Cardiac abnormalities in end stage renal failure and anaemia

K P Morris, J R Skinner, C Wren, S Hunter, M G Coulthard

Abstract
Thirteen anaemic children on dialysis were assessed to determine the incidence of cardiac changes in end stage renal failure. Nine children had an increased cardiothoracic ratio on radiography. The electrocardiogram was abnormal in every case but no child had left ventricular hypertrophy as assessed by voltage criteria. However, left ventricular hypertrophy, often gross, was found on echocardiography in 12 children and affected the interventricular septum disproportionately. Cardiac index was increased in 10 patients as a result of an increased left ventricular stroke volume rather than heart rate. Left ventricular hypertrophy was significantly greater in those on treatment for hypertension and in those with the highest cardiac index. Abnormal diastolic ventricular function was found in 6/11 children.

Children with end stage renal failure have significant cardiac adnormalities that are likely to contribute to the high cardiovascular mortality in this group. Anaemia and hypertension, or its treatment, probably contribute to these changes. Voltage criteria on electrocardiogram are of no value in detecting left ventricular hypertrophy. Echocardiography must be performed, with the results corrected for age and surface area, in order to detect and follow these abnormalities.

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Many studies in adult patients with end stage renal failure have documented cardiac abnormalities.[1-3] In addition to accelerated atherosclerosis, an increased cardiac output and left ventricular hypertrophy are often found. Left ventricular systolic function usually remains normal despite these abnormalities but a minority of patients develop left ventricular dysfunction and heart failure.[4] Recent studies have documented abnormal right and left ventricular diastolic function in these patients.[5] A number of factors may alter cardiovascular dynamics in renal failure including anaemia, hypertension, volume overload, ischaemic heart disease, electrolyte imbalance, hyperlipidaemia, acidaemia, and arteriovenous fistulas. In addition there is still debate about the existence of a specific uraemic cardiomyopathy independent of these factors.[6]

Cardiovascular complications are the most frequent cause of death in children with chronic renal failure.[7] Children provide an ideal group for study as they are free of potentially confounding factors such as atherosclerosis, diabetes, and smoking. There are only a few studies of cardio-

vascular function in paediatric patients with end stage renal failure,[8-12] and some of these concentrate on systolic time interval assessments of left ventricular function without including an echocardiographic assessment.[9] There have been no studies of diastolic ventricular function in a paediatric population with end stage renal failure.

Previous studies have assessed children predominantly on haemodialysis. Haemodialysis has marked effects on both cardiac dimensions and function, related to improvements in volume overload and possibly to removal of uraemic toxins; the timing of investigation in relation to dialysis therefore dramatically alters cardiovascular findings.[13 14] In addition, an arteriovenous fistula, the commonest form of access for haemodialysis, can itself increase cardiac output and alter left ventricular function.[15 16]

Cardiac output has previously been measured in children with end stage renal failure using the M mode 'cube method'; M mode echocardiography is used to measure left ventricular end diastolic diameter (LVEDD) and end systolic diameter (LVESD). Left ventricular diastolic volume (LVEDD^3) and systolic volume (LVESD^3) are then calculated and their difference taken as an approximation of left ventricular stroke volume. Developments in Doppler ultrasound now allow a more reliable noninvasive assessment of cardiac output from direct measurements of aortic stroke distance and aortic root cross sectional area (equation 1),[17] as well as investigation of diastolic ventricular function. We therefore studied a group of 13 anaemic children (haemoglobin concentration <90 g/l) with end stage renal failure on dialysis, 12 of whom were on overnight peritoneal dialysis. In addition to conventional cross sectional and M mode echocardiography, continuous and pulsed wave Doppler were used to determine aortic stroke distance and assess right and left ventricular diastolic function.

