

Pediatric Myocardial Stunning Underscores the Cardiac Toxicity of Conventional Hemodialysis Treatments

Daljit K. Hothi,* Lesley Rees,* Jan Marek,[†] James Burton,[‡] and Christopher W. McIntyre^{†§}

Departments of *Nephro-urology and [†]Pediatric Cardiology, Great Ormond Street Hospital for Children, London,

[‡]Department of Renal Medicine, Derby City General Hospital, Derby, and [§]School of Graduate Entry Medicine and Health, University of Nottingham, Nottingham, United Kingdom

Background and objective: In adults, hemodialysis (HD)-induced ischemia causes reversible myocardial dysfunction (myocardial stunning) that is progressive with raised attendant mortality. Children share an increased risk for death from a spectrum of uremia-related cardiovascular abnormalities but in the absence of significant classical atheromatous coronary artery disease; therefore, we elected to assess children who were on HD for the occurrence of myocardial stunning to investigate the relative importance of characteristic uremic cardiovascular abnormalities in the development of ischemic cardiac injury.

Design, setting, participants, & measurements: We included all single-center long-term HD patients ($n = 12$; range 2 to 17 yr), excluding those with structural cardiac disease. Patients underwent conventional thrice-weekly HD for 4 h using high-flux membranes. We measured regional left ventricle wall motion using serial echocardiography (before HD, during HD, and 15 min after HD). Significant stunning was defined as a 20% reduction in regional wall motion (RRWM) in two or more segments and hyperkinesis as an either >20 or >50% increase in shortening fraction (SF).

Results: Eleven of 12 patients developed myocardial stunning with varying degrees of compensatory hyperkinesis in unaffected segments, maintaining left ventricular ejection fraction throughout HD. The mean segmental %SF_[Overall] and %SF_[RRWM] fell during HD (2.19 to 1.77 and 2.72 to 1.37, respectively). Intradialytic BP reduction was significantly associated with mean segmental %SF_[RRWM].

Conclusions: Children who receive conventional HD experience myocardial stunning. These data, in combination with previous adult studies of intradialytic myocardial blood flow, suggest a characteristic cardiovascular phenotype in HD patients that predisposes to significant demand ischemia.

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Cardiovascular mortality is grossly elevated in hemodialysis (HD) patients. Patients with chronic kidney disease (CKD) have a 30-fold increase in mortality than age-matched control subjects and an even higher risk of up to 800-fold for dialysis and young adults (1). This excess of cardiovascular death is only partly explained by an increase in traditional risk factors, and several mechanisms of cardiac damage specific to the uremic milieu have been identified. It is also becoming increasingly apparent that HD in itself confers a risk, but the pathophysiologic mechanisms remain elusive. In adults, there is evidence from isotopic (2), electrocardiographic (3,4), biochemical (5,6), and echocardiographic (7,8) studies implicating HD as a source of recurrent subclinical myocardial cell injury, even in the absence of preexisting large-vessel epicardial coronary artery disease (CAD). Using single photon emission computed tomography, we demonstrated acute reductions in global and segmental myocardial blood flow during HD, with

matched reversible reductions in segmental contractile function (2), consistent with the definition of myocardial stunning (9). The number of stunned segments and the intensity of stunning within segments correlate with intradialytic BP changes and ultrafiltration volume (10). These acute changes can be abrogated by improving the hemodynamic tolerability of the HD treatment with the use of biofeedback HD or cooling (7,8). In the model of CAD, repeated stunning leads to myocardial hibernation, defined as ischemic, noninfarcted myocardium that exists in a state of contractile dysfunction (9). Hibernation in turn contributes to congestive heart failure (11) and has been shown to be marker of poor prognosis (12). Within the renal HD cohort, transient myocardial ischemia precipitated cardiac arrhythmias (13), regional fixed systolic dysfunction, and reduced overall systolic function (2).

Children and young adults with uremia have a similar constellation of ischemia-predisposing factors to adults, including increased intima media thickness and pulse wave velocity, vascular calcification, early atherosclerosis, and endothelial dysfunction (14,15), but without significant atheromatous CAD. In our experience, the incidence of HD-induced hemodynamic disturbance is comparable to adults, with a 20 to 30% incidence of intradialytic hypotension associated with a relative blood volume reduction of 20 to 25% (16). It is therefore plau-

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Correspondence: Dr. Christopher W. McIntyre, Department of Renal Medicine, Derby City General Hospital, Uttoxeter Road, Derby DE22 3NE, UK. Phone: +44-1332-340131; Fax: +44-1332-625975; E-mail: chris.mcintyre@nottingham.ac.uk

sible that children may also display a similar pathophysiology of dialysis-induced cardiac injury as a result of characteristic uremic cardiovascular abnormalities.

Children are our best model of patients with uremia for defining the risk for demand myocardial ischemia because they lack “classical” epicardial plaque-based CAD. The aim of our research was to determine the direct cardiac consequence of dialysis treatments. Our objective was to measure sequentially segmental left ventricular (LV) function in children who were on conventional intermittent HD treatments to demonstrate evidence of acute cardiac injury.

Materials and Methods

Patients

All patients at Great Ormond Street Hospital who had been on HD for at least 1 mo were considered for inclusion in the study. We excluded patients with congenital heart disease or a concurrent respiratory illness or when it was not possible to obtain echocardiographic images of sufficient quality to allow meaningful analysis owing to poor windows for visualizing the heart. Ethics approval for this study was granted by the Institute of Child Health Local Research Ethics Committee, and informed consent was obtained from patients or their guardians.

