More and better donors for cardiac transplantation

John H. Dark

Freeman Hospital and Newcastle University, Newcastle upon Tyne, UK

Online publish-ahead-of-print 27 May 2009

This editorial refers to ‘The haemodynamic effects of adjunctive hormone therapy in potential heart donors: a prospective randomized double-blind factorially designed controlled trial’, by R.V. Venkateswaran et al., on page 1771

Cardiac transplantation is unrivalled as a treatment for end-stage heart failure. Nothing else offers the degree of improvement in both symptoms and survival. Whilst transplantation can never be the solution to the epidemic of advanced heart failure, for the fortunate few recipients it is very effective, and outcomes continue to improve. The inexorable decline in transplant activity is thus doubly frustrating.

In the EuroTransplant area there were 782 cardiac transplants in 1997, falling to 577 ten years later. Lung, liver, kidney, and pancreas transplants all increased in this period. Over the same time period there was an almost catastrophic fall in UK activity, from 220 to 127. Overall numbers of organ donors remain largely unchanged, but the demographics—age and disease profile—are unhelpful to cardiac transplantation. In 2009 the typical donor is a middle-aged female dying of an intracerebral haemorrhage perhaps related to untreated hypertension. Concomitant left ventricular hypertrophy and coronary artery disease exclude use of the heart when other organs will still function well after transplant.

As the proportion of donors with usable hearts falls below 20%, optimization of as many ‘marginal’ organs as possible is essential. To an extent, because of the damaging effects of brainstem death and subsequent ischaemia and reperfusion, all donor hearts are ‘marginal’—they all show some dysfunction. Primary graft failure is by far the most common cause of early death after a transplant, and is difficult to manage satisfactorily. There is therefore benefit in optimizing function in all donors. The importance of donor management is widely recognized, and guidelines and recommendations abound. They are based on laboratory studies of the physiology of brain death, and a handful of clinical series. The latter are almost entirely retrospective.

Thus observations of the cardiac effects of brain death, made 20 years ago in baboons, were coupled with observations of falls in tri-iodothyronine ($T_3$) levels in patients who became organ donors. This led to the administration of additional $T_3$, and an apparent improvement in some haemodynamic observations compared with historical controls. When the group at Papworth hospital demonstrated a very real increase in the yield of donor hearts from previously ‘marginal’ donors treated with a cocktail of $T_3$, steroids, and vasopressin, it became widely used. There was further support from a large retrospective study and finally the blessing of a Consensus Conference. Some of the data for $T_3$ in particular were inconclusive, and based on small numbers. Out of >10 000 donors in the oft-quoted Rosendale study, only 6.8% received the ‘cocktail’, and only 47 (<0.5%) had $T_3$.

In their recent report, Venkateswaran and colleagues have replaced questionable evidence with elegantly established clinical fact. Good clinical studies of donor management are rare because they are so difficult to perform. Heterogeneity of subjects, problems of consent, and the sometimes unhelpful environments of unfamiliar hospitals present huge challenges. The Birmingham group studied 80 donors in a prospective fashion and with invasive haemodynamic monitoring. They compared two components of the hormone replacement therapy cocktail, $T_3$ and methylprednisolone (MP) in a double-blind, placebo-controlled 2 x 2 factorially designed trial. The design, coupled with the statistical techniques to confirm non-interference, is a wonderful demonstration of how to gain a lot of information from a limited group of patients.

In this meticulously performed study, neither intervention proved advantageous. More than 50% of donors had low $T_3$ levels at the start, but there was no association with baseline haemodynamics. All those in the treatment arm reached therapeutic levels, with again no advantage over untreated controls. A similar lack of effect was seen for MP.

