Short term correction of anaemia with recombinant human erythropoietin and reduction of cardiac output in end stage renal failure

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Abstract
Children with end stage renal failure and anaemia have an increased cardiac index and often gross ventricular hypertrophy. The contribution of anaemia to these abnormalities is uncertain. Eleven children with end stage renal failure and anaemia (haemoglobin concentration <90 g/l) were enrolled into a single blind, placebo controlled, crossover study to assess the cardiovascular effects of reversing anaemia using subcutaneous human recombinant erythropoietin (r-HuEpo). Each limb lasted 24 weeks; seven children completed both limbs of the study.

Haemoglobin increased with r-HuEpo, remaining above 100 g/l for a mean of 11 weeks. Cardiac index fell as a result of a reduction in both left ventricular stroke volume and heart rate. Left ventricular end diastolic diameter also decreased. In five children left ventricular wall thickness and left ventricular mass decreased with r-HuEpo, but this failed to reach significance for the whole group.

Blood pressure did not change in six normotensive children completing an r-HuEpo limb; the decrease in cardiac index was therefore balanced by an increase in peripheral vascular resistance. Three children were taking antihypertensive treatment at the start of the study; one required an increase, and one a decrease, in treatment during the r-HuEpo limb.

Short term treatment with r-HuEpo reduces cardiac index. A longer study is needed to determine whether this will, in time, result in a significant reduction in left ventricular hypertrophy.
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Cardiovascular complications are the commonest cause of death in children with end stage renal failure.[1] Children with end stage renal failure and anaemia frequently have an increased cardiac index and marked left ventricular hypertrophy, particularly affecting the interventricular septum.[2] The relative contributions of anaemia and hypertension to these findings are uncertain; children on antihypertensive treatment have the most marked abnormalities, despite apparent optimal blood pressure control.[2]

Studies in adults with end stage renal failure have documented similar cardiac abnormalities and have assessed the cardiovascular effects of reversing anaemia by means of red cell transfusion or recombinant human erythropoietin (r-HuEpo) administration. Neff *et al* documented a normalisation of cardiac index after serial transfusion,[3] while Teruel and colleagues found a similar fall in cardiac index after four months' treatment with r-HuEpo,[4] with a reduction in left ventricular hypertrophy detectable by 12 months.[5]

There are no reports in children with end stage renal failure of cardiovascular changes occurring with r-HuEpo treatment. We have therefore assessed the cardiovascular effects of 24 weeks' r-HuEpo treatment in a group of children with end stage renal failure and anaemia, using a single blind, placebo controlled crossover study design.

Patients and methods
Eleven children (nine boys, two girls) were enrolled into the study. Their median age was 6·7 years (range 2·3–12·3), and median haemoglobin concentration 73 g/l (range 42–81).

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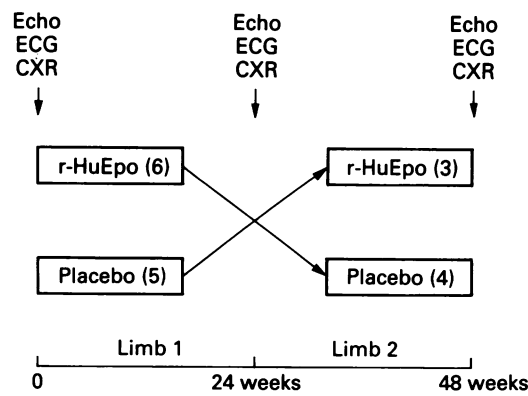
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Table 1   Clinical details of the 11 children entering the study

Patient No	Sex	Age (years)	Haemoglobin (g/l)	Duration of dialysis (years)	Mode of dialysis	Diagnosis	Treatment for hypertension
Group 1 (r-HuEpo/placebo)							
1	M	10·4	42	3·2	PROD	Familial HUS	Yes
2	M	2·8	72	2·5	PROD	Dysplasia	No
3	F	4·5	81	3·8	PROD	Dysplasia	No
4	M	3	80	1·7	PROD	Congenital nephrotic syndrome	Yes
5	M	6·4	73	3·1	Haemodialysis	PUV	No
6	F	8·9	66	0·4	PROD	Unknown	Yes
Group 2 (Placebo/r-HuEpo)							
7	M	12·3	76	0·4	PROD	FSGS	Yes
8	M	8·8	68	0	None	Reflux associated dysplasia*	No
9	M	6·7	76	3·2	PROD	Dysplasia	No
10	M	2·3	64	1	PROD	Infantile PCKD	Yes
11	M	8·8	75	7·9	PROD	PUV	No

