Randomised controlled trial of enalapril and β blockers in non-diabetic chronic renal failure

T Hannedouche, P Landais, B Goldfarb, N El Esper, A Fournier, M Godin, D Durand, J Chanard, F Mignon, J-M Suc, J-P Grünfeld

Abstract

***Objective*—To compare the ability of angiotensin converting enzyme inhibitors and β blockers to slow the development of end stage renal failure in non-diabetic patients with chronic renal failure.**

***Design*—Open randomised multicentre trial with three year follow up.**

***Setting*—Outpatient departments of six French hospitals.**

***Patients*—100 hypertensive patients with chronic renal failure (initial serum creatinine 200-400 μmol/l). 52 randomised to enalapril and 48 to β blockers (conventional treatment).**

***Interventions*—Enalapril or β blocker was combined with frusemide and, if necessary, a calcium blocker or centrally acting drug in patients whose diastolic pressure remained above 90 mm Hg.**

***Results*—17 patients receiving conventional treatment and 10 receiving enalapril developed end stage renal failure. The cumulative renal survival rate was significantly better in the enalapril group than in the conventional group ($P<0.05$). The slope of the reciprocal serum creatinine concentration was steeper in the conventionally treated patients (-6.89×10^{-4} l/μmol/month) than in the enalapril group (-4.17×10^{-4} l/μmol/month; $P<0.05$). No difference in blood pressure was found between groups.**

***Conclusion*—In hypertensive patients with chronic renal failure enalapril slows progression towards end stage renal failure compared with β blockers. This effect was probably not mediated through controlling blood pressure.**

Department of Nephrology, Hôpital Necker, Paris, France
T Hannedouche, *professor*
J-P Grünfeld, *professor*

Laboratoires de Biostatistique, Hôpital Necker, Paris, France
P Landais, *senior registrar*
B Goldfarb, *senior registrar*

Department of Nephrology, Hôpital Sud, Amiens, France
N El Esper, *research fellow*
A Fournier, *professor*

Hôpital de Bois-Guillaume, Rouen, France
M Godin, *professor*

Hôpital de Rangueil, Toulouse, France
D Durand, *professor*
J-M Suc, *professor*

Hôpital Maison-Blanche, Reims, France
J Chanard, *professor*

Hôpital Teron, Paris, France
F Mignon, *professor*

Correspondence to:
Professor T Hannedouche, Department of Nephrology, Hôpitaux Universitaires de Strasbourg, 67091, Strasbourg, France.

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Introduction

Chronic renal diseases are characterised by a continual deterioration eventually leading to end stage renal failure and expensive renal replacement therapy. Renal function deteriorates independently of the initial cause of the renal disease, suggesting that there is a final common pathway.[1] Although the mechanisms underlying progression remain ill defined, experimental data on rats with diabetes mellitus or reduced renal mass have suggested a role for alterations in glomerular haemodynamics[1] or for maladaptive glomerular hypertrophy,[2] which eventually leads to glomerular sclerosis and further deterioration of renal function. In these models antihypertensive treatment gave some protection against renal lesions, and thus indirectly slowed progression of renal damage. Angiotensin converting inhibitors were claimed to be better than conventional drugs,[3,4] although this has been challenged.[5]

The clinical consequences of these experimental findings have so far been tested mainly in insulin dependent diabetic nephropathy, where the rate of progression is relatively rapid and uniform. Prospective studies have clearly shown the benefits of antihypertensive drugs,[6] and recently angiotensin converting enzyme inhibitors were found to give more protection than a conventional treatment including β blockers.[7]

Few studies have looked at patients with chronic renal failure due to other renal diseases. These nephropathies are heterogeneous, with differing rates of progression of renal failure and more diverse mechanisms than those in the experimental renal ablation model and diabetic nephropathy. We conducted a randomised three year trial to compare the effects of two antihypertensive regimens on renal function in patients with various chronic renal diseases.

Patients and methods

We recruited patients aged 18 to 70 years with chronic renal failure as defined by a serum creatinine concentration of 200-400 μmol/l. Patients were entered into a one month run in period, in which no antihypertensive drugs were taken, to assess blood pressure. Hypertension was defined as diastolic blood pressure above 90 mm Hg when not taking antihypertensive drugs.

We excluded patients with the nephrotic syndrome (serum albumin concentration <30 g/l); systemic diseases including diabetes; malignant hypertension; renovascular hypertension; evolving obstructive nephropathy; and serious extrarenal disorders including malignancy, heart failure, and coronary artery disease. We also excluded women who were breast feeding, pregnant, or intending to become pregnant and patients who had taken converting enzyme inhibitors in the three months before inclusion; had contraindications to converting enzyme inhibitors or β blockers; were unlikely to comply; or were unwilling to give consent.

The study was designed as an open multicentre trial in the nephrology divisions of six French hospitals. After the run in period eligible patients were allocated at random either to enalapril or to conventional treatment (β blockers). Randomisation was based on random permuted blocks within strata, by using random numbers,[8] and delivered by centre. Treatment was started just after randomisation. The study was approved by the local ethics committee, and all patients gave informed consent.

Treatment in both arms of the trial was aimed at maintaining diastolic blood pressure below 90 mm Hg. The treatment schedules for the two groups were as follows. Enalapril was started at a dose of 5-10 mg once a day, according to the serum creatinine concentration. If diastolic blood pressure at three months was not below 90 mm Hg, frusemide was added at 20 to 120 mg per day. The third step, if necessary, included either a calcium antagonist (nifedipine or nicardipine) or

a central acting drug (methyldopa or clonidine). In the conventional group, treatment was started with a β blocker (acebutolol 400 mg/day or atenolol 100 mg/day). The second and third steps were similar to those described for the enalapril group.

Patients were not advised to modify protein and sodium intakes during the study. We measured blood pressure and took blood and 24 hour urine samples every three months; compliance and adverse effects were recorded at the same intervals. Glomerular filtration rate was assessed by inulin clearance before starting treatment and every six months thereafter.

We measured supine blood pressure after 10 minutes' rest with a mercury sphygmomanometer. Serum creatinine and electrolytes, urinary protein, and urea concentrations were measured by standard automated methods. Protein intake was estimated from daily urea excretion according to the formula developed by Maroni *et al.*[9] Serum angiotensin converting enzyme activity was measured by using an artificial substrate. Results were expressed as a percentage of the lower limit of normal.

Clearances were determined from three 30 minute urine collections and a constant infusion technique of inulin and para-aminohippurate.[10] Inulin and para-aminohippurate clearances were representative of glomerular filtration rate and effective renal plasma flow respectively, and the filtration fraction was calculated as the glomerular filtration rate divided by effective renal plasma flow.

STATISTICAL ANALYSIS

We estimated the required sample size using the following assumptions based on the reciprocal of serum creatinine concentration. We expected a mean (SD) difference in response of 5·1 (7·9) $\times 10^{-5}$ l/μmol/month between the enalapril and conventional groups. For a type 1 error of 0·05 and a power of 0·90, the required number of patients in each group was 41. Fifty patients were then included in each group.

Data were analysed on an intention to treat basis. Analysis of variance was used for intergroup comparison and the paired *t* test for intragroup comparisons. Changes in reciprocal serum creatinine concentration were analysed with an unbalanced repeated measures model to take account of censorship with restricted maximum likelihood including the test of linear fit (BMDP 5 V). Inulin clearance was analysed with an unbalanced repeated measures model without a hypothesis on the decrease with time since neither a linear nor a quadratic relation between inulin clearance and time seemed tenable. Need for dialysis was analysed as the end point of renal function by the Kaplan-Meier estimation of survival. The log rank test was used to compare effects of enalapril and conventional treatment, and prognostic factors for end stage renal disease (blood pressure at entry and treatment) were entered into a Cox regression model. Analysis was done with BMDP and SAS statistical software.[11,12]

Results

We enrolled 100 patients who presented with chronic renal failure and high blood pressure during May 1986 to May 1988. Table I shows the characteristics of patients and the cause of renal failure. No significant difference was found between the two treatment groups. Three patients died during the trial of causes unrelated to treatment (one enalapril, two conventional). A 61 year old man with polycystic kidney disease and a 68 year old women with renal hypoplasia died suddenly at home, and a 63 year old man with chronic interstitial nephritis died at month 22 after surgery for acute ischaemia of the leg.

Six patients developed adverse reactions and had to withdraw. In the enalapril group two patients had hyperkalaemia and one poorly tolerated cough. In the conventionally treated group one patient had acute heart failure, one patient had severe asthma, and one patient had a generalised skin rash attributed to frusemide.

Seventeen other patients withdrew from the study for various reasons: lost from follow up (seven in enalapril group, four in conventional group) deviation from protocol (one conventional), non-compliance with treatment (one enalapril, three conventional) and accelerated phase hypertension (one conventional).

PROGRESSION TO RENAL FAILURE

Ten patients (19%) in the enalapril group and 17 (35%) in the conventional group developed end stage renal failure. The relative risk of renal failure in the conventional group compared with the enalapril group was 3·5 (95% confidence interval 1·5 to 7·6) after blood pressure and type of treatment were adjusted for.

The characteristics of the patients reaching end stage renal failure were similar in both groups (table II) except for the final mean serum creatinine concentration, which was significantly lower in the enalapril group than in the conventional group. The cumulative renal survival rate was significantly better with enalapril than with conventional treatment ($P < 0.05$) (figure), indicating that patients taking enalapril reached end stage renal failure later. The difference between the groups became evident within the first 15 months of the study.

We also estimated the rate of progression of renal failure from the change in the reciprocal of serum creatinine concentrations with time. The slope of the graph was $-4{\cdot}17 \times 10^{-5}$ l/μmol/month in the enalapril group and $-6{\cdot}89 \times 10^{-5}$ l/μmol/month in the con-

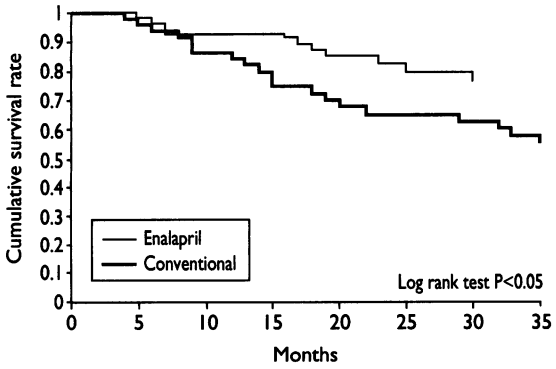
TABLE I—*Main characteristics of patients at start of trial and cause of renal failure. Numbers are means (SD) unless stated otherwise*

	Enalapril (n=52)	Conventional group (n=48)
Age (years)	52 (2)	50 (2)
Sex (M/F)	27/25	26/22
Weight (kg)	67 (2)	66 (2)
Systolic blood pressure (mm Hg)	167 (3)	166 (2)
Diastolic blood pressure (mm Hg)	103 (2)	101 (1)
Serum creatinine (μmol/l)	264 (9)	265 (10)
Serum potassium (mmol/l)	4·44 (0·06)	4·28 (0·06)
Proteinuria (g/24 h)	2·2 (0·3)	2·2 (0·3)
Natriuresis (mmol/24 h)	104 (7)	101 (9)
No of patients with:		
Primary glomerulonephritis	25	22
Polycystic kidney disease (autosomal dominant)	7	9
Other hereditary nephritis	5	1
Nephroangiosclerosis	1	7
Interstitial nephritis	12	7
Unknown cause	2	2

TABLE II—*Characteristics of patients who developed end stage renal failure. Numbers are means (SD) unless stated otherwise*

	Enalapril group (n=10)	Conventional group (n=17)
Age (years)	50 (21)	41 (15)
Sex (M/F)	4/6	8/19
Initial serum creatinine (μmol/l)	312 (86)	305 (73)
Final serum creatinine (μmol/l)	675 (56)	758 (39)*
Initial inulin clearance (ml/min 1·73 m²)	18·6 (7·9)	21·0 (11·6)
Final inulin clearance (ml/min 1·73 m²)	10·3 (3·8)	9·4 (3·4)
Median time between end stage renal failure and last clearance measurement (months)	4·5	4·5
Underlying renal disease (No of patients):		
Primary glomerulonephritis	4	8
Polycystic kidney disease	1	3
Other hereditary nephritis	1	1
Nephroangiosclerosis	0	2
Interstitial nephritis	3	2
Unknown	1	1

*$P < 0.001$.



Survival rate in hypertensive patients treated with enalapril or conventional treatment

ventional group ($P < 0.03$). The global standard error was 1.4×10^{-5}l/μmol/month.

No clear effect of treatment on inulin clearance was found. The mean differences between initial and final inulin clearance per month of follow up (that is, the mean loss of glomerular filtration rate per month) were −0·33 ml/min/month in the enalapril group and −0·57 ml/min/month in the conventional group.

OTHER MEASUREMENTS

Table III shows the changes in blood pressure during the trial. Control of diastolic blood pressure was achieved in 38 (73%) of the patients taking enalapril and 30 (63%) receiving conventional treatment (NS). No differences in blood pressure were seen at any point of the follow up between the two groups. After 12 months 24 (57%) patients in the enalapril group were still receiving enalapril alone but only 10 (29%) in the conventional group were still receiving a β blocker alone ($P < 0.02$). A similar trend was found after 24 months but it was not significant (table IV). The difference had disappeared at 36 months.

The median daily dose of enalapril during the trial was 10 mg. In all, 93 patients complied with treatment as assessed by inhibition of converting enzyme activity below 30% of the lower limit of normal at each three monthly measurement.

The urinary protein excretion rate was measured in the 47 patients with glomerular diseases. For the 25 patients receiving enalapril daily urinary protein excretion decreased significantly from 2·7 (1·85) g/24 h at the start of the trial to 1·85 (2·01) g/24 h at six months ($P < 0.05$, paired t test). The excretion rate remained unchanged for the 22 conventionally treated patients (2·99 (2·12) to 3·02 (1·87) g/24 h). The fall in urinary protein excretion persisted at 12 months in the enalapril group ($P < 0.05$, paired t test). The excretion rate was significantly different between the enalapril and conventional groups at six months ($P < 0.05$, unpaired t test) but not at 12 months or subsequently (table V). In the enalapril group the filtration fraction fell significantly between inclusion and month 12 (mean difference −0·05 (0·02) ($P < 0.05$, paired t test). No such decrease was observed in the conventionally treated group.

Initial serum potassium concentrations were similar in both groups (table I) and remained stable in conventionally treated patients. In patients taking enalapril serum potassium concentration increased to 4·9 (0·5) mmol/l as early as month 3 and remained raised. Two patients taking enalapril had potassium concentrations greater than 6 mmol/l and had to be withdrawn.

Body weight remained stable during the study and was similar in the two groups. Protein intake was 0·94 (0·04) g/kg/day in the enalapril group and 0·96 (0·05) g/kg/day in the conventional group (table V). No difference between the groups was found during follow up. Total serum cholesterol concentration was identical in both treatment groups ranging between 5·94 and 6 mmol/l.

Natriuresis at inclusion was similar in enalapril and conventional groups (104 (7) mmol/24 h and 101 (9) mmol/24 h respectively). At six months natriuresis was 135 (13) mmol/24 h in the enalapril group compared with 101 (8) mmol/24 h in the conventional group ($P < 0.005$). The enalapril group maintained higher values after 12 months, although the difference from the conventional group was not significant.

TABLE III—*Mean (SD) blood pressures (mm Hg) in patients receiving enalapril and conventional treatment*

	No of patients		Systolic pressure		Diastolic pressure	
Months	Enalapril group	Conventional group	Enalapril group	Conventional group	Enalapril group	Conventional group
0	52	48	167 (3)	166 (2)	103 (2)	101 (1)
12	42	35	148 (21)	150 (17)	90 (9)	89 (9)
24	32	25	152 (19)	149 (19)	91 (12)	89 (10)
36	30	22	147 (5)	153 (5)	88 (2)	90 (1)

TABLE IV—*Antihypertensive drugs taken by patients in enalapril and conventional arms of the trial. Figures are numbers (percentages) of patients*

	12 Months	24 Months	36 Months
Enalapril group:			
Enalapril only	24 (57)	14 (42)	11 (38)
Enalapril plus frusemide	12 (29)	19 (30)	9 (30)
Enalapril plus frusemide plus third drug	6 (14)	9 (28)	10 (32)
Conventional group:			
β Blocker alone	10 (29)*	6 (24)	6 (25)
β Blocker plus frusemide	10 (29)	6 (23)	6 (31)
β Blocker plus frusemide plus third drug	15 (42)	13 (53)	10 (44)

*$P < 0.05$ compared with patients treated with enalapril only.

TABLE V—*Mean (SD) values of parameters of renal function during follow up*

	0 Months		12 Months		24 Months		36 Months	
	No of patients	Value	No of patients	Value	No of patients	Value	No of patients	Value
Serum creatinine (μ mol/l):								
Enalapril	52	264 (64)	43	310 (106)	32	315 (84)	30	369 (161)
Conventional	48	265 (67)	34	336 (139)	25	345 (131)	22	398 (215)
Inulin clearance (ml/min 1·73²):								
Enalapril	50	24·8 (9·9)	42	22·4 (9·0)	31	23·8 (10·9)	30	17·8 (7·4)
Conventional	47	26·6 (11·2)	31	22·5 (12·4)	25	22·5 (12·9)	21	18·2 (11·8)
Protein intake (g/kg 24 h):								
Enalapril	49	0·93 (0·32)	40	1·09 (0·36)	31	0·99 (0·31)	24	0·98 (0·45)
Conventional	46	0·96 (0·40)	33	0·97 (0·46)	26	0·90 (0·32)	21	0·88 (0·24)
Proteinuria* (g/24 h):								
Enalapril	25	2·72 (1·85)	19	1·91 (2·13)	16	2·13 (2·36)	14	2·06 (2·22)
Conventional	22	2·99 (2·12)	13	2·91 (1·95)	10	2·59 (1·47)	9	3·04 (1·85)

*Primary glomerulonephritis only.

Discussion

Our three year study shows that enalapril slows the rate of progression to end stage renal failure more than conventional therapy. Hypertension is known to be associated with an increased rate of loss of renal function in patients with non-diabetic chronic renal disease,[13] and the degree of reduction in mean blood pressure induced by antihypertensive drugs correlates with the decrease in the rate of loss of renal function.[14-16] Few clinical studies have compared the ability of antihypertensive drugs to slow progression of renal failure. Those reported are based on retrospective analysis[17] or include small numbers of patients for short follow up or during two successive periods.[18] Recently, Kamper *et al* reported a randomised open controlled trial in 70 patients followed up for at least two years or until dialysis was required.[19] They also found that the median fall in glomerular filtration rate, estimated by the plasma clearance of chromium-51 EDTA, was significantly lower (by 32%) in the enalapril group than in the control group.