Patients and methods

We studied 13 children (11 boys, two girls), median age 6·7 years (range 2·3–14·5), median haemoglobin concentrations 73 g/l (range 42–85). The range of underlying conditions and other clinical details are summarised in table 1. None of the conditions has recognised cardiac associations. The median age at diagnosis of chronic renal failure was 0·1 years (range 0–13·4) and the median duration of dialysis 2·9 years (range 0·4–7·9). They therefore represent a group with early onset end stage renal failure; four started dialysis in infancy. All were on dialysis at the time of the study; peritoneal rapid

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Table 1 Clinical details of the 13 children studied

Patient No	Sex	Age (years)	Age at chronic renal failure (years)	Age at dialysis (years)	Duration of dialysis (years)	Mode of dialysis	Diagnosis	Treatment for hypertension
1	M	10·4	7·2	7·2	3·2	PROD	Familial HUS	Yes
2	M	2·3	Newborn	1·3	1	PROD	Infantile PCKD	Yes
3	F	4·5	Newborn	0·7	3·8	PROD	Dysplasia	No
4	M	3	0·8	1·3	1·7	PROD	Congenital nephrotic syndrome	Yes
5	M	6·4	Newborn	3·3	3·1	Haemodialysis	PUV	No
6	M	8·8	Newborn	0·9	7·9	PROD	PUV	No
7	F	8·9	8·5	8·5	0·4	PROD	Unknown	Yes
8	M	12·3	11·9	11·9	0·4	PROD	FSGS	Yes
9	M	2·8	Newborn	0·3	2·5	PROD	Dysplasia	No
10	M	6·7	Newborn	3·5	3·2	PROD	Dysplasia	No
11	M	8·3	Newborn	5·4	2·9	PROD	PUV	Yes
12	M	3·1	Newborn	0·1	3	PROD	Dysplasia	No
13	M	14·5	13·4	14·1	0·4	PROD	FSGS	Yes

PROD=Peritoneal rapid overnight dialysis; HUS=haemolytic uraemic syndrome; PCKD=polycystic kidney disease; PUV=posterior urethral valves; FSGS=focal segmental glomerulosclerosis.

overnight dialysis (PROD)[18] in 12 cases and haemodialysis in one. Two children had a functioning ateriovenous fistula.

Although seven children were receiving treatment for hypertension, six of these were normotensive,[19] assessed regularly at home using an automatic blood pressure machine (Waeschle DS40). Six children were receiving a combination of propranolol and hydralazine, one propranolol alone, and three were also taking captopril.

A detailed clinical examination was performed in 11 children. Systolic and diastolic blood pressure was measured by auscultation using the largest cuff that could be applied to the upper arm. The cardiothoracic ratio was measured on chest radiography; a standard posteroanterior view was taken in the oldest children (n=9) and an erect or supine anteroposterior view in the youngest children (n=4). A standard 12 lead electrocardiogram was performed in the semirecumbent position after five minutes rest (Marquette Instruments). The measured parameters (table 2) were compared with the published standards of Davignon et al[20]; a value lying above the 95th centile or below the 5th centile for appropriate age was classified as abnormal.

A single experienced observer (JRS) performed all the echocardiograms using the same Hewlett Packard Sonos 1000 machine. The subject was placed in a semirecumbent position and the echocardiogram performed after five minutes rest, within six hours of finishing PROD or within 24 hours of the last haemodialysis session. One child required sedation with oral trimeprazine and triclofos. Examinations were

recorded and M mode measurements were made according to standard techniques accepted by the American Society of Echocardiography.[21] A list of the measurements is shown in table 2. Aortic root diameter (AoDiam) was measured from a cross sectional long axis view, immediately below the insertion of the aortic valves. Aortic stroke distance (AoSD) was measured with continuous wave Doppler at the second right intercostal space, the suprasternal notch and the apex. The highest value was assumed to be most in line with the beam and was selected for analysis. A minimum of four consecutive beats were averaged. Mitral and tricuspid valve diastolic flow were recorded from the apex, with the pulsed Doppler sample at the tip of the valves. A minimum of four consecutive beats were analysed and peak 'E' and 'A' waves were averaged, and the ratio calculated (E:A ratio). From these measurements the following were derived:

Equation 1.
$$\text{Left ventricular stroke volume (SV)} = \text{AoSD} \times \pi \times (\text{AoDiam}/2)^2$$

Equation 2.
$$\text{Stroke index (SI)} = \text{SV/body surface area}$$

Equation 3.
$$\text{Cardiac output (CO)} = \text{SV} \times \text{heart rate}$$

Equation 4.
$$\text{Cardiac index (CI)} = \text{CO/body surface area}$$

Equation 5.
$$\text{Left ventricular mass index} = \frac{0 \cdot 77 \{ (\text{LVEDD} + \text{LVPW} + \text{IVS})^3 - (\text{LVEDD})^3 \} + 2 \cdot 4}{\text{Body surface area}}$$

Equation 6.
$$\text{Fractional shortening} = (\text{LVEDD} - \text{LVESD})/\text{LVEDD}$$

As virtually all echocardiographic measurements vary with age and body surface area it was necessary to correct for these before comparing children of differing age and size. Henry et al studied a large healthy paediatric population and generated prediction equations for most echocardiographic measurements based on age and body surface area,[22] allowing us to generate standard deviation or z scores for each measurement and to make comparisons between individuals.

Table 2 Parameters measured on electrocardiography and echocardiography

Electrocardiography	P wave (II), Q wave (III, V5), R wave (aVR, V2, V5) S wave (V2, V5), T wave (V2, V5), PR interval (II) QRS axis, QRS interval (V5), QTc interval (V5) R/S ratio (V1, V5), RV5+SV2
Echocardiography Cross sectional M mode	Aortic root diameter (AoDiam) Left atrial diameter Interventricular septum (IVS) Left ventricular posterior wall (LVPW) Left ventricular end diastolic diameter (LVEDD) Left ventricular end systolic diameter (LVESD)
Doppler CW PW	Aortic stroke distance (AoSD) Peak diastolic flow (E and A waves) Mitral and tricuspid flow

PW=pulsed wave, CW=continuous wave.

Results

On examination nine of the 11 children had an

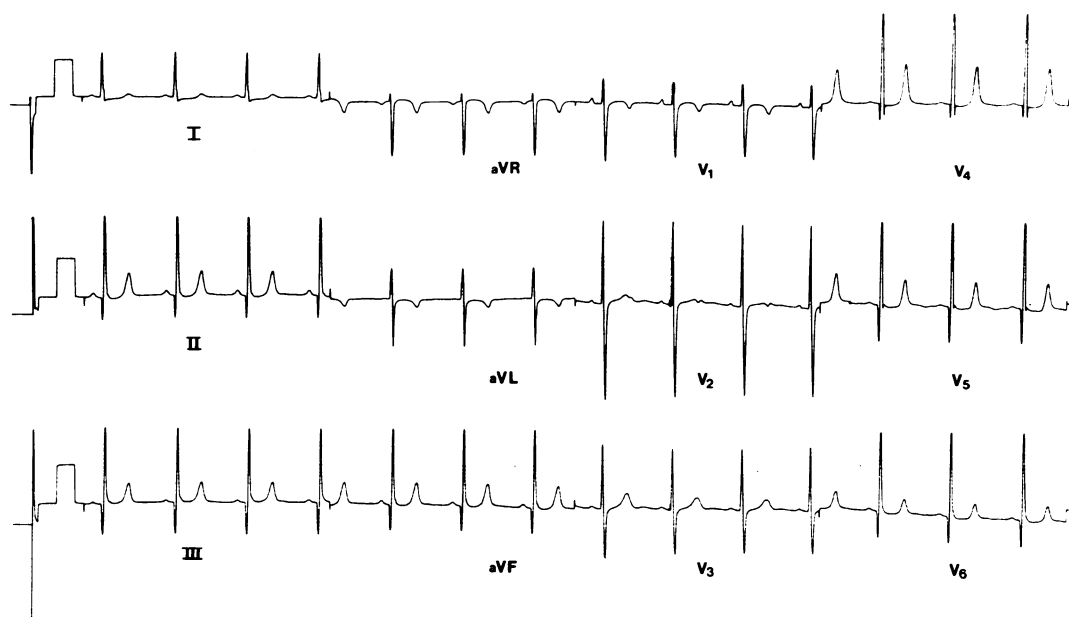Figure 1 *Electrocardiogram demonstrating the typical abnormalities in a 10 year old boy.*

Table 3 *Abnormalities of electroencephalography (n=13)*

	No of abnormalities
QRS prolongation	10
Small S wave V5	8
Deep Q wave III/V5	8
Increased R/S ratio V5	7
Flat T wave V5	4
QT prolongation	3
Small R wave V2	3
Tall R wave V2	2
Small R wave V5	2
Decreased RV5+SV2	2
Abnormal QRS axis	2

ejection systolic murmur best heard over the pulmonary area. Six children had a venous hum heard in the right infraclavicular or supraclavicular areas, there was a right ventricular heave in three, a left ventricular heave in four, and a displaced apex beat in three. There was no hepatomegaly or other clinical evidence of congestive heart failure and no additional heart sounds were heard. Twelve of 13 children were normotensive at the time of investigation.

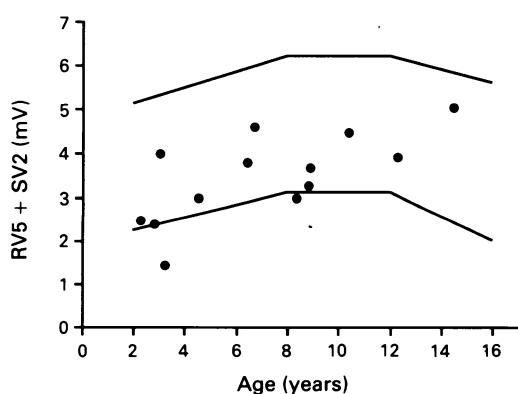The median cardiothoracic ratio was 53% (range 44–61). The cardiothoracic ratio was greater than 50% in nine and greater than 55% in four. There was no relationship between cardiothoracic ratio and echocardiographic left ventricular dimensions or severity of left ventricular hypertrophy.

The electrocardiogram was abnormal in every child with at least three of the measurements lying outside the normal range on the centiles of Davignon et al. The commonest abnormalities are shown in table 3 and a typical electrocardiogram in fig 1. Many of these abnormalities are compatible with left ventricular hypertrophy but the more widely used voltage criteria of left ventricular hypertrophy, such as the height of the R wave in V5 or V6, or the depth of the S wave in V1 or V2, or the sum of RV5+SV2, were not met in any of the children. In 11 the sum of RV5+ SV2 in fact lay below the 50th centile, with one child well below the 5th centile (fig 2).
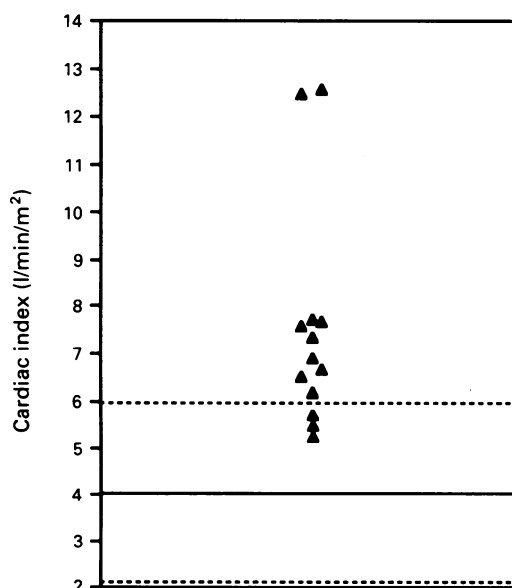

Figure 2 *The electrocardiographic sum of R wave in lead V5 and S wave in V2 against age. The 5th and 95th centiles for a normal population are also plotted.*[20]

Figure 3 *Cardiac index represented by z scores. Solid horizontal line represents normal mean value and dotted lines 95% confidence intervals.*
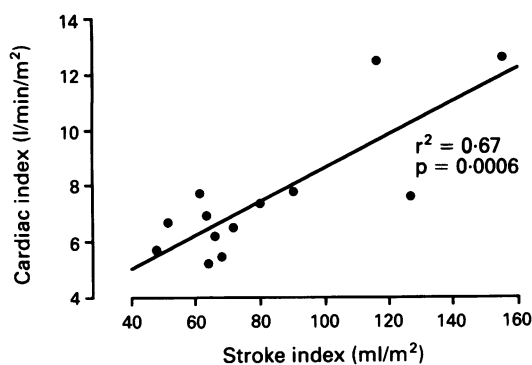
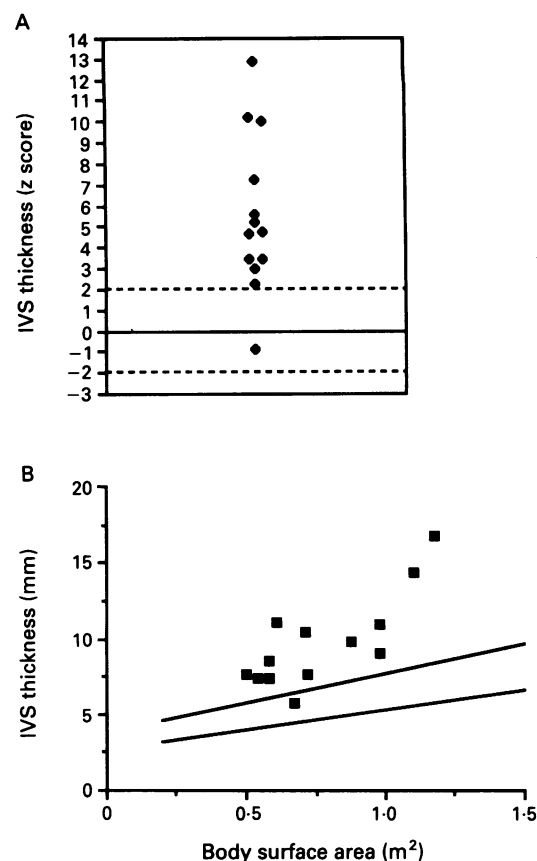*Figure 4   Relationship between cardiac index and stroke index.*

Figure 5   Interventricular septal (IVS) thickness represented as (A) z scores (with normal mean and 95% confidence intervals) and (B) plotted against body surface area (with 95% normal prediction limits).

The cardiac index was raised in 10 children, and in two was more than three times normal (fig 3). This resulted from an increase in stroke index (fig 4) rather than heart rate, which was not raised in any child (median z score −0·37; range −2·06 to +1·14). Twelve children had hypertrophy of the interventricular septum; in several the septal thickness was more than twice normal (fig 5). Septal hypertrophy was consistently more marked than hypertrophy of the left ventricular posterior wall (LVPW) which was, however, present in seven children. As a result, the ratio of interventricular septum to LVPW was abnormally high in six children (median 1·26, range 0·90–2·15; normal <1·33). The mean left ventricular mass index was well above the normal mean value (106·5 v 70·0 g/m²).[23] Those with the highest cardiac index had the highest left ventricular mass index (fig 6). We found no relationship within the group between haemoglobin and either cardiac index or severity of left ventricular hypertrophy, but they were all anaemic. For the group as a whole there was no consistent evidence of volume overload contributing to these abnormalities, though four of the 10 children with an increased cardiac index were found to have an increase in LVEDD and LVESD.

In the seven children on antihypertensive treatment there was a significantly higher cardiac index, as a result of a higher stroke index, and greater ventricular hypertrophy compared with the untreated group (table 4). However their mean systolic blood pressure z score was only +0·63, well within the normal range (−2·00 to +2·00) and not significantly different from the untreated children (−1·15). If the one child with poorly controlled blood pressure is excluded, in whom there was non-compliance with treatment, the blood pressure z scores for the two groups become even more comparable but the

differences in cardiac index and left ventricular hypertrophy persist.

We found no evidence of left ventricular systolic dysfunction; only one child had a shortening fraction below the normal lower limit of 28% (median 35; range 27–43). No child had more than trivial mitral regurgitation, tricuspid regurgitation, or pulmonary regurgitation. Tricuspid regurgitation was pansystolic in one child, the peak velocity predicting normal systolic right ventricular and pulmonary arterial pressures (20 mm Hg). None of the children had a pericardial effusion.

Abnormalities of right and left ventricular diastolic function were found in six of the 11 children with complete data. Normally there are two phases of ventricular filling. The early (E)
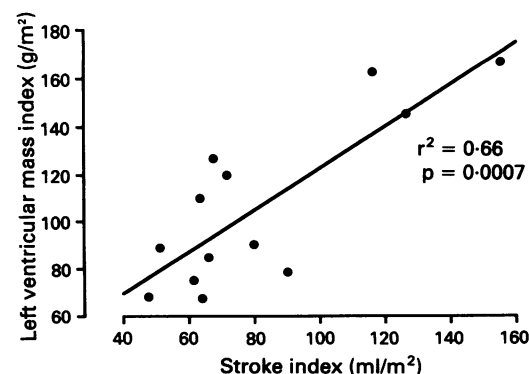
Table 4   Differences found in the groups having or not having antihypertensive treatment. Values expressed as mean (SD)

	Antihypertensive treatment	No antihypertensive treatment	p Value
Systolic blood pressure (z score)	0·63 (2·35)	−1·15 (0·74)	0·100
Cardiac index (l/min/m²)	8·74 (2·60)	6·17 (0·90)	0·043
Stroke index (ml/m²)	100·5 (33·3)	59·7 (8·24)	0·014
Interventricular septal thickness (z score)	7·31 (3·68)	3·49 (2·78)	0·062
Left ventricular mass index (g/m²)	124·8 (34·4)	85·2 (21·9)	0·034

Statistical analysis using unpaired *t* test (two tail).

Figure 6   Relationship between left ventricular mass index and stroke index.
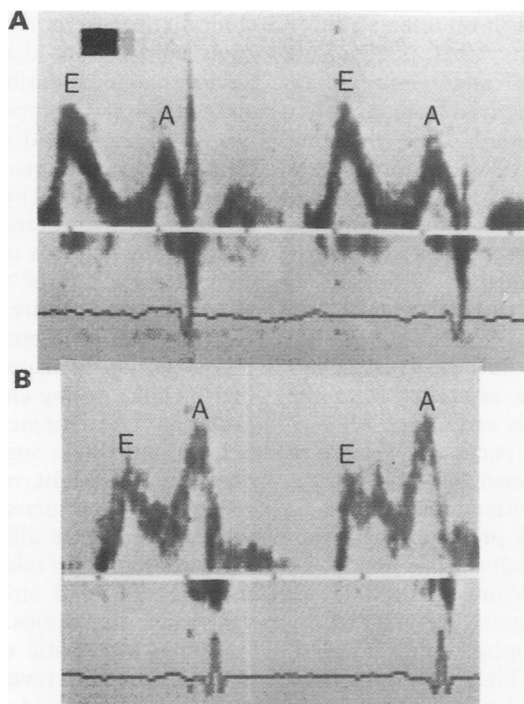
Figure 7 An example of (A) normal and (B) abnormal right ventricular diastolic function. E =early, A=atrial contraction.

rapid filling phase has a higher velocity than the later phase coinciding with atrial contraction (A), such that the normal E:A ratio is greater than 1·0 (fig 7). Three children had a reversal of the normal tricuspid valve E:A ratio only (ratio <1·0), one child a reversed mitral valve E:A ratio only, and two had a reversal of both tricuspid and mitral E:A ratios. An example of normal and abnormal tricuspid valve diastolic flow is shown in fig 7.

Discussion

Cardiac complications account for nearly 50% of deaths in children with chronic renal failure.[7] Despite this we have only a poor understanding of the cardiac pathophysiology that is responsible. Peritoneal dialysis affects the haemodynamic state less than haemodialysis, adult evidence suggests that left venticular hypertrophy may even regress on changing to peritoneal dialysis.[24] Echocardiographic findings in patients on haemodialysis are highly dependent on the timing of study in relation to the last period of haemodialysis whereas a peritoneal dialysis exchange produces no significant echocardiographic change.[25] Although peritoneal dialysis is now the preferred form of dialysis for small children with end stage renal failure there are no reported cardiac studies in this group.

The majority of children had an easily audible flow murmur or venous hum in keeping with the findings of Ulmer *et al* who used phonocardiography to study such murmurs.[9] Systolic flow murmurs were attributed to functional aortic stenosis and the diastolic murmurs to increased flow across the mitral valve and aortic incompetence. Others have found pulmonary incompetence in addition to aortic incompetence at times of fluid overload with severe hyper-

tension.[26] Although evidence of valvular regurgitation was found in several cases using colour Doppler, this technique is very sensitive and detects regurgitation in a high proportion of normal individuals. The regurgitation was haemodynamically trivial in all cases.

None of our children had congestive heart failure and all had normal left ventricular systolic function (shortening fraction). Most studies in adults on regular dialysis and the few in children describe normal echocardiographic left ventricular systolic function, as judged by shortening fraction, ejection fraction, or velocity of circumferential fibre shortening.[4 10] Other reports have used systolic time intervals to assess left ventricular systolic function. O'Regan *et al* found that most children with chronic renal failure of mixed severity had normal function,[11] though a small subgroup (17%) had abnormal systolic time intervals and a reduced shortening fraction together with clinical evidence of congestive heart failure. Ulmer *et al* followed up 11 children prospectively through chronic renal failure managed conservatively to haemodialysis and subsequently transplantation.[9] Systolic time intervals were significantly prolonged even during the predialysis period, deteriorated further during the time on dialysis, but slowly normalised after transplantation. Altogether 39% of their more complete chronic renal failure cohort and 24% of their haemodialysis population had evidence of congestive heart failure.[27]

In this group the cardiac index was increased due to a high stroke index rather than an increase in heart rate. The two children with arteriovenous fistulas were not significantly different to the others. Studies that have included non-anaemic children with chronic renal failure have found an inverse relationship between cardiac index and haemoglobin,[8] and correction of anaemia with erythropoietin has been shown to reduce the cardiac index in adults.[28] The lack of a relationship between the cardiac index and severity of anaemia in this study is probably due to the fact that all the children studied were anaemic.

One of the most striking findings was the increase in left ventricular wall thickness, particularly affecting the interventricular septum. A ratio of interventricular septum to LVPW thickness above 1·33 is indicative of asymmetric septal hypertrophy, as found in hypertrophic cardiomyopathy associated with left ventricular outflow obstruction. It has also been reported in a variety of congenital heart defects, as a normal developmental finding in the human fetus and in infants of diabetic mothers.[29] It has been reported in both adults[30] and children[12] with uraemia, particularly those with hypertension but, with one exception,[12] is not accompanied by outflow obstruction. We found no significant difference in the severity of asymmetric septal hypertrophy in those children requiring antihypertensive treatment.

The severity of left venticular hypertrophy in uraemia has been linked to hypertension,[31] anaemia,[28] circulating catecholamines,[2] and to myocardial calcium content and parathyroid hormone concentration.[32] The use of left ventricular mass as a measure of left ventricular

hypertrophy is attractive as it represents a three dimensional measurement rather than a two dimensional thickness. It cannot however be measured directly and is derived from other left ventricular measurements.[33] The existing formulas for deriving left ventricular mass were validated in populations with concentric rather than asymmetric ventricular hypertrophy, so care is needed when interpreting left ventricular mass values in such individuals.

We found cardiac index and more particularly stroke index to be strongly correlated with left ventricular mass index; thus the greatest left ventricular workloads are associated with the greatest hypertrophy. This severity of left ventricular hypertrophy is of particular concern in view of the increasing evidence that left ventricular hypertrophy, with or without renal disease, is the single most powerful predictor of cardiovascular mortality in adults.[34] We found no relationship between calcium, phosphate, or parathyroid hormone concentration and severity of left ventricular hypertrophy.