PROD=peritoneal rapid overnight dialysis; HUS=haemolytic uraemic syndrome; PCKD=polycystic kidney disease; PUV=posterior urethral valves; FSGS=focal segmental glomerulosclerosis; *patient with Duchenne muscular dystrophy.

Figure 1   Basic study design (number of children). Echo= echocardiography; ECG=electrocardiography; CXR=chest radiography.

The range of underlying conditions and other clinical details are summarised in table 1. Only Duchenne muscular dystrophy has recognised cardiac associations. A boy with Duchenne muscular dystrophy was included in the study because his baseline cardiac findings were compatible with the remainder of the group and it was felt that any short term changes in cardiac function were more likely to relate to r-HuEpo treatment than to changes in his underlying disease process. Ten of the children were on dialysis at the time of the study; peritoneal rapid overnight dialysis (PROD)[6] in nine cases and haemodialysis in one. Five children were receiving treatment for hypertension but all were normotensive, assessed with regular home blood pressure monitoring (Waeschle DS40).

The design was a single blind, placebo controlled, crossover study with two equal limbs of 24 weeks' duration (fig 1). Six children were allocated by stratified randomisation to receive r-HuEpo for 24 weeks followed by placebo, and five the reverse treatment order. Both the echocardiographer and the family were unaware of the treatment order in each child. Cardiac investigations were performed at baseline and then after 24 and 48 weeks. r-HuEpo (Recormon, Boehringer Mannheim) or placebo were administered subcutaneously twice weekly by the child or parent at home. The volume of all injections was fixed at 0·5 ml. r-HuEpo was commenced at 50 U/kg/week and increased in stepwise increments to a maximum of 400 U/kg/week by week 12, thereafter adjusted to maintain a target haemoglobin concentration of 105–120 g/l.

Each child was assessed by clinical examination, chest radiography, electrocardiography, and echocardiography. 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 each chest radiograph. A standard 12 lead electrocardiogram was performed in the semirecumbent position after five minutes rest (Marquette Instruments). A single experienced observer (JRS) performed all the echocardiograms using the same Hewlett Packard Sonos 1000 machine. Details of the echocardiographic methodology have been described in detail previously.[2] A list of the electrocardiographic and echocardiographic measurements is shown in table 2. From these the following were derived.

Equation 1.

Left ventricular stroke volume (SV)=
AoSD×π×(AoDiam/2)^2

Equation 2.

Stoke index (SI)=SV/body surface area

Equation 3.

Cardiac output (CO)=SV×heart rate

Equation 4.

Cardiac index=CO/body surface area

Equation 5.

Minute distance=AoSD×heart rate

Equation 6.

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

Equation 7.

Fractional shortening=(LVEDD−LVESD)/LVEDD

Equation 8.

Total peripheral vascular resistance=
mean blood pressure/cardiac output

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	Aortic root diameter (AoDiam)
M Mode	Left atrial diameter
	Interventricular septum (IVS)
	Left ventricular posterior wall (LVPW)
	Left ventricular end diastolic diameter (LVEDD)
	Left ventricular end systolic diameter (LVES)
Doppler	
CW	Aortic stroke distance (AoSD)
PW	Peak diastolic flow (E and A waves)
	Mitral and tricuspid flow

PW=pulsed wave; CW=continuous wave.