HD Therapy Details

All patients underwent dialysis using Gambro 200S dialysis monitors (Gambro, United Kingdom). Patients received HD for 4 h three times per week. All dialysis membranes were high-flux polysulfone or triacetate cellulose membranes, size-adjusted to be equal to each patient's body surface area. For all treatments, dialysate contained 140 mmol/L sodium, 2 mmol/L potassium, 1.75 mmol/L calcium, 0.5 mmol/L magnesium, and 34 mmol/L bicarbonate. The dialysate temperatures were set at constant value of 37.0°C. Dialysate flow rates were maintained at 500 ml/min. Blood pump speed varied between 80 and 400 ml/min, depending on the patient's size. The dialysis prescription was adjusted monthly to achieve a urea reduction ratio >65% and $Kt/V_{\text{urea}} > 1.2$ (calculated from Daugirdas single-pool kinetics) (17). All patients received unfractionated heparin as required. Patients were permitted to consume one meal during their treatment. For each session, net fluid removal was set on an individual basis and adjusted to restore the ideal dry weight (clinically determined) by the end of the dialysis session. Ultrafiltration (UF) took place in parallel with dialysis, using constant UF rates, unless patients had higher-than-normal UF requirements. In these circumstances, patients received 30 min of isolated UF at the beginning and/or the end of the HD session.

Study Protocol

For each monitored dialysis treatment, serial echocardiography was performed at the start of dialysis (baseline), 2 h into the dialysis session, at the end of the dialysis session, and at recovery 15 min after dialysis, once a saline washback had been given and the patients had been disconnected from the machine. Ideally, we would have preferred a longer period after dialysis before reassessing cardiac function, but owing to travel times and other social reasons, this was not possible. Blood samples were collected before and after each session in lithium heparin and EDTA tubes, and biochemical analysis was performed on a multichannel autoanalyzer for routine electrochemistry, full blood count, and high-sensitivity C-reactive protein (hsCRP). Cardiac troponin I (cTnI) analysis was preformed using a chemiluminescent assay on

a Beckman Access Immunoassay analyzer (Fullerton, CA). Predialysis blood tests were drawn immediately after insertion of access needles or catheter connection, and postdialysis levels were taken from the arterial line after reducing the blood pump speed to 50 ml/min. An investigator was present for the entirety of every dialysis session to record intradialytic symptoms, but BP measurements were taken independently, when deemed necessary by the dialysis nurses without any influence from the investigator. For each patient, echocardiography data were collected during two separate dialysis sessions, separated by no more than 4 wk.

The primary end point of HD-induced myocardial stunning was determined from the degree of change in LV segmental shortening fraction (SF) and the number of segments involved. The secondary end point was to assess whether a relationship existed between reduced segmental LV function and intradialytic BP changes and ultrafiltration volume.

Echocardiography

Two-dimensional echocardiography was performed serially throughout dialysis sessions using commercially available equipment (3.5 MHz 3S probe, Vivid I; GE Medical Systems, Sonigen, Germany). A single experienced operator carried out all measurements with the patients in the left lateral position. Standard apical two- and four-chamber views (to visualize the LV endocardial border in two planes at 90° to each other) were recorded and then copied onto CDs in DICOM format for off-line analysis, and suitability of these images for analysis was independently assessed by J.B. Subsequently, the DICOM images were analyzed, again by one investigator (D.H.), using a personal computer-based digitizing program (Echo-CMS, MEDIS; Leiden, Netherlands) as described previously (18). Three consecutive heartbeats were analyzed for each time point (extrasystolic beats were excluded). Endocardial borders (excluding papillary muscles) were traced semiautomatically for each video frame of the three-beat sequence, and any anomalies were corrected manually. Maximal displacement of the endocardial border from a center point was then measured over each of 10 chords around the LV wall, corrected for end-diastolic LV circumference and expressed as %SF. Each apical view was divided into five segments, and SF for the chords in each segment was averaged so that 10 regions of the left ventricle were assessed at each time point. Any segmental endocardial border that was not clearly visible was excluded from analysis. Segmental reduction in regional wall motion (RRWM) was defined as a decline in SF of >20% from baseline, and degrees of hyperkinesis 20% and 50% were defined as segments that demonstrated an increase in SF of >20% and >50%, respectively. We calculated mean SF for all 10 segments ($SF_{\text{[Overall]}}$) for segments that developed new RRWM ($SF_{\text{[RRWM]}}$) and segments that did not develop RRWM ($SF_{\text{[Non-RRWM]}}$). Ejection fraction was calculated from the apical four-chamber and two-chamber view by the Simpson's rule. The LV posterior and septal wall thicknesses were measured from parasternal long axis M-mode images and represented as z scores after adjustment for age and body surface area.

Statistical Analysis

The primary objective of this study was to determine the prevalence of myocardial stunning in a pediatric cohort; however despite having data on 24 dialysis sessions, this was made up of two data sets of 12 from the same patients and therefore we present prevalence data using one of the data sets that was selected at random, by tossing a coin, blinded to the authors. The second objective of the study was to determine whether factors related to the patients or the dialysis treatment predicted the severity of stunning. In these analyses, by incorporating a repeated measures analysis, we were able to use both data sets and thus used information from 24 dialysis sessions.

