood pressure *mm Hg*	135 (range 81 to 179)	120 (range 65 to 186)
Mean diastolic blood pressure *mm Hg*	83 (range 45 to 112)	79 (range 43 to 116)
Interventricular septal thickness *mm*	10.9 (SD 2.4)	9.7 (SD 2.9)
Posterior wall thickness *mm*	10.8 (SD 2.0)	9.3 (SD 1.8)[b]
Left ventricular end-diastolic diameter *mm*	50.7 (SD 6.0)	47.0 (SD 5.2)
Left ventricular mass *g*	257 (SD 91)	186 (SD 65)[b]
Left ventricular mass index g/m^2	150 (SD 45)	119 (SD 43)[b]
Left ventricular hypertrophy[a] *number*	35 (47%)	25 (39%)[b]
Left ventricular mass/left ventricular volume ratio *g/mL*	2.1 (range 1.0 to 3.4)	1.8 (range 1.0 to 4.6)
E/A ratio	1.5 (range 0.5 to 3.6)	1.6 (range 0.9 to 3.2)
E/A ratio <1.0 *number*	9 (12%)	9 (14%)
Aortic valve regurgitation *number*	17 (23%)	15 (23%)
Mitral valve regurgitation *number*	22 (29%)	19 (29%)
Shortening fraction %	39 (range 27 to 61)	39 (range 28 to 85)
Aortic valve calcifications *number*	19 (25%)	8 (12%)
Wall irregularities *number*	24 (32%)	14 (22%)

Abbreviations are: E, early diastolic transmitral peak blood flow; A, atrial diastolic transmitral peak blood flow.
[a] Left ventricular hypertrophy (LVH), defined as left ventricular mass index (LVMI) >150 in male patients and LVMI >120 in female patients
[b] Posterior wall thickness, left ventricular mass, and left ventricular mass index measured in 64 of 65 female patients

Relation between diastolic function and ventricular dimensions

In all patients, decrease in E/A ratio was associated with an increase in the interventricular septal thickness (IVST) ($R = -0.21$; $P = 0.01$), weakly with an increase in the PWT ($R = -0.17$; $P = 0.05$), but not with the left ventricular end-diastolic diameter. Also, a decrease in E/A ratio was correlated with an increase in LVM/left ventricular volume ratio ($R = -0.23$; $P = 0.007$; Table 3). A stronger ($R = -0.35$) association was found between a low E/A ratio and an increase in the interventricular septal thickness in dialysis patients, whereas in transplanted patients a low E/A ratio was equally associated with an increase in interventricular septal and PWT. However, these associations were not statistically significant, probably due to the small numbers (all $P = 0.06$; Table 3).

Effect of renal function on outcome measures

Mean E/A ratio of patients currently on dialysis was 1.26, and of all transplanted patients 1.59 (Δ0.32; 95% CI 0.12; 0.53, $P < 0.002$). Mean LVMI of transplanted patients with a GFR below 25 mL/min/1.73 m^2 ($N = 7$) was 177 g/m^2, of transplanted patients with a GFR above 25 mL/min/1.73 m^2 ($N = 103$) was 135 g/m^2(Δ42; 95% CI 6, 77; $P = 0.04$). No significant difference was found between the mean LVMI of transplanted patients with a GFR above 25 mL/min/1.73 m^2 and dialysis patients (Table 4).

Determinants of LVH, diastolic dysfunction, and aortic valve calcification

Multiple regression analysis revealed the following associations between a high LVMI with a high current mean blood pressure ($\beta = 0.46$; $P < 0.001$) and male

Table 3. Univariate analysis: Correlation between E/A ratio and left ventricular dimensions in all patients, transplanted and dialysis patients

	E/A: All patients		EA: Transplant patients		EA: Dialysis patients	
	R	*P* value	R	*P* value	R	*P* value
Interventricular septal thickness	−0.21	0.01	−0.19	0.06	0.35	−0.06
Left ventricular end-diastolic diameter						
Posterior wall thickness	−0.17	0.05	−0.19	0.06		
Left ventricular mass/left ventricular volume	−0.23	0.007	−0.20	0.04		

Abbreviations are: E, early diastolic mitral peak blood flow; A, atrial diastolic mitral peak flow. Note: Only significant associations are shown (set at $P < 0.2$).

