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Graft protection in organ transplantation

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Preserving donor organs in optimal condition is a prerequisite for successful transplantation. The donor organ is subjected to a multitude of stresses. In this review, we will discuss the consequences of brain death on donor organs. The effects of an extended ischaemic period followed by the reperfusion necessary for the harvest, storage and implantation of transplant organs will be evaluated. As progressively more is known about the underlying pathophysiological mechanisms, focused and efficient therapeutic interventions can be developed. We will review current organ protection techniques and look at possible future strategies to further improve the final donor organ quality.

Key words: organ preservation; organ transplant; transplantation; brain death.

INTRODUCTION

Organ transplantation is a very specialised medical activity that, although limited in number, is often the best opportunity to add quality life time for patients with terminal organ failure. The Eurotransplant region, for example, numbers well over 124 million inhabitants in Austria, Belgium, Croatia, Germany, Luxemburg, the Netherlands and Slovenia. In this region, total transplant activity has been only slightly increasing, with a total number of around 6600 transplants per year.[1] About 800 of these transplants are performed with donor organs from a living donor, but the majority of donor organs are procured from brain dead donors. Limited donor availability is the most important factor preventing further growth in transplant activity. Organ transplantation is the pre-eminent surgical activity in which organ protection is required. Fortunately, improvements in

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anaesthetic techniques, organ protection, immunosuppressive strategies as well as growing experience have improved patient and organ survival.

The transplanted organ is subjected to many stresses, which can be roughly divided into three episodes. The first comprises the time that the graft is still in the donor. During this period, the organ is subjected to the insult that leads to brain death, the brain death process itself and the consequences of remaining for hours in an environment with a plethora of haemodynamic, endocrine and metabolic disturbances. The second episode is the process of organ retrieval, transport and reimplantation. This time is characterised by a considerable period of ischaemia. The third episode is reperfusion, with potential reperfusion injury and the first attacks by the recipient's immunological system. Since the second and third episodes, in particular, are foreseeable, they have the largest potential for protective interventions.

In this review we will focus on several pathophysiological mechanisms in the different episodes of potential harm to the graft and possible ways to influence them. Our knowledge is still partial and future investigations will need to clarify these items further.

BRAIN DEATH PHASE

Fewer than 15% of transplant organs are derived from living donors for kidney or partial liver transplantation. Because of the shortage of donor organs from brain dead people, the proportion of living donors is increasing.[1] An even smaller proportion of organ donors are non-heart-beating donors for lungs[2], kidneys[3,4] and livers[5] and this is an area of intense research.

Most donor organs are, thus, explanted after brain death. Although some inconsistencies in clinical criteria and technical examinations still exist, the concept of brain (stem) death has gained worldwide acceptance.[6] