PAPERS AND ORIGINALS

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Agonal Phase, Ischaemic Times, and Renal Vascular Abnormalities and Outcome of Cadaver Kidney Transplants

C. L. HALL, J. R. SANSOM, M. OBEID, P. DAWSON-EDWARDS, B. H. B. ROBINSON, A. D. BARNES, J. D. BLAINEY

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Summary

A retrospective study of 250 cadaver kidney transplants was carried out to determine the effects of the agonal period, the warm and cold ischaemic times, and the use of kidneys with vascular anomalies on the primary success and failure and the subsequent level of function of the transplants.

Kidneys with vascular anomalies or from non-ventilated donors had a primary failure rate of over 30%, whereas those with normal vasculature or from ventilated donors had a rate of 17%. An initial warm ischaemic time of more than 60 minutes was associated with a primary failure rate of 57% and a cold ischaemic time of over 550 minutes with a primary failure rate of 47%. The interrelationship between the warm and cold ischaemic times in the primary success or failure of the transplants was examined and criteria defined for selecting potentially viable cadaver kidneys for transplantation, as follows: (1) The donor should be (a) ventilated, (b) aged 6-50 years, and (c) have normal ante-mortem renal function and have secreted more than 1·5 l of urine in the 24 hours before death (or an equivalent volume if the urinary output was recorded for less than 24 hours before death); (2) the kidney should have normal renal vasculature enabling single arterial and venous anastomoses to be performed; (3) kidneys with I.W.I.T.s of longer than 60 minutes should not be used; (4) for kidneys with I.W.I.T.s of less than 20 minutes the C.I.T. is not critical but should not exceed 12 hours; (5) for kidneys with I.W.I.T.s of 20-60 minutes the C.I.T. should not exceed 450 minutes.

M.R.C. Renal Research Laboratory, Queen Elizabeth Hospital, Birmingham B15 2TH

C. L. HALL, M.D., M.R.C.P., Member of External Scientific Staff
J. D. BLAINEY, M.D., F.R.C.P., Member of External Scientific Staff

Queen Elizabeth Hospital, Birmingham B15 2TH

J R SANSOM, M.B., F.R.C.S., Surgical Registrar, Renal Unit
M. OBEID, M.B., F.R.C.S., Senior Surgical Registrar
P. DAWSON-EDWARDS, M.B., F.R.C.S., Consultant Urological Surgeon
B. H. B. ROBINSON, M.B., F.R.C.P., Consultant Physician, Renal Unit
A. D. BARNES, M.CH., F.R.C.S., Consultant Surgeon

Introduction

Cadaver kidney transplantation is an established and successful means of treating end-stage chronic renal failure. But though patient survival has increased progressively, the survival and duration of function of the transplanted kidney has not, despite advances in postoperative care, immunosuppressive treatment, and tissue typing. [1 2] The shortage of kidneys available for transplantation[3 4] encourages the use of cadaver kidneys that might otherwise be abandoned because of vascular anomalies, long ischaemic times, an unsatisfactory donor agonal phase, or poor HL-A matching. No fewer than 17% of cadaver kidneys fail within the first week of transplantation, and one of the major reasons is thought to be the poor quality of some of the kidneys used.[5]

Studies on dogs have shown that when there is no agonal ischaemic damage and the initial warm ischaemic time (I.W.I.T.) is zero kidneys may be preserved successfully by simple hypothermia for 8-12 hours.[6 7] The same duration of cold ischaemia, however, renders many kidneys non-viable if subjected to an I.W.I.T. of 15 minutes.[8 9] In clinical practice the problem is complicated further by agonal ischaemic damage, which in some countries is prevented by careful maintenance of the cardiovascular and respiratory systems of the donor until the kidneys have been removed. In Britain, however, nephrectomy is usually carried out after respiratory and cardiac arrest have occurred.

This paper examines retrospectively the effect of the agonal period, the warm and cold ischaemic times, and the use of kidneys with vascular anomalies on the primary success or failure and level of subsequent function of 250 cadaver kidneys transplanted during 1969 to 1975.

Materials and Methods

The 250 kidneys were obtained either locally or through the London Hospital Group[10] or the National Organ Matching Service, Bristol. Those obtained locally (130) were removed by a standard en-bloc method,[11 12] separated—each bearing an aortic and a vena caval patch—and perfused with 150-250 ml dextran 40 in 5% dextrose. The kidneys obtained through the London Hospital Group and the National Organ Matching Service (120) had been removed by various techniques, and many had been perfused with complex "cell-preservation" solutions.[13 14] After nephrectomy the kidneys were stored and transported double-wrapped in sterile plastic bags immersed in an ice-water mixture in isothermic polystyrene containers. The transplant operations were performed by a team of surgeons using a standard technique that remained substantially unchanged during the six-year period.