While it may be that the higher left ventricular mass index and stroke index in patients being treated for hypertension are explained by unidentified differences in blood pressure, for example during exercise or stress, an alternative explanation is that the high cardiac output at rest and more particularly any subsequent increase that occurs during exercise can, in the presence of β blockade, be maintained only at the expense of a further increase in stroke index, leading to further compensatory left ventricular hypertrophy. A drug with a primary vasodilatory action might therefore have theoretical advantages over a β blocker provided it does not also greatly increase cardiac output.

The incidence of pericardial effusion in previous paediatric reports has varied widely from 12 to 40%.[10 35] None of our series had an effusion on M mode or cross sectional echocardiography, although one child had previously required pericardiocentesis for a large effusion shortly after developing end stage renal failure secondary to familial haemolytic uraemic syndrome. Whether the apparent absence of pericarditis reflects the greater efficiency of PROD in clearing urea or other possible toxins is uncertain.

It has been suggested that ventricular diastolic function is abnormal in adult patients with end stage renal failure,[5] based on peak inflow velocity measurements in the rapid early (E) filling phase of diastole and the later atrially mediated phase (A). Typically the peak E wave velocity is decreased and the A wave velocity increased, so that the E:A ratio is also decreased. This has been largely attributed to reduced compliance of the ventricle as a result of hypertrophy, but this is almost certainly too simplistic since these indices are not reliable measures of ventricular compliance. Because we did not study diastolic function in a control group we can only comment on those with the grossest abnormalities, that is where there was a reversal of the normal E:A ratio from greater than 1·0 to less than 1·0. We found 6/11 children to have a reversed ratio, with diastolic dysfunction of the right ventricle predominating. There was no relationship between the ratio and left ventricular mass index. The

clinical relevance of these findings is uncertain; adult studies link diastolic dysfunction to a tendency to hypotension during haemodialysis[36] and to clinical decompensation, with congestive heart failure, around the time of transplantation.[37] In addition ventricular filling might be seriously jeopardised by an atrial arrhythmia.

The incidence of cardiomegaly found on chest radiography depends on the definition used. A cardiothoracic ratio of >50% is found in as many as two thirds of children on regular haemodialysis,[27] and in nine of our 13 children, but clearly this definition is inappropriate in a population that includes young children in whom anterioposterior and supine views are necessary. Scharer and Ulmer suggested that radiographic cardiomegaly might represent a physiological adaptation to an increased stroke index rather than a pathological dilatation,[27] but the present study did not find a relationship between cardiothoracic ratio and stroke index or other left ventricular dimensions.

Careful systematic evaluation of a standard electrocardiogram revealed at least three abnormalities in every child, contradicting claims that electrocardiographic changes are only rarely observed in paediatric patients with end stage renal failure.[8] The commonest abnormalities of a prolonged QRS complex and deep Q waves in inferior and anterolateral leads are compatible with left venticular hypertrophy but the much more frequently used voltage criteria such as the height of an R wave in V5 or V6, or the depth of an S wave in V1 or V2 were not met in any child, with values predominantly in the low normal range. The same was true for the sum of RV5+ SV2, a measure often calculated by general paediatricians but not generally regarded as valuable by paediatric cardiologists. It is worth stressing that 50% of normal children aged 8 to 12 years will have a sum in excess of 4·7 mV[20] so that defining left ventricular hypertrophy as a sum greater than 4 or even 5 mV, values often used, will include a substantial number of normal children. Electrocardiography should no longer be used as the only tool to identify left ventricular hypertrophy in any population as it consistently underestimates the prevalence of left ventricular hypertrophy confirmed echocardiographically in both adults[34] and children.[38]

Children with end stage renal failure on peritoneal dialysis have an increased cardiac index, an increased stroke index, and often gross ventricular hypertrophy, particularly of the interventricular septum. These findings are most marked in children on antihypertensive treatment despite apparent optimal blood pressure control. Systolic function is usually normal but diastolic function may be abnormal with a reversal of the normal E:A peak velocity ratio. A chest radiograph and electrocardiogram have very limited usefulness, often failing to detect even gross ventricular hypertrophy; a detailed echocardiogram must be performed with the necessary corrections made for age and body surface area. The role of anaemia in the pathogenesis of these abnormalities will become clearer after studying the cardiac effects of erythropoietin in such a paediatric population.

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