Table 3   Echocardiographic, radiographic, and blood pressure changes at different stages in children completing both limbs of the study. Values are mean (SD)

	Group 1: r-HuEpo/placebo (n=4)		Group 2: placebo/r-HuEpo (n=3)		Overall mean effect (% change) of r-HuEpo minus effect of placebo	
	After 24 weeks r-HuEpo	After 24 weeks placebo	After 24 weeks placebo	After 24 weeks r-HuEpo		p Value
Cardiac index (l/min/m^2)	6·71 (1·94)	9·92 (0·77)	6·65 (0·41)	5·58 (1·56)	−2·29 (−27)	0·01
Heart rate (beats/min)	94 (14·4)	118·3 (19·7)	106 (6·6)	82·3 (12·2)	−24·0 (−21)	0·002
Stroke index (ml/m^2)	66·7 (23·7)	84 (19·4)	67·1 (7·5)	55 (8·7)	−15·1 (−20)	0·03
LVEDD (cm)	3·72 (0·85)	3·88 (0·64)	3·52 (0·07)	3·02 (0·12)	−0·31 (−8)	0·04
LVESD (cm)	2·52 (0·52)	2·46 (0·64)	2·16 (0·06)	1·98 (0·17)	−0·04 (−2)	0·52
Interventricular septum (cm)	0·84 (0·19)	0·90 (0·22)	0·73 (0·10)	0·72 (0·26)	−0·04 (−5)	0·26
LVPW (cm)	0·66 (0·20)	0·75 (0·15)	0·74 (0·10)	0·72 (0·26)	−0·06 (−8)	0·57
Left ventricular mass index (g/m^2)	101·2 (41·9)	120 (48·6)	87·6 (16·5)	62·9 (11·8)	−21·3 (−20)	0·16
Mean blood pressure (mm Hg)	73·5 (13·6)	65·3 (8·4)	67·3 (11·2)	59·3 (11·8)	+1·3 (+2)	0·96
Peripheral vascular resistance (mm Hg/min/l)	16·8 (7·8)	9·2 (2·9)	13·9 (3·8)	15·8 (8·6)	+5·2 (+46)	0·07
Shortening fraction (%)	32 (2·8)	37·3 (6·7)	38·3 (2·5)	34·3 (5·9)	−4·7 (−12)	0·11
Cardiothoracic ratio (%)	53·5 (3·7)	55 (1·8)	47 (3·6)	42·7 (5·5)	−2·7 (−5)	0·21
Aortic stroke distance	22·5 (6·7)	26·3 (3·5)	25·7 (0·5)	20·4 (3·4)	−4·4 (−17)	0·01
Minute distance	2240 (440)	3154 (357)	2580 (447)	2074 (634)	−739 (−25)	0·03

LVEDD=left ventricular end diastolic diameter; LVESD=left ventricular end systolic diameter; LVPW=left ventricular posterior wall.
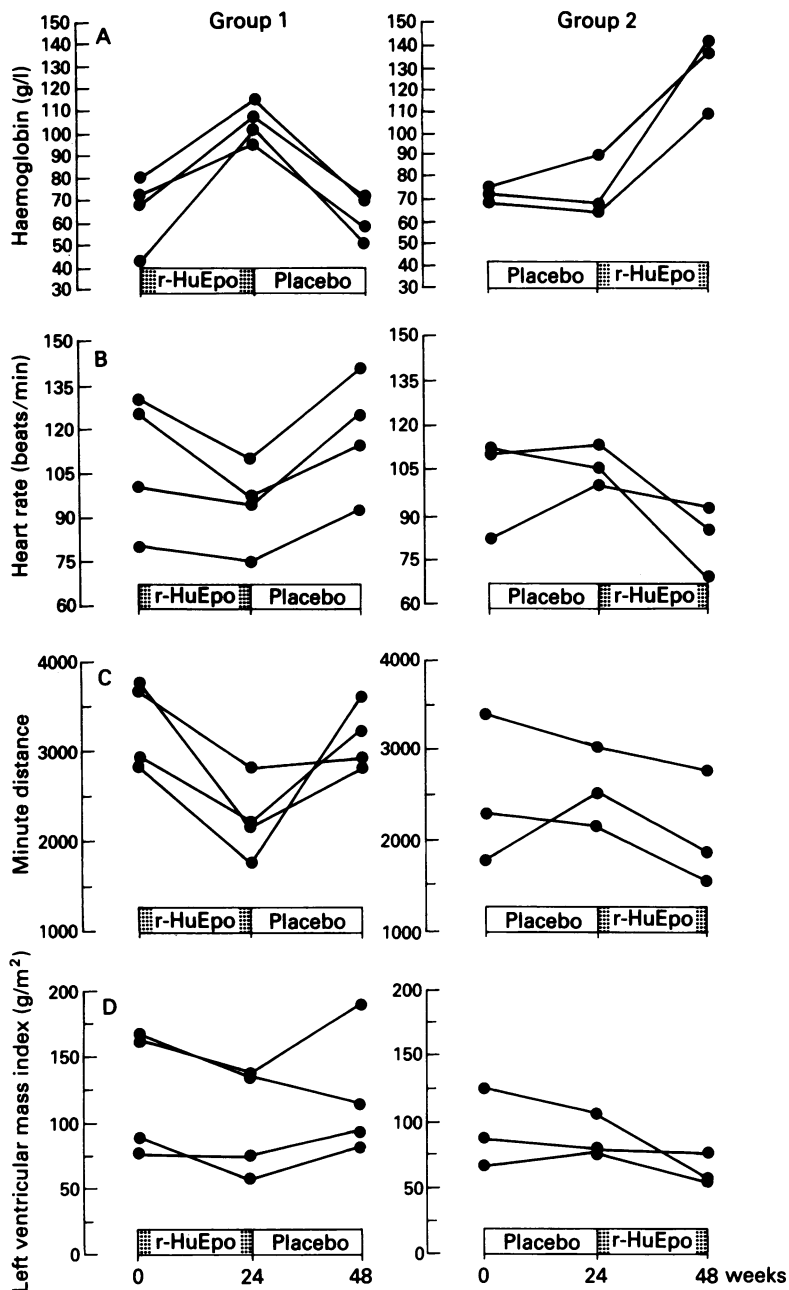
Figure 2 Individual changes in (A) haemoglobin, (B) heart rate, (C) minute distance, and (D) left ventricular mass index in seven children completing both limbs of the study.