The following data were obtained from the records. *Donors*: age; whether or not donor was ventilated; blood urea before death; urinary output in the 24 hours before death; duration of hypotension before death; time from switching off ventilator to cardiac arrest; and any vascular anomaly of donor kidney (anything other than a single renal artery and a single vein). *Recipients*: I.W.I.T.—that is, the time from cardiac arrest to the immersion of the kidneys in ice after removal; cold ischaemic time (C.I.T.)—that is, the time from the immersion of the kidneys in ice to the start of the vascular anastomoses; oliguric phase—that is the time elapsing after transplantation before the kidney secreted more than 2 l of urine/24 h; serum creatinine level three months after transplantation; and rejection episodes occurring within three months after transplantation.

In many cases the records were incomplete, those for the donors containing some 55-75% of the data sought and those for the recipients some 85-95%.

During the oliguric phase rejection was diagnosed on the basis of pyrexia and a swollen, tender transplant. During the diuretic and post-diuretic phases the same changes together with a decreased urinary output and a rise in the serum creatinine level of more than 88 μmol/l (1 mg/100 ml) were regarded as diagnostic of a rejection episode.

A successful transplant was one that secreted urine and maintained the recipient without the need for dialysis. A primary failure was a transplant that failed to secrete urine or to maintain the recipient without continuing dialysis.

Results

DONOR INFORMATION

Examination of each item of donor information in relation to the subsequent success or failure of the kidney transplants (table I) showed that the primary failure rate of the kidneys transplanted from donors who had been ventilated was 17·5%, whereas that of kidneys from non-ventilated donors was 31·0% ($P<0·02$). The primary failure rates of transplants from donors with ante-mortem blood urea of less than 6·6 mmol/l (40 mg/100 ml), 6·6-10·0 mmol/l (40-60 mg/100 ml), and over 10 mmol/l were 19·5%, 24·4%, and 26·7% respectively.

The primary failure rate of kidneys from donors secreting more than 1·5 l of urine in the 24 hours before death was 17·8% as opposed to 27·3% for those from donors secreting less than 1 l of urine. The primary failure rate did not increase significantly with the duration of hypotension before death, even when this exceeded 600 minutes, with the time between switching off the ventilator and the onset of cardiac arrest, or with age, even when the donor was more than 60 years old. The serum creatinine levels in patients whose transplants were functioning successfully three months postoperatively bore no relation to the age of the donor, the ante-mortem blood urea or urinary output, the duration of hypotension, or the time between switching off the ventilator and the onset of cardiac arrest.

The primary failure rate of kidneys with vascular anomalies was 38·2% as compared with 16·8% for those with a single artery and vein ($P<0·001$) (table II), and the incidence of thrombosis of the renal artery or vein or both of kidneys with vascular anomalies was 21·8% as compared with 3·4% for those with a normal vasculature ($P<0·001$) (table II).

TABLE II—*Incidence of Primary Failure and Renal Vascular Thrombosis in Transplants with Normal and Abnormal Vasculature*

	No. of Transplants	No. (%) of Primary Failures	No. (%) with Renal Vascular Thrombosis
Normal vasculature ..	179	30 (16·8)	6 (3·4)
Abnormal vasculature	55	21 (38·2)	12 (21·8)
Significance (χ^2) ..		$P<0·001$	$P<0·001$

ISCHAEMIC TIMES

The mean I.W.I.T. of the primary failures (26·9 min), though biased by two kidneys with an I.W.I.T. exceeding 100 minutes, was similar to that of the primary successes (23·8 min) (table III). The mean C.I.T. of the primary failures (432·9 min), however, was significantly greater ($P<0·02$) than that of the primary successes (370·0 min) (table III). With I.W.I.T.s of less than 60 minutes the primary failure rates ranged from 15·9% to 26·4%, but when the I.W.I.T. exceeded 60 minutes the primary failure rate increased to 57·1% ($P<0·05$).

TABLE III—*Warm and Cold Ischaemic Times of Successful and Unsuccessful Transplants*

	Primary Failure	Primary Success	Unpaired *t* test Result	Significance
No. of transplants	54	184		
Mean initial warm ischaemic time (min) ± S.D.	26·9 ± 18·0	23·8 ± 13·8	1·3482	$P>0·1$
Mean cold ischaemic time (min) ± S.D. ..	432·9 ± 166·0	370·0 ± 150·4	2·5424	$P<0·02$

TABLE IV—*Primary Failure Rates in Relation to Initial Warm Ischaemic Times*

Initial Warm Ischaemic Time (min)	No. of Transplants	No. of Primary Failures	Primary Failure Rate (%)	Significance
<20	82	13	15·9	}
20-39	110	29	26·4	} } $P>0·05$
40-59	35	8	22·9	} } $P>0·5$
⩾60	7	4	57·1	} $P<0·05$

The primary failure rate increased progressively with the duration of cold ischaemia (table V). With C.I.T.s of less than 250 minutes and 250-449 minutes the primary failure rates were 13·7% and 21·9% respectively, but with C.I.T.s exceeding 450 and 550 minutes the failure rates were 30·6% and 46·7% respectively ($P<0·02$). When the donor kidneys were divided into two groups according to the duration of the I.W.I.T. (table VI) it was apparent that when the I.W.I.T. was less than 20 minutes the primary failure rate was not affected by an increasing C.I.T. When the I.W.I.T. exceeded 20 minutes, however, the primary failure rate increased from 18·7% to

TABLE I—*Incidence of Primary Failure of Transplants in Relation to Donor Values*

	Ventilated	Not Ventilated	Blood Urea (mmol/l)			Urine Output (l/24 h)			Time from Switching off Ventilator to Cardiac Arrest (min)	
			<6·6	6·6–10·0	>10·0	<1·0	1·0–1·5	>1·5	0–9	>10
No. of primary failures ..	29	9	16	10	4	3	8	21	14	19
No. of primary successes	137	20	66	31	11	8	36	97	64	71
Primary failure rate (%) ..	17·5*	31·0*	19·5	24·4	26·7	27·3	18·2	17·8	18·0	21·1

* $P<0·02$.

Conversion: S.I. to Traditional Unit—Blood urea: 1 mmol/l ≈ 6 mg/100 ml.

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TABLE V—*Primary Failure Rates in Relation to Cold Ischaemic Times*

Cold Ischaemic Time (min)	No. of Transplants	No. of Primary Failures	Primary Failure Rate (%)	Significance
<250	51	7	13·7	P>0·2
250–449	96	21	21·9	P>0·2
≥450	72	22	30·6	P<0·02
≥550	30	14	46·7	

TABLE VI—*Interrelationship between Warm and Cold Ischaemic Times in Primary Failure of Transplants*

Initial Warm Ischaemic Time (min)	Cold Ischaemic Time (min)	No. of Transplants	No. of Primary Failures	Primary Failure Rate (%)	Significance
<20	<450	54	10	18·5	P<0·8
	≥450	26	4	15·4	
≥20	<450	91	17	18·7	P<0·02
	≥450	47	18	38·3	
	≥550	20	11	55·0	P<0·01

TABLE VII—*Duration of Oliguric Phase in Relation to Warm and Cold Ischaemic Times*

Initial Warm Ischaemic Time (min)	No. of Transplants	Mean Oliguric Phase (Days) ± S.D.	Cold Ischaemic Time (min)	No. of Transplants	Mean Oliguric Phase (Days) ± S.D
0–19	68	11·2 ± 8·7	<250	43	16·2 ± 10·4
20–39	80	16·8 ± 11·0	250–449	75	13·9 ± 9·7
≥40	27	19·1 ± 7·6	≥450	49	14·0 ± 9·7
			≥550	15	15·1 ± 10·7

38·3% when the C.I.T. exceeded 450 minutes and to 55·0% when the C.I.T. exceeded 550 minutes.

The length of the oliguric phase was related closely to the I.W.I.T. but not to the C.I.T. The mean oliguric phase of kidneys with I.W.I.T.s of less than 20 minutes was significantly shorter (11·2 days) than the oliguric phases of kidneys with I.W.I.T.s of 20-39 minutes (16·8 days) or more than 39 minutes (19·1 days) (P<0·001; table VII).

The mean serum creatinine level in 65 patients with transplanted kidneys that were functioning successfully with no signs of rejection three months postoperatively was 133 μmol/l (1·5 mg/100 ml). This was significantly lower than that (230 μmol/l; 2·6 mg/100 ml) in 53 patients with kidneys that had survived rejection episodes in this time (P<0·001). In the absence of rejection episodes, though not reaching statistical significance, the serum creatinine level increased progressively with the I.W.I.T. (table VIII). There was little difference in the mean serum creatinine levels between kidneys with C.I.T.s of less than 250 minutes (124 μmol/l; 1·4 mg/100 ml) and those with a C.I.T. of 250-449 minutes (115 μmol/l; 1·3 mg/100 ml), but when the C.I.T. exceeded 450 minutes the mean serum creatinine level increased significantly (159 μmol/l; 1·8 mg/100 ml) (P<0·02).

TABLE VIII—*Serum Creatinine Levels of Patients with Successful Transplants Three Months after Operation in Relation to Warm and Cold Ischaemic Times. Results expressed ± S.D.*

Initial Warm Ischaemic Time (min)	Serum Creatinine (μmol/l)		Cold Ischaemic Time (min)	Serum Creatinine (μmol/l)	
	No Rejection	Rejection Episodes		No Rejection	Rejection Episodes
0–19	115 ± 44	203 ± 133	<250	124 ± 44	230 ± 141
20–39	133 ± 62	256 ± 150	250–449	115 ± 35	221 ± 150
≥40	150 ± 71	248 ± 159	>450	159 ± 80	256 ± 141

Conversion: S.I. to Traditional Unit
Serum creatinine: 1 μmol/l ≈ 0·0113 mg/100 ml.

Discussion

Some of the information in the donor's records was subjective, especially that on the duration of ante-mortem hypotension, and the recorded ischaemic times contained considerable observer error. Furthermore, as noted above, many records were incomplete. Two important items of information were found in the donor's records. Firstly, in agreement with the report of Festenstein *et al.*[10] the primary failure rate of transplants from donors who had not been ventilated was 31% as opposed to 17·5% for kidneys from ventilated donors. Secondly, the primary failure rate of kidneys with vascular anomalies (anything other than a single artery and a single vein) was 38·2% as opposed to 16·8% for kidneys with a normal vasculature, which was due mainly to a sixfold increase in the incidence of renal arterial or venous thrombosis.

No statistically significant relationships were established between the other donor values and either the primary failure rate or the level of function of the successful transplants three months postoperatively. Consistent trends were observed, however, between an increasing level of ante-mortem donor blood urea and a decreasing urinary output in the 24 hours preceding death and an increasing primary failure rate after transplantation. No relationship was found between the age of the donor and the primary failure rate after transplantation, probably because of the few (37) kidneys transplanted from donors over 50 years old. In a study of more than 12 000 cadaver kidney transplants,[2] kidneys from donors over 50 years old were shown to have a significantly higher failure rate in the first six months after transplantation than those from donors aged 6-50 years.

Our findings confirm reports[15 16] that an I.W.I.T. of up to 60 minutes is not associated with an increasing primary failure rate. Nevertheless, when the I.W.I.T. exceeded 60 minutes no fewer than 57% of the cadaver kidneys failed to function. Cadaver kidneys with I.W.I.T.s of less than 20 minutes have the advantages of a low primary failure rate (16%) and a short oliguric phase (11 days) and, as reported previously, are able to withstand considerably longer than 450 minutes of cold ischaemia without an increase in the primary failure rate.[14 17–20] In our study, when the I.W.I.T. exceeded 20 minutes the primary failure rate increased progressively with the C.I.T. from 18·7% when the C.I.T. was less than 450 minutes to 38·3% when it exceeded 450 minutes, and to no less than 55% when it exceeded 550 minutes. Clearly, in the transplantation of cadaver kidneys, when the I.W.I.T. exceeds 20 minutes the C.I.T. must be kept as short as possible and should not exceed 450 minutes. Indeed, it must be questioned whether cadaver kidneys with I.W.I.T.s of longer than 20 minutes should be transported under the conditions of simple hypothermia used at present, as the increasing primary failure rate associated with an increasing C.I.T. quickly eliminates any advantage that closer HL-A matching of donor and recipient might confer.

At present the viability of some of the cadaver kidneys that are transplanted is in doubt. Improvement in the results of transplantation would undoubtedly be achieved if more kidneys were available and if it was possible to maintain the cardiorespiratory support of the donor until nephrectomy had been completed. This, however, may require changes of both medical and legal attitudes. We suggest the following criteria as a guide to the selection of potentially viable kidneys for transplantation under the conditions of removal, storage, and transportation by simple hypothermia that prevail in Britain at present:

(1) The donor should be (*a*) ventilated, (*b*) aged 6-50 years, and (*c*) have normal ante-mortem renal function and have secreted more than 1·5 l of urine in the 24 hours before death (or an equivalent volume if the urinary output was recorded for less than 24 hours before death); (2) the kidney should have normal renal vasculature enabling single arterial and venous anastomoses to be performed; (3) kidneys with I.W.I.T.s of longer than 60 minutes should not be used; (4) for kidneys with I.W.I.T.s of less than 20 minutes the C.I.T. is not critical but should not exceed 12 hours; (5) for kidneys with I.W.I.T.s of 20-60 minutes the C.I.T. should not exceed 450 minutes.