Using a single data set, we expressed the results as mean \pm SD when parametric or the median and interquartile range when nonparametric. Echocardiographic and hemodynamic data were analyzed using one-way ANOVA, with a design for repeated measures. Depending on Gaussian distribution, all other data were analyzed using either the paired or unpaired *t* test or the Mann-Whitney or Wilcoxon matched pair test.

To test for the association between both the mean %SF_[RRWM] and SF_[non-RRWM] at 240 min against dialysis-related factors (ultrafiltration volume [ml/kg dry weight], intradialytic BP) and patient-related factors (dialysis vintage, age), we used univariate regression analysis adjusting for repeated measures. We did not attempt multivariate logistic regression analysis because of the relatively small sample size. In all analyses, an α error at $P < 0.05$ was judged to be significant.

Results

Patient Characteristics

A total of 12 patients were included (Table 1), their age ranging from 2.2 to 17.1 yr. One patient, aged 15 yr, was excluded because her echocardiography images were of insufficient quality to allow meaningful analysis. All but three of the included patients had arteriovenous fistulas as their dialysis vascular access; in the remainder, central tunneled venous catheters were used. Patients had been on long-term HD for 4 to 89 mo. Four patients had previous failed transplants, and one patient had 3 mo of peritoneal dialysis before HD. Residual urine output varied among the study group. Five patients were anuric, four patients passed <1 ml/kg per h urine, and two patients passed between 1 and 2 ml/kg per h. At their baseline examinations, only one patient had LV hypertrophy (LVH) and three patients had borderline hypertrophy (see Table 1).

Global and Segmental Ventricular Function

The median LV ejection fraction (LVEF) was 51.80% (range 38.20 to 68.10%) at baseline, 55.70% (range 44.20 to 66.70%) at

120 min of HD, 53.21% (range 37.80 to 71.50%) at 240 min, and 55.00% (range 43.50 to 64.00%) on recovery 15 min after dialysis (Figure 1), but the differences between all of the time points were not statistically significant ($P = 0.56$). Four patients had LVEF below the lower limit of normal, namely 50%.

All 12 patients developed segments with RRWM in one to five segments (Figure 2), with coexisting 20% hyperkinesis in one to four nonstunned segments in 11 of 12 patients from 120 min that persisted into recovery. In addition, nine of 12 patients exhibited 50% hyperkinesis in as many as three segments. Again, this was evident at 120 min and persisted into recovery (Figure 2). Of the 35 of 120 segments that stunned, midcavity segments dominated followed by basal and then apical segments.

The resultant effect on segmental SF was a fall of the mean segmental %SF_[Overall] from 2.2 ± 0.4 (mean \pm SD) at baseline to 1.9 ± 0.3 by 120 min and 1.8 ± 0.4 at 240 min with an increase to 2.1 ± 0.5 after dialysis (Figure 1). The difference was statistically significant when comparing baseline segmental %SF_[Overall] with that at 120 and 240 min ($P < 0.05$) but did not reach significance on comparing %SF_[Overall] at 120 min, 240 min ($P = 0.34$), and recovery. There was a statistically significant fall in the mean segmental %SF_[RRWM] from 2.7 ± 1.1 at baseline to 1.9 ± 0.7 at 120 min, 1.4 ± 0.6 at 240 min, and 2.2 ± 0.7 at recovery ($P < 0.05$). Ten of 12 patients showed evidence of resolution of RRWM on recovery as early as 15 min after completing dialysis (Figures 3 and 4). This pattern of dialysis-induced segmental RRWM is consistent with the definition of myocardial stunning. The mean segmental %SF_[non-RRWM] increased from baseline to 240 min 2.0 ± 0.6 to 2.3 ± 0.6 but did not reach statistical significance ($P = 0.07$; Figure 4). The mean segmental %SF in the segments that developed RRWM was higher at baseline compared with those that did not (2.35 ± 0.52 versus 1.98 ± 0.63 ; Figure 4).

Table 1. Patient demographics and baseline cardiac parameters^a

Patient	Age (yr)	Cumulative Time on HD and Peritoneal Dialysis (mo)	Time on HD (mo)	Cause of ESRD	AVF	LV Septum (z score)	LV Posterior Wall (z score)	LVDD (z score)	EF (%)
1	5.7	4	4	Renal dysplasia	Yes	1.3	1.7	2.04	45.4
2	17.1	130	89	Cystinosis	Yes	1.6	0.3	-1.91	43.3
3	15.7	43	43	FSGS	Yes	0.1	1.4	4.06	55.4
4	15.0	24	4	Renal dysplasia	Yes	0.3	0.2	-0.53	49.8
5	15.7	32	32	FSGS	Yes	2.6	1.9	0.89	46.9
6	13.8	7	4	Renal dysplasia	Yes	5.9	6.3	-3.27	50.9
7	11.2	41	35	Renal dysplasia	Yes	0.5	-0.6	0.89	54.7
8	13.6	15	15	FSGS	Yes	0.6	-1.1	0.80	50.7
9	2.2	7	7	Glomerulocystic	Yes	1.5	1.7	0.67	61.2
10	17.0	12	12	Bilateral VUR	Yes	1.9	1.7	1.94	53.6
11	7.6	62	62	ARPKD	Yes	1.0	0.3	-1.74	61.1
12	14.6	23	6	Cystic dysplasia	Yes	2.6	1.2	-1.65	60.0

^aARPKD, autosomal recessive polycystic kidney disease; AVF, arteriovenous fistula; EF, ejection fraction; LV, left ventricular; LVDD, left ventricular diastolic dimension; VUR, vesicoureteral reflux.