study and one child died; this was related to his primary disease (patient 10). Treatment effects were calculated using statistical methods appropriate for the analysis of crossover trials, after excluding a significant period effect.[8] To test for the presence of a treatment effect, the difference in any measured variable between week 24 (end of period 1) and week 48 (end of period 2) is calculated, and the mean difference found in group 1 compared with that found in group 2, using a standard two sample t test. In the absence of a treatment effect the differences are the same, and the t test non-significant.

Results

The relevant results are summarised in table 3. r-HuEpo produced a significant rise in mean haemoglobin from 69 g/l to 115 g/l after 24 weeks' treatment (p=0·0001) (fig 2A). In association with this there was a significant fall in cardiac index, as a result of a fall in both left ventricular stroke index and heart rate (fig 2B). These findings were further supported by a fall in aortic stroke distance and minute distance (fig 2C).

Left ventricular end diastolic diameter and shortening fraction fell after r-HuEpo. Although in some patients there was a reduction in thickness of the interventricular septum and left ventricular posterior wall, this did not reach significance after 24 weeks' treatment. The same was true for estimated left ventricular mass index (fig 2D). No significant change was found in mitral or tricuspid valve diastolic flow after r-HuEpo. Significant changes in the electrocardiogram after 24 weeks' treatment with r-HuEpo were an increase in the height of the T wave in V5 (p=0·002), and a prolongation of the QT interval (p=0·05), appropriate in relation to the reduction in heart rate. The mean cardiothoracic ratio fell from 51·6% to 48·9% (nonsignificant). Subjectively there was a reduction in murmur intensity in five of the six children with audible ejection murmurs before r-HuEpo.

Three children on antihypertensive treatment completed an r-HuEpo limb. One required an increase in treatment, one a reduction, and one no change. None of the remaining children needed to start antihypertensive treatment. Overall there was no significant change in systolic, diastolic or mean blood pressure related to r-HuEpo. Peripheral vascular resistance was not measured directly but was derived from mean blood pressure and cardiac output measurements (equation 8). Mean blood pressure did not change; the fall in cardiac output was therefore balanced by an appropriate rise in peripheral vascular resistance.