What are the implications? $T_3$ can be discarded in donor care. This will save effort, and a little money, but there may be other
advantages. Hepatic function may be less good in ‘cocktail’-treated liver donors. This is backed up by recent mouse studies showing that both steroids and thyroxine are bad for the reperfused steato-
tic liver, with thyroid supplementation in particular associated with more hepatic necrosis. 9

The position of MP is more problematic, as the authors admit. Brain death is followed by the generation of high levels of inflam-
mmatory cytokines, which may be damaging to all organs. Expression of tumour necrosis factor-α (TNF-α) in the donor heart is associ-
ated with poorer outcomes. 9 Steroids given early benefit the lung in experimental models, 10 and probably have clinical benefit. 11

The most important lesson from this study is that active inter-
vention, with measurement of flow, substitution of vasopressin for vasoconstrictors such as noradrenaline, and optimization of filling pressures, results in more and better donor hearts. Thirty-five percent of hearts initially regarded as unsuitable for transplant were improved to a position where they could be used, and for those transplanted (10 out of 14) there was no early mortality. Only by assessing flow can appropriate adjustments to vasoconstrictors (almost invariably needed because of the post-
brain death vasoplegia) be made. The cardiac transplant team must insist on invasive monitoring and titration of vasoconstrictor, and must be prepared to consider a much greater proportion of donor hearts as potentially usable, and therefore worth optimizing. Vasopressin is more logical than noradrenaline, although the latter, because of ease of adjustment, has become the drug of choice in neurosurgical intensive care units. Catecholamines increase myocardial oxygen consumption and deplete high energy substrates in the donor heart. In anything more than a modest dose (0.07 μg/kg/min) noradrenaline is associated with worse cardiac recipient outcome. 12 For cardiac patients it is a drug to be avoided in this setting.

To a certain extent this is also true for the recipients of other organs. Donors donating hearts are more likely to donate kidneys, with a higher primary function rate. The goal should be of improving the cardiac function of all donors.

Unfortunately, what is best for the heart is not always best for the other organs, and abandoning catecholamines may not be the ideal. Dopamine, for instance, has an anti-inflammatory effect in the kidney’s of brain-dead donors, reducing monocyte infiltrata-
tion and major histocompatibility complex (MHC) class II and P-selectin expression, and preventing TNF-α up-regulation. 13 Noradrenaline has similar effect in the lung, and β-stimulation speeds absorption of fluid from the alveoli. In one substantial series, kidneys from donors treated with catecholamines had better early and 4-year survival compared with those given no ino-
tropes. 14 It is not clear to what extent all these effects stem from the specific drugs, and which are related to the general benefit of better perfusion and higher cardiac output. In the brain-dead rat, vasopressin, almost certainly by improving blood pressure, reduces systemic and intra-alveolar inflammatory cytokines 4 h after the cerebral insult. 15

In summary, this report from Venkateswaran et al. provides for better and more scientific management of the cardiac donor. The next challenge is to confirm that better cardiac output and blood pressure is better for all the organs coming from brain-dead donors, and that good, active management is of benefit to all our recipients.

Conflict of interest: none declared.

References
4. Wheelton DR, Potter CD, Oduo A, Wallwork J, Large SR. Transforming the ‘unacceptable’ donor: outcomes from the adoption of a standardized donor man-
7. Venkateswaran RV, Steeds RP, Quinn DW, Nightingale P, Wilson IC, Mascaro JG, Thompson RD, Townsend JN, Bonser RS. The haemodynamic effects of adjunctive hormone therapy in potential heart donors: a prospective randomized double-
8. Elliott JD, Evans ZP, Fiorini JH, Fiorini RN, Haines JK, Schmidt MG, Chavlin KD. The use of the Papworth Cocktail is deleterious to steatotic livers after ischaemia–
9. Birks EJ, Burton PB, Owen V, Mullen AJ, Hunt D, Banner NR, Barton PJ, Yacoub MH. Elevated tumor necrosis factor-alpha and interleukin-6 in myocar-
10. Wigfield CH, Golledge HD, Flecknell P, Kirby J, Dark JH. Ameliorated reperfusion injury in lung transplantation after reduction of brain-death induced inflam-
15. Rostron AJ, Avlonitis VS, Cork DM, Grenade DS, Kirby JA, Dark JH. Hemody-