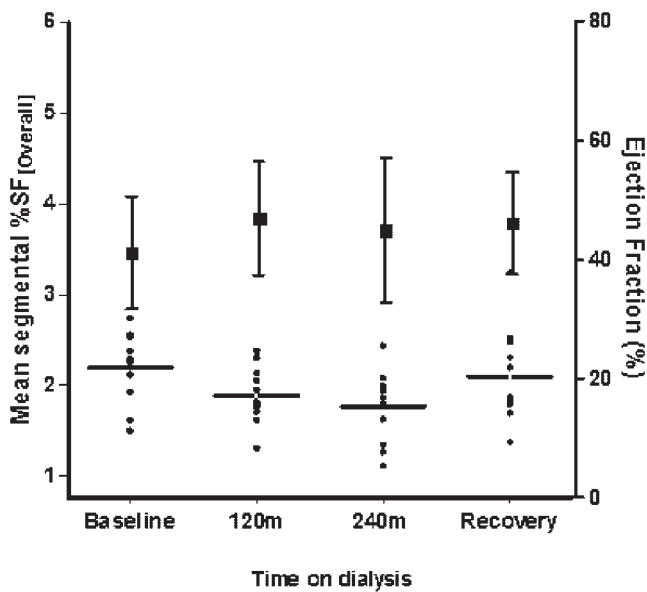


Figure 1. Changes in global and segmental LV function during hemodialysis. Ejection fraction represented as mean and SD. The difference at the four time points was not statistically significant ($P = 0.56$). Mean segmental overall percentage of shortening fraction (%SF_[Overall]) is represented as the cohort mean and box plot of the individual results. The difference between the baseline and both 120 and 240 min was statistically significant ($P < 0.05$).

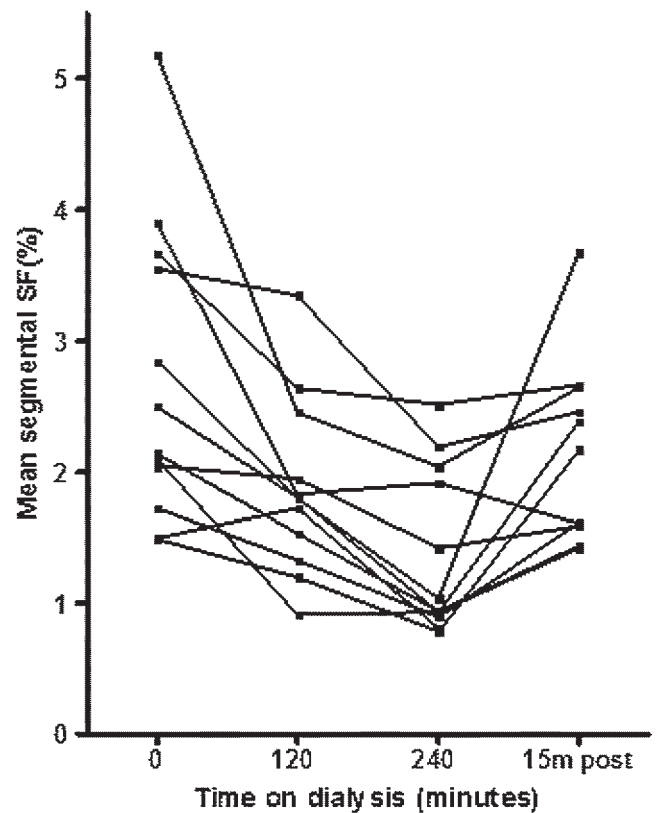


Figure 3. Mean segmental %SF in those who developed RRWM.

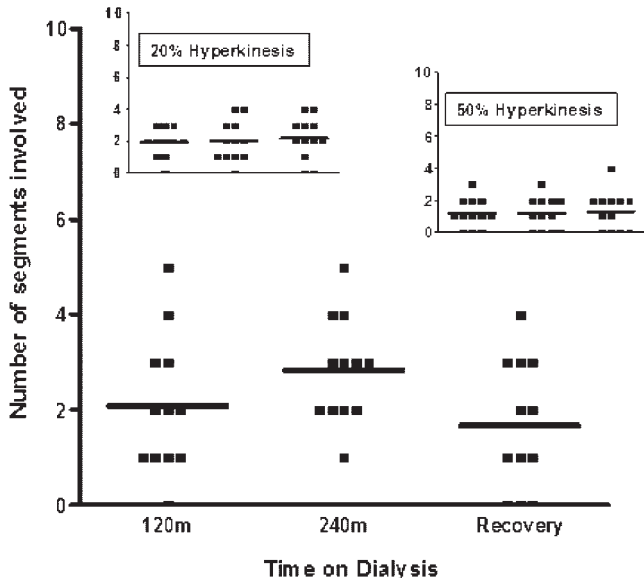


Figure 2. Segmental reduction in regional wall motion (RRWM) and hyperkinesis during hemodialysis.

Factors Associated with the Development of Myocardial Stunning

The median intradialytic systolic BP fall for the group was 25 mmHg (range 6 to 90 mmHg), and the lowest intradialytic systolic dialysis BP ranged from 58 to 110 mmHg. We found a strong correlation between intradialytic systolic BP change and

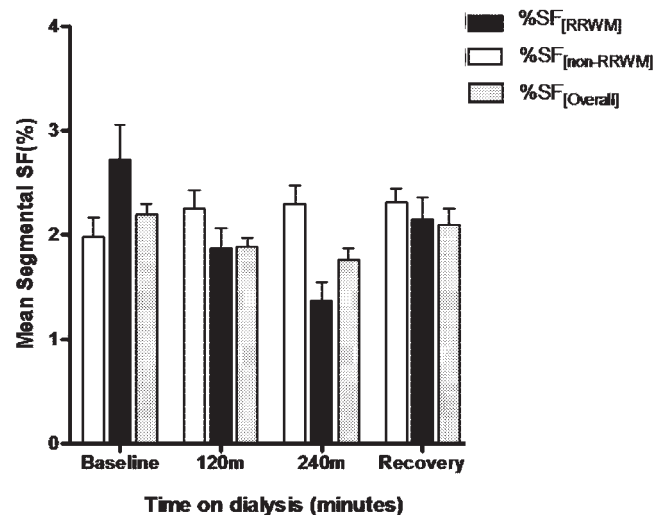


Figure 4. Mean segmental %SF relative to time on hemodialysis. *Significant difference between %SF_[Overall] baseline versus 120 min and baseline versus 240 min ($P < 0.05$). †Significant difference between %SF_[RRWM] baseline versus 120 min, baseline versus 240 min, 120 versus 240 min, and 240 versus recovery ($P < 0.05$). ‡In the remaining groups, the difference was NS.

mean segmental %SF_[RRWM] ($r = 0.56, P < 0.05$). On univariate linear regression analysis, there was a significant association between intradialytic systolic BP changes and mean segmental %SF_[RRWM] ($P < 0.05$) but not against lowest intradialytic systolic BP ($P = 0.68$).

The median UF volume for the group was 29.4 ml/kg (range 2 to 94 ml/kg), and in one patient no ultrafiltration was attempted. We saw no significant association between UF volume and the number of segments that developed RRWM or the mean segmental %SF_[RRWM]. On univariate linear regression analysis, we found no association between UF volumes and mean segmental %SF_[RRWM] ($P = 0.6$). When considering both intradialytic BP change and UF against the mean segmental %SF_[RRWM], the relationship between intradialytic BP change and the mean segmental %SF_[RRWM] disappeared ($P = 0.24$). In this patient group, UF volume correlated with change in BP during HD ($r = 0.56$, $P < 0.05$). We saw no significant relationship between the number or intensity of RRWM as measured by the mean %SF_[RRWM] against patient age, dialysis vintage, predialysis plasma urea levels, anemia, LV mass, hsCRP, or cTnI.

Hematologic and Biochemical Profile and Markers of Cardiac Injury

The biochemical and hematologic profile was typical of HD patients, showing a prevalence of anemia ($n = 5$), hyperparathyroidism ($n = 7$), hyperphosphatemia ($n = 5$), and acidosis ($n = 4$). Routine laboratory values and dialysis adequacy are summarized in Table 2. Values for hsCRP exceeded 1 $\mu\text{g/L}$ in six patients after dialysis and 3 $\mu\text{g/L}$ in one patient after dialysis. In eight of 12 patients, the postdialysis cTnI levels remained the same as predialysis levels of <0.04 $\mu\text{g/L}$. In the remaining four patients, we saw a rise in cTnI levels after dialysis up to 0.07 $\mu\text{g/L}$.

Discussion

We have shown for the first time in children that pediatric patients who receive conventional HD experience dialysis-induced myocardial stunning. As in adults, this reflects the degree of HD-induced hemodynamic instability. These data, in combination with previous adult studies (2), suggest that even in the absence of conventional epicardial CAD, the characteristic cardiovascular phenotype in HD patients with uremia is

severe enough to limit the microvasculature response to hemodynamic stress and predisposes to significant demand myocardial ischemia.

The prevalence of myocardial stunning is high, cumulative, and associated with an attendant risk for increased cardiovascular events and mortality. Burton *et al.* (12) reported in dialysis patients progression from reversible segmental LV dysfunction to fixed segmental systolic dysfunction after 1 yr of conventional HD, with a resultant reduction in global LV function both at rest and during stress with an impaired hemodynamic tolerance to UF during subsequent dialysis treatments. Encouraging, it may be possible to abrogate these acute adverse cardiac effects of HD through changes in the dialysis prescription, such as the introduction of cooled dialysate (8) or hemodiafiltration (7). One previous study of adults demonstrated myocardial stunning in “low risk” non-cardiac-compromised patients without diabetes (19), but, until now, there has been no evaluation of the risk in children and thus we present novel findings of myocardial stunning during conventional 4-h HD sessions with a prevalence over a broad age spectrum from 2 to 17 yr. The segments most likely to be affected were those with higher baseline contractile activity, and this may represent their proportionately higher metabolic demand and increased vulnerability to demand ischemia. Nonetheless, through an early compensatory hyperkinetic response in regions of the left ventricle, the global LVEF did not fall, but neither did it rise as one would normally expect after a significant hemodynamic challenge.