Left ventricular stroke volume is the product of the aortic flow integral on Doppler echocardiography (aortic stroke distance; AoSD), and the aortic cross sectional area, derived from aortic diameter measurement (AoDiam) on cross sectional echocardiography. In serial measurements over a limited period of time aortic diameter should change little, but considerable measurement error can occur.[7] To avoid this potential source of error it is possible to follow changes in aortic stroke distance and minute distance, variables which correspond to stroke volume and cardiac output respectively, but avoid the variability of aortic diameter measurement.

Nine of the 11 children completed a 24 week period of r-HuEpo but only seven children completed both limbs of the study and were included in the analysis; three of the remaining four underwent renal transplantation during the

Discussion

Several studies have assessed the cardiac effects of r-HuEpo in adult patients with end stage renal failure and anaemia.[4 5 9-13] The majority have demonstrated a fall in cardiac index even after short treatment periods, as a result of a reduction in stroke index,[5 11] heart rate,[9] or both.[10] Others, however, have found no change,[12] or even an increase in cardiac index.[13] Most short term
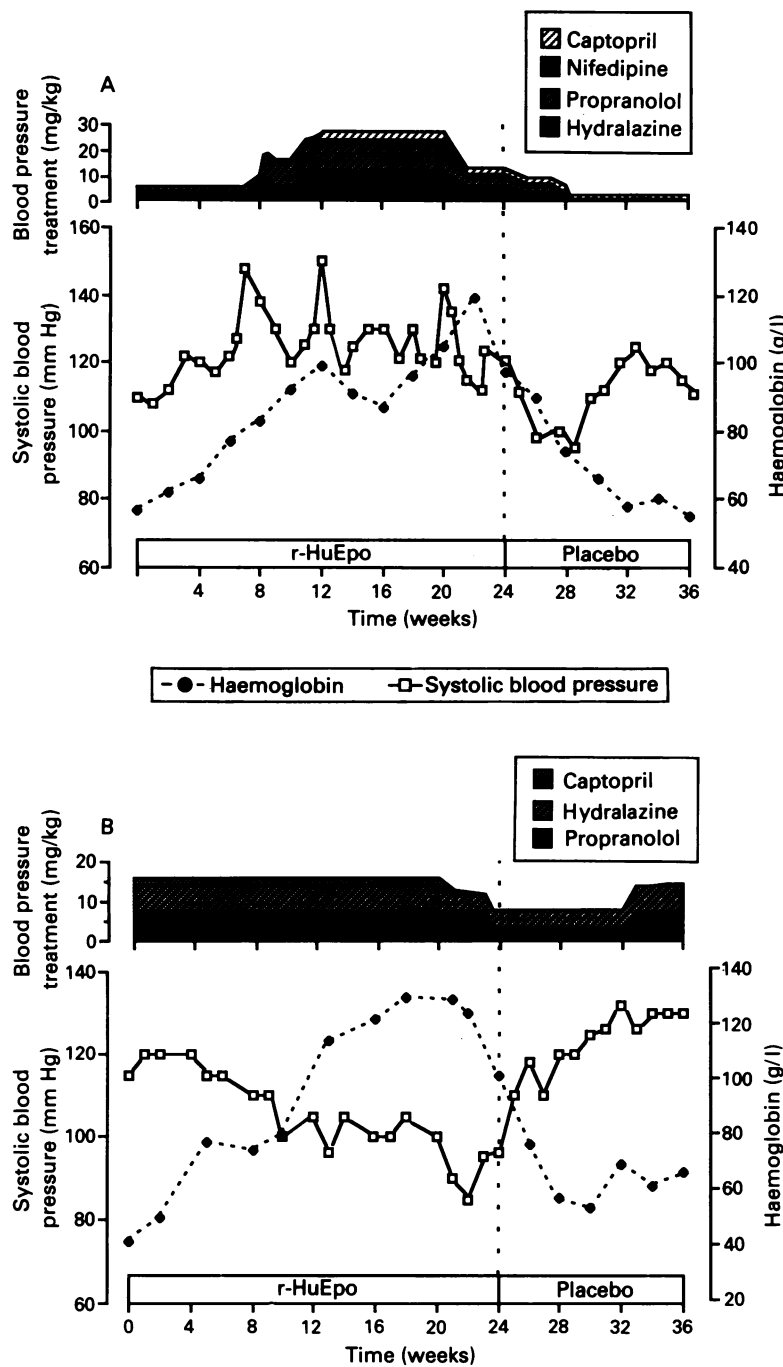
Figure 3   Changes in systolic blood pressure and haemoglobin in (A) a child requiring an increase in antihypertensive treatment during treatment with r-HuEpo and (B) a child requiring a reduction in antihypertensive treatment during treatment with r-HuEpo.

