THE SIGNIFICANCE OF ISCHAEMIA IN RENAL ALLOTRANSPLANTATION

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In this paper we are considering the significance of ischaemia in 28 cadaver renal allografts in man. Ischaemic damage is very important to those interested in cadaver kidney transplantation, and in the past has probably been responsible for more failures than immunological reactions.

The following seven factors have been considered possibly to influence the recovery of renal function in the postoperative phase:

1. The warm ischaemic time; this is the time from the death of the donor to removal of the kidney and cooling it to 4°C, plus the time taken for the vascular anastomosis. It includes any period of external cardiac massage that is necessary prior to the onset of removal of the kidney.
2. The cold ischaemic time; this is the time the kidney is kept at 4°C.
3. The total ischaemic time; this is the combination of warm and cold ischaemic times.
4. Donor hypotension is present when the mean blood pressure is less than 80 mm Hg.
5. Donor ventilation considers the use of the respirator prior to death.
6. Donor age.
7. Donor renal function.

![Graph showing the relationship between days and onset of renal function.](attachment:image)

$r = 0.456$

$y = 0.162x - 4.98$

$0.01 > P < 0.05$

Fig. 1. Warm ischaemia.
Except for donor renal function, all these factors have been subjected to statistical analysis so that it is possible to exclude the other factors when considering any one and its relation to the onset of renal function in the recipient.

For example, the period of hypotension does not affect the influence ventilation has on the time of function of the grafted kidney.

In all cases the donor was fully heparinised after death by the intravenous administration of 25,000 units of Heparin and the kidney was perfused with 500 ml of Hartmann’s solution at 4°C. It was then placed in a sterile plastic bag surrounded by ice till the subsequent transplantation.

The definition of onset of renal function in this series is very important. The onset of renal function in the recipient is defined as the time when the patient begins excreting more than 6 g of urea per day. At this amount of urea excretion the kidney function is just able to support life using dietary restriction only.

Figure 1 relates the period of warm ischaemia in minutes to the onset of renal function in the recipient in days. There is a wide scatter due to other factors influencing the onset of renal function besides the period of warm ischaemia. However, the slope is significant at the 5% level. Our mean warm ischaemic time was 95 minutes, but kidneys functioned after a period of 140 minutes of warm ischaemia. However, the longest period of warm ischaemia associated with survival of the recipient beyond 28 days and subsequent kidney function was 125 minutes.

Table I shows the period of warm ischaemia in two groups.

Firstly, those that functioned in less than 4 days after transplantation, and secondly those that functioned in more than 4 days. The arbitrary figure of 4 days has been taken because after this period dialysis is very likely to be necessary. In those that functioned in less than 4 days the mean period of warm ischaemia was 75 minutes and in those that functioned in more than 4 days it was 109 minutes. S.D. is the standard deviation and these results are significant at the 3% level.

Table II shows the warm ischaemic time in paired recipients. These are the results in 14 recipients who received their kidneys from 7 donors. Thus one donor gave 2 kidneys to 2 recipients, thus excluding factors in the donor prior to death from the analysis. It does not mean that the 7 in group 1 received the first kidney and the 7 in group 2 received the second kidney from a donor. The mean warm ischaemic time in those that functioned in less than 4 days was 72 minutes and in those that functioned in more than 4 days 118 minutes. These results were highly significant at the 1% level and emphasize the importance of warm ischaemia despite the scatter shown in Figure 1.

In considering the cold ischaemia time we found no statistical difference between those that functioned in less than 4 days and in those that functioned in more than 4 days (Table III). Kidneys functioned after 225 minutes of cold ischaemia though the longest period of cold ischaemia which resulted in kidney function and survival of the recipient was 160 minutes.

Similarly with total ischaemia there was no statistical difference between those that functioned within 4 days and those that functioned after 4 days. Kidneys would recover in function after 300 minutes of total ischaemia but the longest period of total ischaemia which resulted in kidney function and survival was 240 minutes.

Table IV shows the role donor hypotension has to play in the onset of renal function in the recipient. The first column considers the onset of renal function if the period of hypotension is under 1 hour. We had 14 recipients who received a kidney which had been subjected to less than 1 hour of hypotension in the donor prior to death. Eight functioned within 4 days. On the other hand, we had 9 who received a kidney which had been subjected to more than 6 hours of hypotension. Only one functioned within 4 days.