One feature that distinguishes children from adults is the absence of significant epicardial atheromatous CAD. They do, however, share a high prevalence of risk factors for adult-type cardiovascular disease (CVD) that have been associated with a reduced coronary flow reserve and thus a propensity to demand ischemia (20). Of these, hypertension, anemia, hyperparathyroidism, and hyperphosphatemia were significantly prevalent in our cohort. Children can also display a constellation of altered functional and morphologic cardiovascular features that predispose them to ischemic insults. LVH, for exam-

Table 2. Biochemical and hematologic profile^a

Parameter	Mean \pm SD	Range
Predialysis urea (mmol/L)	22.50 \pm 4.20	15.20 to 28.20
Postdialysis urea (mmol/L)	4.50 \pm 1.50	1.50 to 6.90
KT/V _{urea}	2.00 \pm 0.50	0.50 to 3.10
URR (%)	80.00 \pm 6.00	72.00 to 91.00
Hemoglobin (g/dl)	11.50 \pm 1.40	9.10 to 13.10
Potassium (mmol/L)	5.30 \pm 0.70	3.70 to 6.40
Phosphate (mmol/L)	1.50 \pm 0.60	0.60 to 2.90
Albumin (g/L)	38.30 \pm 2.50	34.00 to 41.00
PTH (pmol/L)	22.40 \pm 22.90	0.30 to 89.00
Ionized calcium (mmol/L)	1.20 \pm 0.10	1.09 to 1.44
Bicarbonate (mmol/L)	23.90 \pm 2.40	20.00 to 27.00
hsCRP ($\mu\text{g/L}$)	1.90 \pm 1.50	0.40 to 5.50

^ahsCRP, high-sensitivity C-reactive protein; PTH, parathyroid hormone; URR, urea reduction rate.

ple, progresses to maladaptive cardiac remodeling characterized by decreased capillary density, subendothelial perfusion (21), and decreased coronary contractile reserve (22). Overt LVH was present in one patient and borderline hypertrophy in another three patients. Five of 12 of our patients were common to a study conducted by Shroff *et al.* (15) reporting findings of diminished arterial wall compliance and coronary and carotid artery calcification. Such vascular abnormalities are accepted markers of asymptomatic arteriosclerosis and mortality (23) and perhaps indicative of coronary microcirculation abnormalities. Evidence for inappropriately raised sympathetic nerve activity in dialysis patients (24) raises the possibility of an alternative explanation for the regional LV dysfunction, namely takotsubo, or “stress,” cardiomyopathy (25); however, Dasselhaar *et al.* (19) demonstrated a fall in regional and global myocardial blood flow 30 min into a HD session in the absence of UF that preceded regional LV dysfunction. This is the inverse of the causal sequence of takotsubo, or stress, cardiomyopathy. In addition, we failed to see any evidence of apical ballooning, a feature typical of classical takotsubo cardiomyopathy. Nevertheless, the effects of raised sympathetic nerve activity may be relevant by mediating microvasculature derangement and vasospasm. We found no significant association between these aforementioned risk factors and the severity of myocardial stunning, possibly because cardiorenal performance is influenced by a number of humoral and genetic factors (26) that act collectively to exert an effect but in isolation, particularly in pediatrics, are too small to be detectable from our sample size.

The major determinant of intradialytic BP is cardiac output and end diastolic volume (27), but clearly regional LV function is important as evidenced by reports of reduced hemodynamic stability in patients developing myocardial stunning despite below average UF volumes (13). Shoji *et al.* (28) found BP reduction during dialysis and not hypertension in adult HD patients as a factor that influenced survival negatively. We found the reduction in BP and not the absolute intradialytic BP to be related to the severity of dialysis-induced LV dysfunction. The implication is that actual BP is not as important as the failure to maintain BP in initiating and propagating myocardial stunning during dialysis. Contrary to adult data (10), we found no association between severity of myocardial stunning and UF volumes, despite a significant relationship between UF volumes and absolute BP during HD. Nevertheless, the findings bear resemblance to pediatric data pertaining to the relationship between relative blood volume changes during HD, UF volumes, and morbidity. UF volume was found not to be predictive of hemodynamic instability (16), especially in nonanuric patients who also demonstrated a lower absolute reduction in relative blood volume before the development of intradialytic hypotension (16). Children seem to be different from adults, with a more direct relationship between BP and UF volumes. In addition, as a consequence of residual renal function, some exist closer to their dry weight and are thus very sensitive to fluid shifts during dialysis. Combined with a poorly compliant left ventricle (29) and peripheral conduit vessels (15), UF mediates a reduction in cardiac output and BP. In the face of an attenuated coronary reserve, ischemia prevails

when the hemodynamic demand of HD is not met by an adequate increase in myocardial blood flow.

There is considerable evidence alluding to the value of both CRP and cTnI as markers of CVD and mortality in ESRD. CRP is specifically recognized as a marker of inflammation and atherosclerosis (30), whereas cTnI levels in HD patients are indicative of subclinical myocardial ischemic injury (5,6,31). We found elevated levels of hsCRP in half of the children on HD and a rise in cTnI levels in 25% of this pediatric cohort, and this may be an indicator of early subclinical atheromatous disease in our patients. Neither marker demonstrated a correlation with the severity of myocardial stunning. More important, owing to the lack of patients who failed to develop RRWM, we were unable to perform multivariate regression analyses to test the predictive ability of hsCRP, cTnI, or any other factors such as BP or dialysis vintage for the development and severity of myocardial stunning during conventional HD; therefore, it is difficult to speculate on markers for the identification of “at risk” patients. We can be certain, however, that as a result of current practices, which at best screen only global cardiac function, segmental myocardial dysfunction on conventional HD programs is likely to progress silently and unnoticed and thus preventing the opportunity for intervention.