studies (<6 months) have not shown a reduction in left ventricular wall thickness or left ventricular mass,[4 11] while longer term studies have.[5 9]

The results of this study are therefore in agreement with adult studies of similar duration, showing a fall in cardiac index but only a trend towards a reduction in left ventricular hypertrophy, probably because the haemoglobin concentration was maintained above 100 g/l for a mean of only 11 weeks. A significant reduction in left ventricular hypertrophy may follow a longer period of treatment.

Cardiac index fell as a result of a fall in left ventricular stroke volume and heart rate. We have previously attributed the high cardiac index found in these children to an increase in left ventricular stroke volume rather than heart rate,

because heart rate was found to lie within a normal age matched range.[2] The present study suggests that both make a contribution. The increase in cardiac index in anaemia is a consequence of poor tissue oxygenation, leading to compensatory peripheral vasodilation. Cropp showed that administration of oxygen to non-uraemic anaemic children partially reverses peripheral vasodilatation and leads to a reduction in cardiac index.[14] Similarly, in patients with end stage renal failure, correction of anaemia by transfusion or r-HuEpo increases peripheral vascular resistance and decreases cardiac index, while improving tissue oxygenation.[15] Changes in cardiac index are not due to a change in total blood volume, which is unaltered by r-HuEpo treatment; an increase in red cell mass being balanced by a decrease in plasma volume.[9]

The fall in left ventricular end diastolic diameter after r-HuEpo is probably the consequence of a fall in left ventricular stroke volume, a common finding with adult studies.[5 10 11] Likewise the reduction in shortening fraction is more likely to reflect changes in stroke volume and left ventricular end diastolic diameter, rather than a real deterioration in myocardial contractility.

Hypertension can theoretically be due to an increase in cardiac output[17] or an increase in peripheral vascular resistance.[16] Ledingham et al have suggested that an increase in cardiac output underlies all hypertension, eventually stimulating a sustained increase in peripheral arteriolar resistance, with a return of cardiac output to normal.[17]

Patients with end stage renal failure with anaemia and hypertension have a high cardiac output, which could, in theory, contribute to hypertension. In the majority of patients, however, correction of anaemia leads to a fall in cardiac output without a corresponding fall in blood pressure, suggesting that an increase in peripheral vascular resistance is the predominant factor in most cases. The development, or exacerbation, of hypertension has been the commonest and most worrying side effect of r-HuEpo administration, on occasions leading to encephalopathy.[18] Risk factors appear to be pre-existing hypertension at the start of treatment, and the rate of rise of haemoglobin rather than the absolute level reached. We elected to increase haemoglobin slowly, but one child required a marked increase in antihypertensive treatment on r-HuEpo, despite a fall in cardiac index (6·9 to 4·5 l/min/m²). After switching to placebo her blood pressure fell and treatment was reduced again (fig 3A). A minority of patients are reported to show a fall in blood pressure on r-HuEpo; one child, with a particularly high cardiac index (12·6 l/min/m²), required a marked reduction in antihypertensive treatment during the r-HuEpo limb, followed by an increase during the placebo limb once his haemoglobin had fallen, and his cardiac index increased again (fig 3B). This suggests that an increased cardiac output contributes to hypertension in some patients. None of six previously normotensive children needed to start antihypertensive treatment while on r-HuEpo, and no significant change in blood pressure occurred. Although there is currently no way of predicting an

individual's blood pressure response to r-HuEpo at the time of starting treatment, the height of the cardiac output may prove to be of value. Children with hypertension associated with a very high cardiac output may be more likely to show a fall in blood pressure with r-HuEpo, while those with hypertension and a lower cardiac output, in whom peripheral vascular resistance is higher, may be more likely to develop an increase in blood pressure on r-HuEpo. Careful monitoring of blood pressure is essential, particularly during the induction phase in patients with pre-existing hypertension.