As we wanted to compare the effect of two antihypertensive regimens on chronic renal failure we did not change other parameters known to influence the development of chronic renal failure—that is, underlying nephropathy,[16] protein excretion rate,[20] protein intake, and hypercholesterolaemia. Since control of blood pressure was similar in both groups the beneficial effect of converting enzyme inhibition could be related to mechanisms other than lowering blood pressure. The beneficial effect of converting enzyme inhibitors in experimental models has been ascribed to a better long term reduction of intraglomerular hypertension,[3,4] although benefit has also been shown in models without raised glomerular pressure.[2] We did not stratify patients according to their underlying nephropathies because it would have greatly increased the number of patients required. Not restricting protein intake could have favoured the enalapril group since high protein intake stimulates synthesis and release of renin.[21]

URINARY EXCRETION OF PROTEIN

The antiproteinuric effect of converting enzyme inhibitors has been shown in human and animal studies.[3,22] This effect could slow progression of renal changes by decreasing protein traffic through glomerular mesangial cells or by improving serum lipid abnormalities and subsequent lipid mesangial accumulation.[23] We found that the antiproteinuric effect was significant in the enalapril group for only the first year. These findings agree with those reported by Kamper *et al.*[19]

The lack of sustained antiproteinuric effect could have been related to the progressive increase in salt intake, since liberal sodium intake impedes the reduction in protein excretion associated with converting enzyme inhibitors.[24] The filtration fraction dropped significantly at 12 months in the enalapril group, suggesting that beneficial effects of enalapril could be related to a preferential postglomerular vasodilatation and drop in capillary glomerular pressure.[3,4] However, the reduction in filtration fraction was not evident at six months, when proteinuria fell in the enalapril group. Converting enzyme inhibitors could also exert protective effects through non-haemodynamic mechanisms—for example, inhibition of the mitogenic action of angiotensin II,[25] preservation of endothelial cell structure and function, or promotion of the local action of bradykinin.[26]

STUDY DESIGN

Several types of study have been designed to explore the effect of interventions on the progression of chronic renal failure. We followed the recommendations of the Modification of Diet in Renal Disease Study Group: a follow up period of two to four years, measurements of glomerular filtration rate, and comparison of the rate of progression of chronic renal failure in the therapeutic group with a control group.[27,28] There seemed to be a discrepancy between the results for reciprocal serum creatinine concentration and those for inulin clearance. The observed rate of decrease in glomerular filtration rate estimated by inulin clearance does, however, agree with the observed value in non-diabetic nephropathies and with the estimate presented by the study group.[27]

The discrepancy could be related to wide intra-individual variation in sequential measurement of glomerular filtration rate[29] and to the lower statistical power of the analysis for inulin clearances. The number of subjects required was evaluated on the basis of changes in the reciprocal of serum creatinine concentration rather than on inulin clearance because no good data existed on changes in glomerular filtration rate when the feasibility phase of our study was designed in 1985 and because it is difficult to measure clearances more often than every six months. Inulin clearances were measured every six months but because of end stage renal disease and withdrawals only 61% of patients had four to six measurements of clearance in the 36 month follow up. The analysis of glomerular filtration rate is therefore less powerful than that for the reciprocal in serum creatinine concentration, which was measured every three months. The slopes for the reciprocal of serum creatinine concentration agreed with our initial hypothesis. Levey *et al* explored the effect of duration of follow up on correlations between reciprocal serum creatinine concentration and glomerular filtration rate. They showed higher correlations (0·70 and above) in subgroups of patients with longer follow up.[28]

TREATMENT OF PATIENTS

Converting enzyme inhibitors should be used with caution in patients with moderate chronic renal failure. Three patients in the enalapril group were withdrawn from the trial because of adverse effects—namely, hyperkalaemia (two patients) and poorly tolerated cough (one patient). These well known side effects occurred soon after starting treatment. Hyperkalaemia is of special concern in patients with chronic renal failure. Its incidence should be reduced by giving frusemide sooner and by correcting metabolic acidosis more vigorously.

Intervention studies including patients with nephropathies of various types should be interpreted with caution. Though the efficacy of converting enzyme inhibitors in retarding progression of renal failure has been established in diabetic nephropathy, similar benefit may not be extrapolated to every non-diabetic type of renal disease. No evidence exists that the mechanisms leading to progression of renal failure are uniform in all human renal diseases. Although our results suggest a potential benefit of converting enzyme inhibitors in non-diabetic renal diseases, further studies are needed to explore the advantages of these drugs in specific nephropathies before they are widely used for all patients with chronic renal failure.