Table 4. Mean values of left ventricular mass index (LVMI) and E/A ratio, and the prevalence of calcification of the aortic valve (AoVc) in transplanted patients with a glomerular filtration rate (GFR) >25 m/min/1.73 m^2, transplanted patients with a GFR<25 mL/min/1.73 m^2, and in all dialysis patients

	Transplanted GFR >25 ($N = 103$)	Transplanted GFR <25 ($N = 7$)	Dialysis ($N = 30$)	ΔTransplanted GFR >25 Transplanted GFR <25	ΔTransplanted GFR >25 Dialysis
Mean LVMI g/m^2	135 ± 42	177 ± 55	130 ± 53	42[a] $P = 0.04$	5[a] $P = 0.3$
E/A ratio	1.61 ± 0.53	1.17 ± 0.40	1.26 ± 43	0.44[a] $P = 0.03$	0.35[a] $P = 0.002$
AoVc n%	15.5%	29.7%	30.0%	3.5[b] $P = 0.08$	3.2[b] $P = 0.07$

Transplanted GFR >25, transplanted patients with a GFR >25 mL/min/1.73 m^2; transplanted GFR <25, transplanted patients with a GFR <25 mL/min/1.73 m^2; Δ, difference.

[a] Mann-Whitney test

[b] χ^2 test

gender ($\beta = 0.21$, $P = 0.001$), a low E/A ratio with a higher age at time of investigation ($\beta = -0.28$; $P < 0.001$), and a GFR <25 mL/min/1.73 m^2 ($\beta = -0.29$; $P < 0.001$), and aortic valve calcification with a long total period of peritoneal dialysis ($\beta = 0.36$; $P < 0.001$). A long duration of anemia was associated with a decrease in E/A ratio and aortic valve calcification in the univariate analysis, but not in the multivariate analysis. No difference in LVMI or in the prevalence of aortic valve calcification was found between transplanted patients and dialysis patients, even if we excluded transplanted patients with a low GFR from the analyses. All univariate and multivariate associations between determinants and outcome for all patients, transplanted and dialysis patients, are shown in Tables 5 and 6.

DISCUSSION

In this study, we aimed to determine the extent of LVH, systolic and diastolic dysfunction and aortic valve calcification in young adults with ESRD since childhood. We also examined relationships between clinical characteristics and outcome measures.

Left ventricular hypertrophy and diastolic dysfunction

We found LVH in nearly 50% of all male and in nearly 40% of all female patients. As expected, LVH was associated with hypertension at time of assessment. However, to our surprise, the burden of hypertension in the past was not directly associated with an increase in LVM, nor was the total duration of RRT or dialysis. The fact that we found no difference in LVMI between dialysis and transplanted patients could imply that LVH in our patients is merely the result of current hypertension and can be regarded as an adequate response to the increased pressure. The physiologic character of LVH as observed in older dialysis patients has been described as the result of an "inadequate" response on volume overload [9, 19, 20]. In these patients, the blood pressure-related increase of the LVM/left ventricular volume ratio is inadequate. In other words, the increase in ventricular mass, which is needed to cope with the increase in ventricular volume caused by volume overload, appears to be insufficient in these older dialysis patients. This seems to contrast with our results in young adults with ESRD. Compared to older dialysis patients, the LVM/left ventricular volume ratio in our patients was high, both in transplanted patients and in patients currently on dialysis. The pattern observed in our patients is more similar to those observed in patients with essential hypertension [21, 22]. Therefore, it seems that in these relatively young patients, the increase of the LVM appears to be mainly caused by the current pressure load. The fact that the LVMI was not apparently associated with the burden of hypertension in the past suggests that an increased LVMI is a reversible condition in these young adult patients with ESRD since childhood.

