Hormonal resuscitation therapy in the management of the brain-dead potential organ donor

In the early 1980s, experiments at the University of Cape Town Medical School by Novitzky and his colleagues demonstrated that brain death, as suffered by all deceased organ donors, had several detrimental effects on organ function. These experimental observations, and their more recent impact on the clinical management of human brain-dead potential organ donors, have recently been reviewed.1

Initially, the extreme vasoconstriction that takes place when the brain is compressed within the skull leads to a short-lived, but devastating, catecholamine 'storm', that is a result of endogenous catecholamine release from post-ganglionic sympathetic nerve endings.2-4 This results in a significant elevation in systemic vascular resistance, leading to systemic hypertension. In extreme cases, the great increase in systemic vascular resistance can cause acute left ventricular failure, with a fall in cardiac output, and even acute transient mitral valve regurgitation, associated with an increase in left atrial pressure. In view of the blood volume displacement into the venous compartment, with pulmonary volume overloading, pulmonary edema and hemorrhage may also develop.5,6 This period of hemodynamic stress is associated with cardiac arrhythmias, and ischemic changes may be seen on the electrocardiogram.5

The transient hemodynamic sequelae of brain death can lead to significant histopathological injury to the myocardium, that can include cell necrosis, and to the lungs.3-5 These changes alone may jeopardize the immediate function of the heart and lungs after transplantation.

However, of even more interest and significance are the endocrine changes that were observed after the induction of brain death.2,4 Plasma levels of free triiodothyronine (T3) and free thyroxine (T4) fell to less than half of control levels within 1 h, and became undetectable a few hours later, even though thyroid-stimulating hormone showed no significant change. Insulin and cortisol levels showed significant declines, and antidiuretic hormone was undetectable within 6 h.5

These endocrine changes were demonstrated to be associated with a marked reduction in utilization of glucose, pyruvate, and palmitate, with an accumulation of tissue and plasma lactate and plasma-free fatty acids, indicating a decrease in aerobic metabolism in the donor.5 Myocardial energy stores are rapidly depleted,6 and it is these changes that almost certainly account for the fact that most brain-dead subjects undergo hemodynamic collapse within 24-48 h, if untreated. These observations indicate that, following brain death, there is a progressive mitochondrial inhibition, and eventually all cells lose the ability to generate ATP via the Kreb’s cycle.

Further experimental studies assessed the effect of hormonal replacement therapy after brain death.6,8 Intravenous therapy in experimental animals, consisting of T3, cortisol, and insulin, demonstrated a substantial increase in glucose, pyruvate, and palmitate utilization, accompanied by a reduction of plasma lactate and free fatty acids, indicating a reversal from anaerobic to aerobic metabolism.7 Myocardial energy stores returned to normal or near-normal values, as did cardiac output and stroke volume.6,8

In an initial clinical trial of hormone replacement therapy at Groote Schuur Hospital in Cape Town, 21 consecutive brain-dead donors were treated with traditional therapy (IV fluids, inotropes, and bicarbonate) but, in addition, received T3, cortisol, and insulin at hourly intervals.9 When compared with 26 historical control donors treated only with standard therapy, the hormone-treated donors showed restoration of their low T3 levels to normal, accompanied by significant hemodynamic improvement, with significantly less demand for inotropic support and bicarbonate. In addition, all electrocardiographic abnormalities disappeared and all 21 hormone-treated donor hearts were transplanted with satisfactory immediate cardiac function.

Several other groups investigated the role of hormonal replacement therapy in brain-dead potential organ donors, some of whom confirmed the data from the Cape Town group, and others who did not (reviewed in Ref.1). These discrepancies may have been for a number of reasons. For example, not all brain-dead donors have total absence of
anterior pituitary function, some groups failed to measure free-T3, not all donors are hemodynamically unstable and therefore may not benefit from T3/T4 therapy, and an inadequate dosage of T3/T4 may have been administered.

However, in March 2001, a conference took place in the US, attended by nearly 100 transplant professionals, with the aim of maximizing the number of organs recovered and transplanted from deceased donors.10 The conference recommended that 4-drug hormonal resuscitation (T3/T4, methylprednisolone, insulin, and arginine vasopressin) of donors with a left ventricular ejection fraction of <45%, and/or unstable hemodynamics, should be initiated. The conference further recommended that the United Network for Organ Sharing (UNOS) should follow the conference guidelines, a recommendation that was implemented by UNOS.11

Recent data from UNOS have indicated that, when 3-drug hormonal replacement (T3/T4, methylprednisolone, vasopressin) is administered, there has been a 22.5% greater number of organs transplanted from such donors than from donors not so treated.12 The increased probability of an organ being transplanted has been estimated to be between 2.8 and 7.3% for the major organs. A second UNOS study indicated that survival of patients whose donors have received hormonal therapy was significantly greater than those whose donors had not (89.9 vs 83.9%). In particular, early heart graft dysfunction occurred in only 5.6% of patients when the organ came from a hormone-resuscitated donor, but in 11.6% of patients when the donor had received no hormonal therapy. Furthermore, if the donor had received hormonal replacement therapy, significantly improved one-year kidney and heart graft survivals were demonstrated, although not for recipients of liver grafts.13

Almost 25 years after the initial experimental observations and the first clinical experience, therefore, hormonal resuscitation is becoming more widely accepted. Whereas only 8.8% of brain-dead organ donors in the US received hormonal therapy in the year 2000, 19.9% received such therapy in 2004.1

It has long been known that there is a significant depletion of free-T3 in patients being supported by cardiopulmonary bypass, and the Cape Town group demonstrated that the IV administration of T3 improves post-cardiopulmonary bypass cardiac function and reverses adverse metabolic changes.14,15 With regard to heart transplantation, they demonstrated the beneficial effect of treatment if both donor and recipient had received hormonal resuscitation therapy.16,17

References