In this study r-HuEpo treatment for 24 weeks led to a fall in cardiac index in a group of children with end stage renal failure and anaemia. This was as a result of a reduction in both heart rate and stroke volume. Further study is needed to determine whether a sustained reduction in cardiac workload will, in time, result in a significant reduction in left ventricular hypertrophy.

1 Broyer M, Brunner FP, Brynger H, Fassbinder W, Guillou PJ, Oules R. Demography of dialysis and transplantation in Europe 1984. Report of the registry. *Nephrol Dial Transplant* 1986; 1: 9-15.

2 Morris KP, Skinner JR, Wren C, Hunter S, Coulthard MG. Cardiac abnormalities in end stage renal failure and anaemia. *Arch Dis Child* 1993; 68: 637-43.

3 Neff MS, Kim KE, Persoff M, Onesti G, Swartz C. Hemodynamics of uremic anemia. *Circulation* 1971; 43: 876-83.

4 Teruel JL, Pascual J, Jimenez M, et al. Hemodynamic changes in hemodialysis patients during treatment with recombinant human erythropoietin. *Nephron* 1991; 58: 135-7.

5 Pascual J, Teruel JL, Moya JL, Liano F, Jimenez-Mena M, Ortuno J. Regression of left ventricular hypertrophy after partial correction of anaemia with erythropoietin in patients on haemodialysis; a prospective study. *Clin Nephrol* 1991; 35: 280-7.

6 Coulthard MG, Sharp J. PROD: peritoneal rapid overnight dialysis in children. *Pediatr Nephrol* 1989; 3: C218.

7 Robson SC, Murray A, Peart I, Heads A, Hunter S. Reproducibility of cardiac output measurement by cross sectional and Doppler echocardiography. *Br Heart J* 1988; 59: 680-4.

8 Armitage P, Berry G. The simple crossover design. *Statistical methods in medical research*. 2nd Ed. London: Blackwell Scientific Publications, 1987: 222-6.

9 Cannella G, La Canna G, Sandrini M, et al. Renormalization of high cardiac output and of left ventricular size following long-term recombinant human erythropoietin treatment of anemic dialysed uremic patients. *Clin Nephrol* 1990; 6: 272-8.

10 London GM, Zins B, Pannier B, et al. Vascular changes in hemodialysis patients in response to recombinant human erythropoietin. *Kidney Int* 1989; 36: 878-82.

11 Tagawa H, Nagano M, Saito H, Umezu M, Yamakado M. Echocardiographic findings in hemodialysis patients treated with recombinant human erythropoietin: proposal for a hematocrit most beneficial to hemodynamics. *Clin Nephrol* 1991; 35: 35-8.

12 Low I, Grutzmacher P, Bergmann M, Schoeppe W. Echocardiographic findings in patients on maintenance hemodialysis substituted with recombinant human erythropoietin. *Clin Nephrol* 1989; 31: 26-30.

13 Verbeelen D, Bossuyt A, Smitz J, Herman A, Dratwa M, Jonckheer MH. Hemodynamics of patients with renal failure treated with recombinant human erythropoietin. *Clin Nephrol* 1989; 31: 6-11.

14 Cropp GJA. Hemodynamic responses to oxygen breathing in children with severe anemia. *Circulation* 1969; 40: 493-500.

15 Nonnast-Daniel B, Deschodt G, Brunkhorst R, et al. Long-term effects of treatment with recombinant human erythropoietin on haemodynamics and tissue oxygenation in patients with renal anaemia. *Nephrol Dial Transplant* 1990; 5: 444-8.

16 Brod J, Fencl V, Hejl Z, Jirka J, Ulrych H. General and regional hemodynamic pattern underlying essential hypertension. *Clin Sci* 1962; 23: 339-49.

17 Ledingham JM, Cohen RD. Circulatory changes during the reversal of experimental hypertension. *Clin Sci* 1962; 22: 69-77.

18 Edmunds ME, Walls J, Tucker B, et al. Seizures in haemodialysis patients treated with recombinant human erythropoietin. *Nephrol Dial Transplant* 1989; 4: 1065-9.