Clinical implications

- Most patients with chronic renal disease progress to end stage renal disease and require dialysis or renal transplantation
- Progression of chronic renal disease is aggravated by hypertension
- This study shows that an angiotensin converting enzyme inhibitor is more effective than β blockers at slowing progression of non-diabetic chronic renal failure
- Studies of the effect of angiotensin converting enzyme inhibitors in other renal disease are needed

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Cognitive function and behavioural status in paediatric heart and heart-lung transplant recipients: the Harefield experience

Jo Wray, Carien Pot-Mees, Harry Zeitlin, Rosemary Radley-Smith, Magdi Yacoub

Abstract

***Objective*—To assess the psychological impact of cardiac and cardiopulmonary transplantation on children.**

***Design*—Retrospective cross sectional study.**

***Setting*—One British centre performing paediatric heart and heart-lung transplant operations, four cardiac units in London, three London schools, two London health centres, and the dental department of a London children's hospital.**

***Subjects*—65 children who had been given heart or heart-lung transplants and two reference groups of 52 children who had had other types of cardiac surgery and 45 healthy children.**

***Main outcome measures*—Development, cognition, and behaviour at home and at school as assessed by measures with proved validity and reliability.**

***Results*—Developmental and cognitive measures indicated that children given transplants had significantly lower scores on several parameters, particularly in terms of development in children under 4½ years of age. Performance on all tests, however, was within the normal range. There were no significant differences in behavioural ratings between the transplant and reference groups, though problem behaviour at home was more prevalent in the transplant group.**

***Conclusions*—Though cognitive development may be within the normal range, there are adverse psychological effects associated with cardiac and cardiopulmonary transplantation. These data indicate the need for a controlled prospective study in which children and their families are seen before and at regular intervals after transplantation. Interventions should be developed that are tailored to the particular needs of this very specialised group of paediatric patients and their families.**

Cardiothoracic Unit, Harefield Hospital, Middlesex UB9 6UJ
Jo Wray, *research psychologist*
Rosemary Radley-Smith, *consultant paediatric cardiologist*
Magdi Yacoub, *consultant cardiothoracic surgeon*

Department of Psychiatry, Charing Cross and Westminster Medical School, Westminster Children's Hospital, London SW1P 2NS
Carien Pot-Mees, *research psychologist*
Harry Zeitlin, *consultant child psychiatrist*

Correspondence to:
Ms Wray.

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Introduction

Cardiac transplantation and cardiopulmonary transplantation have become established treatments for end stage cardiac failure in adults,[1,2] but only recently have they been used to treat children with end stage heart or lung disease. Children with chronic illness are more likely to have severe psychological and social difficulties than their healthy peers,[3] but very little is known about psychological adjustment after heart or heart-lung transplantation.

Late follow up of children after heart transplantation showed that most had returned to activities appropriate for their age, including school, and that few were having cardiac related symptoms.[4-6] A further study of seven patients suggested that children can "adapt" to the experience of transplantation.[7] However, the numbers of patients in these studies were very small. Furthermore, most of them were of school age and were heart rather than heart-lung recipients. Cognitive impairment[8,9] and behavioural and emotional[10,11] disturbance have been reported in children who have had open heart surgery, particularly for cyanotic conditions. Adverse effects have also been reported in parents[12] and siblings[12,13] of children with congenital heart disease. Similar problems have been encountered after paediatric renal transplantation[14] and bone marrow transplantation.[15]

The objective of this study was to examine the behaviour and cognitive function of a group of children who had had heart or heart-lung transplantation and to compare them with another group of children who had had non-transplant cardiac surgery and a group of healthy, non-hospitalised children. This cross sectional study was designed to obtain preliminary observations on children after transplantation and to assess the practicality and acceptability of such studies to families and staff.

Subjects and methods

Patients—Inclusion criteria for the study were that the patients and their families spoke English as their first language, that they were domiciled in the United Kingdom or Irish Republic, that the patients were under 17 years of age, and that they attended Harefield Hospital for follow up. During October 1988 to