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Criteria of Fitness for Anaesthesia in Patients with Chronic Obstructive Lung Disease

J. S. MILLEDGE, J. F. NUNN

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Summary

Twelve patients with severe chronic obstructive lung disease undergoing 15 operations were assessed with preoperative lung function tests and blood gas estimations. Their operative and postoperative course was followed. There were no deaths or serious complications. Patients fell into three groups: those with low respiratory capacity but normal blood gases, who required no special respiratory treatment apart from physiotherapy and antibiotics; those with hypoxaemia but normal arterial carbon dioxide pressure, who needed more prolonged oxygen treatment after operation; and those with hypoxaemia and hypercapnia, who needed postoperative ventilatory support.

While forced expiratory volume in one second (FEV_1) is a good screening test in preoperative assessment it should be supplemented by arterial blood gas estimations in patients with an FEV_1 of less than 1 litre.

Introduction

Doctors are often confronted with the problem of whether to recommend or accept for surgery a patient with chronic obstructive lung disease. The decision rests partly on surgical considerations but also on the likely effect of anaesthesia and surgery on the respiratory state of the patient. This is difficult to predict, and numerous reviews have described techniques for preoperative assessment of respiratory function but given no guidance on interpretation of findings in relation to the expected course of events.

The commonest routine preoperative test of pulmonary function is the measurement of forced vital capacity, with the results expressed as the forced expiratory volume in one second (FEV_1) and also as a percentage of the slow vital capacity (VC). The theoretical hazards of impaired ventilatory capacity in relation to anaesthesia are widely appreciated, but there is no reference to the actual level of reduction of FEV_1 which in itself constitutes a definite hazard or contraindication to anaesthesia and surgery. Diament and Palmer,[1] however, claim that a reduction in FEV_1 below 70% indicates that a patient is at risk of developing postoperative pulmonary complications, but this conclusion was not supported by any study of their patients' progress after operation.

Published works gives little or no guidance on the potential hazard in patients with an exceptionally low FEV_1. The lowest value reported is 0·81 litre.[2] Thornton[3] lists several patients with values below 1 litre who underwent surgery but gives no details of progress during or after surgery. We therefore collected details of 15 anaesthetics in 12 patients with grossly reduced FEV_1 (range 0·45-1·04 litres) to determine whether a reduction of FEV_1 to these low levels in itself introduces a hazard to anaesthesia for routine surgery. In most cases we also noted the preoperative blood gas levels, since Stein *et al.*[2] reported that a raised alveolar carbon dioxide pressure was an important factor discriminating those patients who would develop postoperative pulmonary complications.

Patients and Management

Fifteen operations were performed on 12 patients with chronic obstructive airway disease who presented consecutively for surgery with an FEV_1 of 1 litre or less. The anaesthetic management was entirely at the discretion of the seven different anaesthetists on whose lists the patients came for surgery.

Preoperative Assessment.—Patients were subjected to routine preoperative clinical assessment by the anaesthetist. Tests of ventilatory capacity were also carried out in all patients. FEV_1 and VC were measured with a Vitalograph dry spirometer, usually one or two days before operation. Predicted normal values were taken from the data of Cotes.[4] Arterial gases were measured preoperatively in 10 patients using a Corning Eel model 165, oxygen pressure (Pao_2) calibration being carried out with 30% glycerol in water equilibrated with air. The normal range of blood gases was taken from the data of Raine and Bishop.[5]

Preoperative Management.—All patients received preoperative pulmonary physiotherapy except one patient (case 12) who was admitted as an emergency and four (cases 2, 7, 9, and 11) for whom it was deemed unnecessary. All patients received antibiotics before and after surgery. Details of premedication are given in table I.

Anaesthesia.—Induction of anaesthesia was with thiopentone in all cases. Spontaneous respiration and anaesthesia with halothane and nitrous oxide without endotracheal intubation was used four times for relatively minor operations not requiring relaxation. For the remaining 11 operations, patients were intubated and ventilated artificially with a Manley Ventilator incorporated in a Blease "Northwick Park" anaesthetic apparatus. Anaesthesia was maintained with nitrous oxide supplemented with halothane, fentanyl, or diamorphine. The relaxant pancuronium was used in nine cases. In six cases

Division of Anaesthesia, Clinical Research Centre, Northwick Park Hospital, Harrow, Middlesex HA1 3UJ
J. S. MILLEDGE, M.D., F.R.C.P., Consultant Physician and M.R.C. Scientific Staff member
J. F. NUNN, M.D., F.F.A. R.C.S., Head of Division

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