Despite the high prevalence of LVH, only 13% of our patients had a diastolic dysfunction, defined as an E/A ratio below 1.0. Yet, and also contrary to data obtained in older dialysis patients [9], we found a negative association between the LVM/left ventricular volume ratio and the E/A ratio. In other words, in our patients diastolic dysfunction was associated with a high LVM/left ventric-

Table 5. Univariate analysis: Correlation between left ventricular mass index (LVMI), E/A ratio, calcification of the aortic valve, and potential disease and therapy-related determinants in all patients

	LVMI		E/A		Calcification of aortic valve	
	R	*P* value	R	*P* value	R	*P* value
Male gender	0.34	<0.001			0.17	0.05
Duration renal replacement therapy			−0.22	0.009		
Duration transplantation						
Duration hemodialysis			−0.20	0.02	0.13	0.1
Duration peritoneal dialysis			−0.14	0.1	0.29	<0.001
Age onset renal replacement therapy						
Age at time of investigation			−0.28	0.001		
Mean blood pressure	0.52	<0.001				
Duration hypertension[a]	0.10	0.2	−0.12	0.2		
Glomerular filtration rate <25[b]			−0.31	<0.001	0.16	0.07
Dialysis[c]			−0.25	0.003	0.14	0.1
Duration of anemia[d]			−0.17	0.05	0.22	0.009
Duration of cyclosporine	0.18	0.03				

GFR <25, glomerular filtration rate <25 mL/min/1.73 m^2, included dialysis patients. Note: Only significant associations are shown (set at $P < 0.2$).
[a] Total duration of periods with blood pressure $P > 0.95$
[b] Included dialysis patients
[c] On dialysis at time of investigation
[d] Total duration of hemoglobin <5 mmol/L (8 g/dL)

Table 6. Determinants of left ventricular mass index (LVMI), E/A ratio (EA) and calcification of the aortic valve (AoV) analyzed by multivariate regression with stepwise strategy of all patients

	LVMI		EA		AoVc	
	β	*P* value	β	*P* value	β	*P* value
Male gender	0.21	0.009				
Duration PD					0.36	<0.001
Age at time of investigation			−0.28	<0.001		
Mean BP	0.46	<0.001				
GFR <25[a]			−0.29	<0.001		

Abbreviations are: RRT, renal replacement therapy; Tx, renal transplantation; HD, hemodialysis; PD, peritoneal dialysis; BP, blood pressure; β, standardized coefficient. Note: Only significant associations are shown (set at $P < 0.05$).
[a] GFR <25, glomerular filtration rate <25 mL/min/1.73 m^2

ular volume ratio. This accounted for transplanted patients as well as patients currently on dialysis. This pattern is also more compatible with data obtained in patients with essential hypertension, than with data from (older) dialysis patients [21–23]. In patients with essential hypertension, anatomic ventricular changes precede decrease in diastolic function [23]. The fact that in our patients a low E/A ratio was associated with increased age and with a current low GFR suggests, that in our transplanted patients, loss of diastolic function is only a late complication of LVH under nonuremic conditions.

Strikingly, a decrease in E/A ratio was associated with only an increase of the interventricular septal thickness in dialysis patients, whereas in transplanted patients it was associated with an increase of both interventricular thickness and PWT. This is compatible with data from other studies and it reflects the difference between the concentric character of hypertrophy caused by hypertension and the more asymmetric hypertrophy seen in dialysis patients [19].

Aortic valve calcification

Aortic valve calcification was seen in 25% of all male and 12% of all female patients. Although these calcifications were never associated with a hemodynamically significant obstruction, the appearance of valve calcification is extremely uncommon in healthy subjects of this age. As to the significance of this finding, Otto et al [24] have demonstrated that, even in the absence of a flow obstruction, aortic valve calcification is associated with an increase in mortality risk of 50% in the nondiseased elderly. In the last 10 years, it has been recognized that aortic calcification occur in ESRD patients about 10 to 20 years earlier than in the general population and that it can be regarded as an independent risk factor for mortality in these patients [10, 11, 24, 25]. For example, Mazzaferro et al [26] found 22% to 25% mitral valve calcification in hemodialysis patients aged between 20 and 40 years. Coronary ischemia and cardiac conduction defects are the most probable links between aortic valve calcification and mortality. Aortic valve calcification in ESRD patients could reflect a more generalized artery disease with calcification of the coronary arteries. Braun et al [27], indeed, showed, using computed tomography (CT), that aortic valve calcification in ESRD patients is associated with calcification of the myocardium and large- or medium-sized arteries, including coronary ar-

teries. Such myocardial calcification could impair the conduction system, causing lethal arrhythmia or conduction disturbances. Shurmur et al [28] has, in fact, shown the association between cardiac conduction defects and aortic valve calcification in dialysis patients.