Considering these statistically as before (Table V), in those that functioned in less than 4 days the mean period of donor hypotension was 2 hours, and in those that functioned in more than 4 days the mean period of hypotension was 13 hours.

These results were statistically significant at the 5% level.

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TABLE I  

*Warm ischaemia*

<table>
<thead>
<tr>
<th>Function</th>
<th>No.</th>
<th>Mean time mins.</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 4 days</td>
<td>11</td>
<td>75</td>
<td>21</td>
</tr>
<tr>
<td>+ 4 days</td>
<td>17</td>
<td>109</td>
<td>44</td>
</tr>
</tbody>
</table>

\[ t = 2.32 \quad p = 0.028 \]

TABLE II  

*Warm ischaemia-paired recipients*

<table>
<thead>
<tr>
<th>Function</th>
<th>No.</th>
<th>Mean time mins.</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 4 days</td>
<td>7</td>
<td>72</td>
<td>16</td>
</tr>
<tr>
<td>+ 4 days</td>
<td>7</td>
<td>118</td>
<td>31</td>
</tr>
</tbody>
</table>

\[ t = 3.43 \quad p = 0.004 \]

TABLE III  

*Cold ischaemia*

<table>
<thead>
<tr>
<th>Function</th>
<th>No.</th>
<th>Mean time mins.</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 4 days</td>
<td>11</td>
<td>125</td>
<td>42</td>
</tr>
<tr>
<td>+ 4 days</td>
<td>17</td>
<td>140</td>
<td>39</td>
</tr>
</tbody>
</table>

\[ t = 0.937 \quad p = 0.36 \]

TABLE IV  

*Donor hypotension*

<table>
<thead>
<tr>
<th>No. patients</th>
<th>- 1 hour</th>
<th>1–6 hours</th>
<th>+ 6 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>14</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Function</td>
<td>8</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>- 4 days</td>
<td>8</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

TABLE V  

*Donor hypotension*

<table>
<thead>
<tr>
<th>Function</th>
<th>No.</th>
<th>Mean time hrs.</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 4 days</td>
<td>11</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>+ 4 days</td>
<td>17</td>
<td>13</td>
<td>18</td>
</tr>
</tbody>
</table>

\[ t = 2.15 \quad p = 0.041 \]

TABLE VI  

*Donor ventilation*

<table>
<thead>
<tr>
<th>Ventilation</th>
<th>No.</th>
<th>Mean time days</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>18</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>-</td>
<td>7</td>
<td>18</td>
<td>8</td>
</tr>
</tbody>
</table>

\[ t = 3.57 \quad p = 0.002 \]
ISCHAEMIA IN RENAL ALLOTRANSPLANTATION

The donor was on a ventilator prior to death in 18 cases and the mean period before renal function returned was 5 days (Table VI). In 7 cases the donor was not on a ventilator and the mean period before the return of renal function was 18 days. We had 3 cases who never functioned and in none of these was the donor on a ventilator. These results are very highly significant.

We had 20 donors in this series. They were aged from 13 to 65 years. In the two cases over 60 years the kidneys functioned in the recipients. Age did not have any significant influence on the onset of renal function.

In 16 of the 20 cases the blood urea was measured on the day of death and the mean was 40 mg%. In two cases the blood urea was over 100 mg%, the highest being 140 mg% and in both cases the kidneys functioned with survival of the recipient. The mean urine/plasma urea ratio was 43.9 and our mean creatinine clearance in 4 cases only was 58 ml per minute on the day of death. One fortunate recipient received a kidney from a donor whose urine/plasma urea ratio was 4 and whose creatinine clearance was 10 ml per minute. He is alive and well 18 months after transplantation.

From all these results we can say no function will be present in the recipient if more than one of the following criteria are present:

1. The period of warm ischaemia exceeds 140 minutes.
2. The period of cold ischaemia exceeds 250 minutes.
3. The period of total ischaemia exceeds 300 minutes.
4. The period of donor hypotension exceeds 48 hours.
5. No ventilation of the donor.

On the other hand, function is likely within 4 days if the following criteria are present:

1. The warm ischaemic period is less than 75 minutes.
2. The period of cold ischaemia is less than 130 minutes.
3. The period of total ischaemia is less than 205 minutes.
4. The period of hypotension in the donor is under 6 hours.
5. The donor is on a ventilator.