26-hour storage of a declined liver prior to successful transplantation using *ex vivo* normothermic perfusion

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In 2014, 1821 patients died awaiting a liver transplant in the United States while nearly 10% of livers recovered from deceased donors were not transplanted, usually because of concern that the donor liver would function poorly or not work at all (1). *Ex vivo* assessment of such donor livers by normothermic perfusion may mitigate such fears by demonstrating functional ability and thus permit transplantation. Here we describe the use of *ex vivo* normothermic perfusion to assess a liver deemed unfit for transplantation before it went on to be successfully transplanted after a 26 hour period of extracorporeal storage.

The liver of a 39-year-old brain dead donor dying following hypoxic brain injury was offered for transplantation to all United Kingdom liver transplant units, but declined because of suboptimal *in situ* perfusion at the time of organ recovery. The liver was accepted for research at our centre and upon arrival, underwent normothermic perfusion with an erythrocyte-based perfusate using a Liver Assist machine (Organ Assist, Groningen, Netherlands), starting 618 minutes after cold *in situ* perfusion in the organ donor. At the end of the first hour the perfusate alanine transaminase (ALT) concentration was 284iu/L and the lactate concentration had fallen from 71mg/dL to 4.5mg/dL (figure 1a). The liver maintained physiological pH without support and produced bile. Accordingly we therefore reversed our initial decision to decline the liver for transplantation and after 8.5 hours *ex vivo* normothermic perfusion the liver was flushed with cold Belzer UW solution (Bridge to Life, London, UK) and returned to cold storage pending implantation. The recipient was a 48-year-old man with primary sclerosing cholangitis and a Model for End-Stage Liver Disease score of 26 (2). At operation a suspicious subcapsular liver nodule was found and subject to urgent histological characterisation by frozen section to rule out cholangiocarcinoma. This delayed implantation of the new liver contributed to 412 minutes of cold storage that followed normothermic perfusion before the liver was reperfused in the recipient. The total period of extracorporeal storage was 26 hours and one minute. Reperfusion was uneventful and

there was primary function with a peak ALT of 960iu/l on day 1, and normal liver chemistry by day 26 (figure 1b).

Liver transplantation is limited by a shortage of suitable donor organs (3), yet potentially usable livers such as the one described here are being discarded, due to uncertainty regarding their ability to support life following transplantation. This situation has been heightened in recent years by the use of livers donated after circulatory death or with other factors associated with poor outcomes (4, 5). The ability to assess dynamic liver function and hepatocellular injury following a period of warm and/or cold ischaemia enables an informed decision to be made regarding the suitability of an organ and may, as in this case, permit use of livers that would otherwise have been discarded. The period of normothermic perfusion also allows reperfusion to occur in the absence of some of the mediators of reperfusion injury, such as leucocytes, platelets and complement, and provides an opportunity to pharmacologically manipulate the liver to further reduce reperfusion injury in the recipient.

This is the longest reported successful period of storage of a human liver before transplantation, with normal cold storage times being less than half the 26 hour period herein reported. The extended preservation in this case, involving an intermediate period of normothermia sandwiched between two extended periods of cold ischaemia, suggests that *ex situ* evaluation and treatment of the liver may take place remote from the transplant centre, to where it may be transported by traditional simple cold storage for implantation. Such a hub and spoke model may be the future of organ assessment and resuscitation of marginal organs before transplantation. In an era when proposed changes in liver allocation in the US are causing concern regarding possible increased cold ischaemia times and the deleterious consequences, techniques such as normothermic perfusion hold much promise.

Figure 1. Biochemistry (a) during perfusion and (b) following transplantation.

Lactate concentration in the perfusate fell rapidly during the first hour of normothermic perfusion (1a) with minimal transaminase release. Post transplant liver function is shown in (1b).

Figure 1a

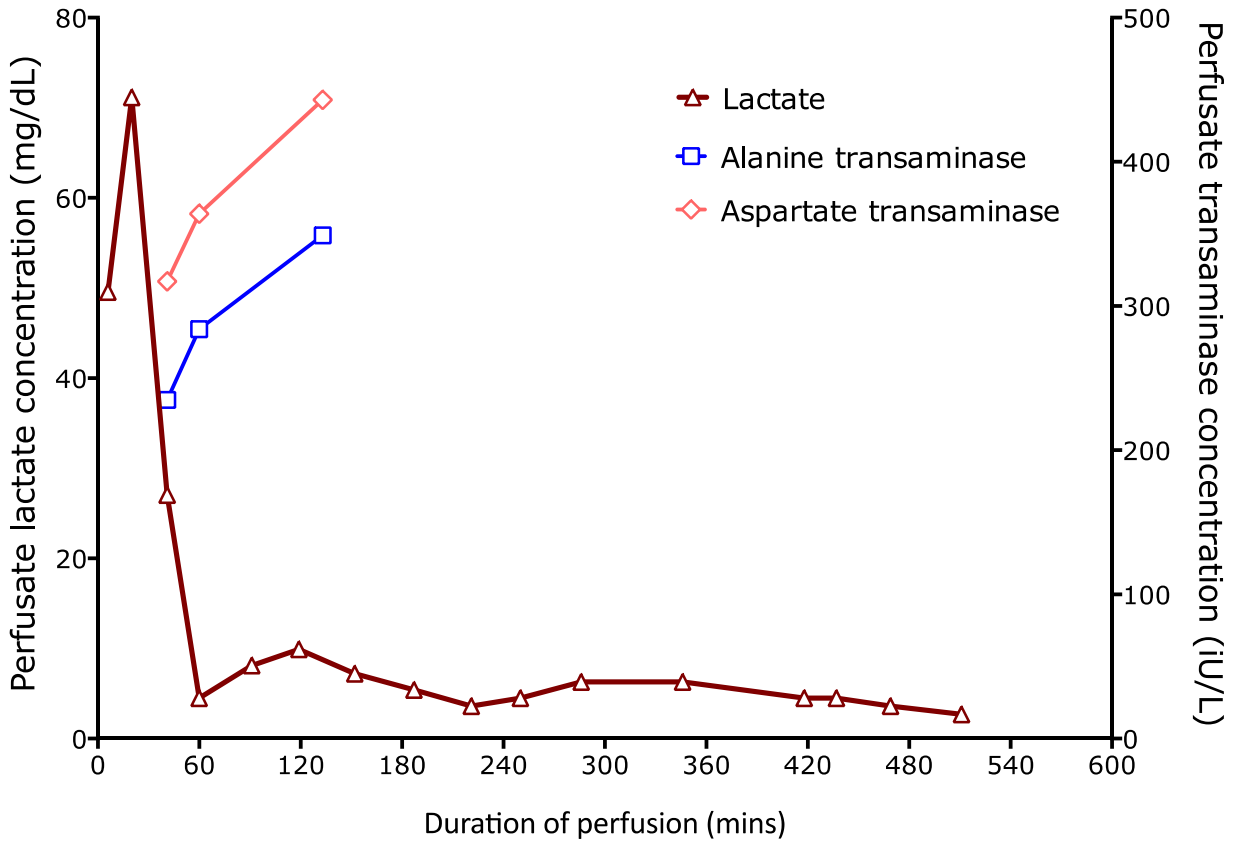
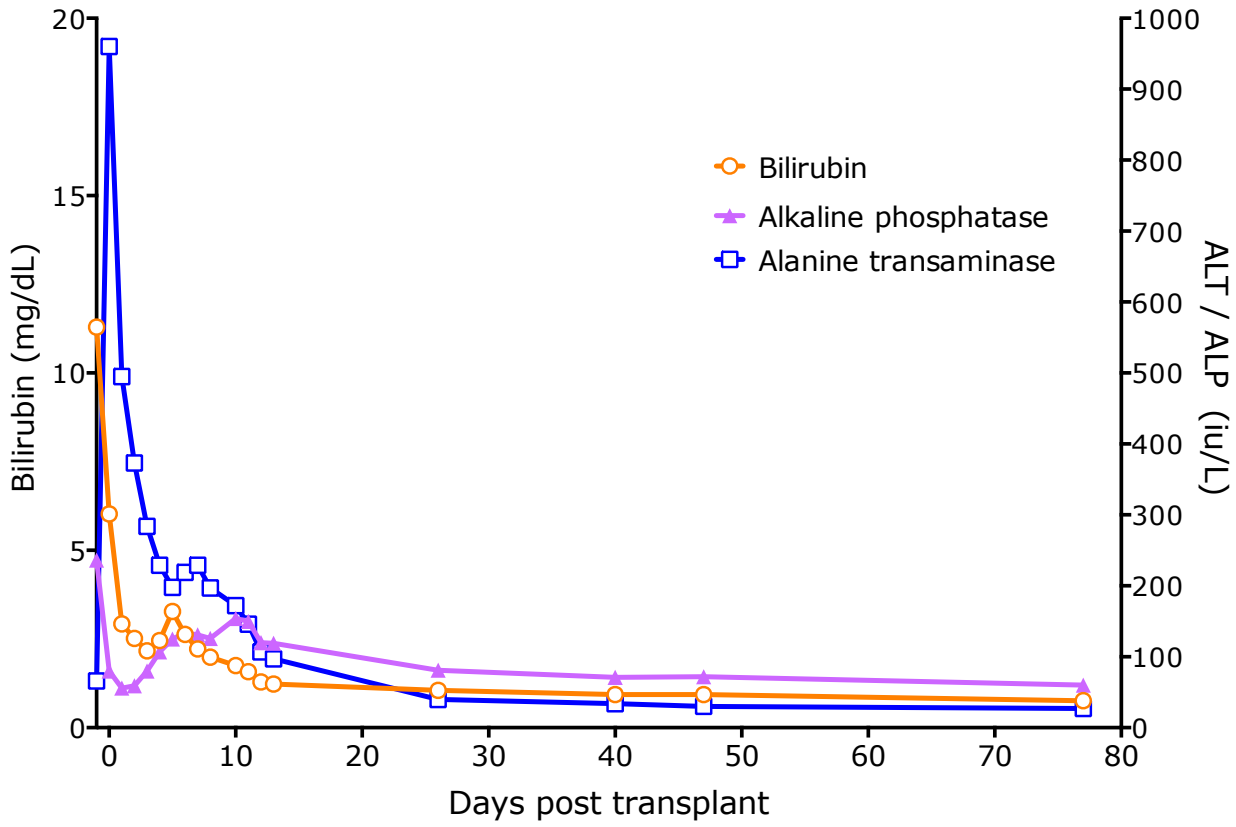


Figure 1b


Bilirubin
Alkaline phosphatase
Alanine transaminase
Bilirubin (mg/dL)
ALT / ALP (iu/L)
Days post transplant
0
5
10
15
20
0
100
200
300
400
500
600
700
800
900
1000
0
10
20
30
40
50
60
70
80

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