We found a strong association between total duration of peritoneal dialysis and the appearance of aortic valve calcification. Aging, a high serum calcium-phosphate product and mechanical stress caused by chronic overhydration have generally been accepted as the most important ethiologic factors [10, 11, 24, 26]. However, and in accordance with our results, Fernandez-Reyes et al [25] found the duration of peritoneal dialysis to be an independent risk factor for mitral and aortic valve calcification in continuous ambulatory peritoneal dialysis (CAPD) patients. An explanation for this phenomenon might be because chronic overhydration is a more common situation in patients on peritoneal dialysis than in hemodialysis patients. Issad et al [29] have reported a frequently occurring and underestimated overhydration in CAPD patients who underwent renal transplantation. In a large multicenter study to the adequacy of dialysis, Merkus et al [30] found that in hemodialysis patients, the cardiovascular co-morbidity at onset of RRT appeared to be the strongest predictor of death. On the contrary, in peritoneal dialysis patients systolic blood pressure was the most important determinant of death. Another explanation of the relation between peritoneal dialysis duration and cardiac valve calcification might be the fact that an uncontrolled serum calcium-phosphate balance has been more apparent in peritoneal dialysis patients than in hemodialysis patients, especially in the period when only high calcium dialysate was available. Indeed, there are studies from the early 1990s that have reported a higher incidence of hypercalcemia in peritoneal dialysis patients compared to hemodialysis patients [31, 32]. Goodman et al [33] found coronary artery calcification by using electron beam CT in dialysis patients between 20 and 30 years of age, even in the absence of apparent cardiac valve calcification [33]. This coronary calcification was associated with the total dialysis duration and with a high calcium-phosphate product, but not exclusively with peritoneal dialysis [33].

Associations of cardiac abnormalities with mortality

Previously we reported that in this cohort cardiac disease accounted for an important number of deaths at a very young age [3]. Although LVH only occurred with diastolic dysfunction in a small minority of our patients, the prevalence and extent of LVH itself was significant and could be partly responsible for the high rate of deaths in these patients. Decrease in coronary reserve and increased risk of arrhythmias is the most likely potential lethal consequences of LVH [34, 35]. Increased coronary calcification could enhance the risk of acute myocardial infarction at a very young age in these patients.

Limitations of the study

Echocardiography was performed in only 140 out of 187 patients, and our cohort comprised only a few patients who had started RRT under the age of 6 years. Nevertheless, since no significant differences in the distribution of disease parameters and therapy mode existed between participants and nonparticipants of the study, we believe that this group is representative for the whole group, and that no obvious selection of a special high-risk group seems to have occurred. As a result of an incomplete registration, we could not obtain reliable data on calcium-containing phosphate binders, vitamin D substitution, and on serum calcium, phosphate, and cholesterol, retrospectively. A prospective study evaluating these potential determinants for aortic valve calcification is warranted.

CONCLUSION

LVH is highly prevalent in young adults transplanted, as well as dialysis patients with ESRD since childhood. It is directly related to the extent of current hypertension, but leads to diastolic dysfunction only in a minority of patients. Diastolic function decreases over time and this is enhanced by a low GFR. The appearance of aortic valve calcification is associated with a long duration of peritoneal dialysis. A stricter reduction of volume overload in children on peritoneal dialysis, prevention of a high serum calcium phosphate, and a more vigorous treatment of hypertension seem to be important targets in order to reduce the incidence of these potentially lethal cardiac abnormalities.

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Reprint requests to J.W. Groothoff, M.D., Department of Pediatric Nephrology, Emma Children's Hospital AMC, University of Amsterdam, P.O. Box 22700, 1100 DE Amsterdam, The Netherlands.
E-mail: j.w.groothoff@amc.uva.nl

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