Study Limitations

We acknowledge the limitations of our work. This was a preliminary study that examined regional LV dysfunction in children on HD, and the sample size was small. Nevertheless, the study was adequately powered for the primary outcome. Echocardiography assessments and analysis were repeated twice in the same patient, and the results showed concordance in the localization of abnormalities but the number of segments involved differed. This may indicate poor reproducibility or, conversely, is the consequence of differences in inpatient UF volumes and intradialytic hemodynamic parameters between treatments. Because there is no evidence pertaining to the presence of significant epicardial CAD in children with ESRD, we elected not to subject our patients to angiography or perfusion imaging. The latter may be considered to be less invasive; however, adult data suggest that myocardial scintigraphy is imperfect in detecting CAD in patients with ESRD (32), and, indeed, doubts about applicability in patients with more severe CKD have led to renal disease currently not being categorized in the most recent “Appropriateness Criteria for Stress Echocardiography” recommendations (33). During our assessment of LV wall motion, we used only the endocardial border as a marker of contraction without accounting for wall thickening or transmural heterogeneity; however, the use of other imaging techniques such as magnetic resonance imaging to assess functional change while the patient was receiving HD would be technically impossible.

Conclusions

Although recurrent HD-based myocardial injury has recently become appreciated as a novel mechanism in the

development of systolic dysfunction, adverse cardiac outcomes, and mortality in adult HD patients, this study describes for the first time an analogous situation in children on HD. The markedly reduced levels of conventional cardiovascular risk factors and atheromatous arterial disease in this group significantly highlights the overwhelming nature of the uremic risk factors in the development of CVD in HD patients, assists in the explanation of the failure of conventional Framingham cardiovascular risk assessments in this population, and focuses therapeutic attention away from the (currently totally unsuccessful) application of therapeutic approaches developed within the paradigm of CVD in patients without significant CKD.

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Disclosures

None.

References

- Foley RN, Parfrey PS, Sarnak MJ: Epidemiology of cardiovascular disease in chronic renal disease. *J Am Soc Nephrol* 9[Suppl]: S16–S23, 1998
- McIntyre CW, Burton JO, Selby NM, Leccisotti L, Korsheed S, Baker CS, Camici PG: Hemodialysis-induced cardiac dysfunction is associated with an acute reduction in global and segmental myocardial blood flow. *Clin J Am Soc Nephrol* 3: 19–26, 2008
- Conlon P, Krucoff M, Minda S, Schumm D, Schwab S: Incidence and long-term significance of transient ST segment deviation in hemodialysis patients. *Clin Nephrol* 49: 236–239, 1998
- Foley R, Parfrey P, Kent G, Harnett J, Murray D, Barre P: Serial change in echocardiographic parameters and cardiac failure in end-stage renal disease. *J Am Soc Nephrol* 11: 912–916, 2000
- Tarakcioglu M, Erbagci A, Cekmen M, Usalan C, Ciçek H, Ozaslan J, Camci C: Acute effect of haemodialysis on serum markers of myocardial damage. *Int J Clin Pract* 56: 328–332, 2002
- Wayand D, Baum H, Schatzle G, Scharf J, Neumeier D: Cardiac troponin T and I in end-stage renal failure. *Clin Chem* 46: 1345–1350, 2000
- Selby NM, Lambie SH, Camici PG, Baker CS, McIntyre CW: Occurrence of regional left ventricular dysfunction in patients undergoing standard and biofeedback dialysis. *Am J Kidney Dis* 47: 830–841, 2006
- Selby NM, Burton JO, Chesterton LJ, McIntyre CW: Dialysis induced regional left ventricular dysfunction is ameliorated by cooling the dialysate. *Clin J Am Soc Nephrol* 1: 1216–1225, 2006
- Braunwald E, Kloner R: The stunned myocardium: Prolonged, postischemic ventricular dysfunction. *Circulation* 66: 1146–1149, 1982
- Burton JO, Korsheed S, John SG, McIntyre CW: Haemodialysis Induced Cardiac Injury Is Associated with Asymptomatic Relative Hypotension. Presented at the annual meeting of the American Society of Nephrology; San Francisco, CA, October 31 through November 5, 2007
- Wijns W, Vatner S, Camici P: Hibernating myocardium. *N Engl J Med* 339: 173–181, 1998
- Petix NR, Sestini S, Marcucci G, Coppola A, Arena A, Nassi F, Taiti A, Guarnaccia V, Mennuti A, Mazzoni V: Can the reversible regional wall motion abnormalities on stress gated Tc-99m sestamibi SPECT predict a future cardiac event? *J Nucl Cardiol* 12: 20–31, 2005
- Burton JO, Kosheed S, McIntyre CW: Haemodialysis induced acute cardiac injury is associated with increased rates of ventricular arrhythmias. *Ren Fail* 30: 1–9, 2008
- Kari JA, Donald AE, Vallance DT, Bruckdorfer KR, Leone A, Mullen MJ, Bunce T, Dorado B, Deanfield JE, Rees L: Physiology and biochemistry of endothelial function in children with chronic renal failure. *Kidney Int* 52: 468–472, 1997
- Shroff RC, Donald AE, Hiorns MP, Watson A, Feather S, Milford D, Ellins EA, Storry C, Ridout D, Deanfield J, Rees L: Mineral metabolism and vascular damage in children on dialysis. *J Am Soc Nephrol* 18: 2996–3003, 2007
- Hothi DK, Harvey E, Goia CM, Geary D: Blood-volume monitoring in paediatric haemodialysis. *Pediatr Nephrol* 23: 813–820, 2008
- Daugirdas JT: Second generation logarithmic estimates of single-pool variable volume Kt/V: An analysis of error. *J Am Soc Nephrol* 4: 1205–1213, 1993
- Bosch JG, Savalle LH, van Burken G, Reiber JH: Evaluation of a semiautomatic contour detection approach in sequences of short-axis two-dimensional echocardiographic images. *J Am Soc Echocardiogr* 8: 810–821, 1995
- Dasselaar JJ, Slart RH, Knip M, Pruijm J, Tio RA, McIntyre CW, de Jong PE, Franssen CF: Haemodialysis is associated with a pronounced fall in myocardial perfusion. *Nephrol Dial Transplant* 24: 604–610, 2009
- Chade AR, Brosh D, Higano ST, Lennon RJ, Lerman LO, Lerman A: Mild renal insufficiency is associated with reduced coronary flow in patients with non-obstructive coronary artery disease. *Kidney Int* 69: 266–271, 2006
- Weber KT, Brilla CG: Pathological hypertrophy and cardiac interstitium: Fibrosis and renin-angiotensin-aldosterone system. *Circulation* 83: 1849–1865, 1991
- Chinali M, de Simone G, Matteucci MC, Picca S, Mastrostefano A, Anarat A, Caliskan S, Jeck N, Neuhaus TJ, Peco-Antic A, Peruzzi L, Testa S, Mehls O, Wühl E, Schaefer F, ESCAPE Trial Group: Reduced systolic myocardial function in children with chronic renal insufficiency. *J Am Soc Nephrol* 18: 593–598, 2007
- London GM, Guérin AP, Marchais SJ, Métivier F, Pannier B, Adda H: Arterial media calcification in end-stage renal disease: Impact on all-cause and cardiovascular mortality. *Nephrol Dial Transplant* 18: 1731–1740, 2003
- Hausberg M, Kosch M, Harmelink P, Barenbrock M, Hohage H, Kisters K, Dietl KH, Rahn KH: Sympathetic nerve activity in end-stage renal disease. *Circulation* 106: 1974–1979, 2002
- Wittstein IS: Acute stress cardiomyopathy. *Curr Heart Fail Rep* 5: 61–68, 2008
- Freedman BI: Genetic factors in common complex renal and cardiovascular diseases. *Adv Chronic Kidney Dis* 13: 105–109, 2006
- Stewart GA, Mark PB, Johnston N, Foster JE, Cowan M,

- Rodger RS, Dargie HJ, Jardine AG: Determinants of hypertension and left ventricular function in end stage renal failure: A pilot study using cardiovascular magnetic resonance imaging. *Clin Physiol Funct Imaging* 24: 387-393, 2004
28. Shoji T, Tsubakihara Y, Fujii M, Imai E: Hemodialysis-associated hypotension as an independent risk factor for two-year mortality in hemodialysis patients. *Kidney Int* 66: 1212-1220, 2004
 29. Mitsnefes MM, Kimball TR, Border WL, Witt SA, Glascock BJ, Khoury PR, Daniels SR: Impaired left ventricular diastolic function in children with chronic renal failure. *Kidney Int* 65: 1461-1466, 2004
 30. Calabro P, Willerson JT, Yeh ET: Inflammatory cytokines stimulated C-reactive protein production by human coronary artery smooth muscle cells. *Circulation* 108: 1930-1932, 2003
 31. Lipshultz SE, Somers MJ, Lipsitz SR, Colan SD, Jabs K, Rifai N: Serum cardiac troponin and subclinical cardiac status in pediatric chronic renal failure. *Pediatrics* 112: 79-86, 2003
 32. De Lima JJ, Sabbaga E, Vieira ML, de Paula FJ, Ianhez LE, Krieger EM, Ramires JA: Coronary angiography is the best predictor of events in renal transplant candidates compared with noninvasive testing. *Hypertension* 42: 263-268, 2003
 33. Douglas PS, Khandheria B, Stainback RF Douglas PS, Khandheria B, Stainback RF, Weissman NJ, Peterson ED, Hendel RC, Stainback RF, Blaivas M, Des Prez RD, Gillam LD, Golash T, Hiratzka LF, Kussmaul WG, Labovitz AJ, Lindenfeld J, Masoudi FA, Mayo PH, Porembka D, Spertus JA, Wann LS, Wiegers SE, Brindis RG, Douglas PS, Patel MR, Wolk MJ, Allen JM: ACCF/AHA/ACEP/AHA/ASNC/SCAI/SCCT/SCMR 2008 appropriateness criteria for stress echocardiography endorsed by the Heart Rhythm Society and the Society of Critical Care Medicine. *Circulation* 117: 1478-1497, 2008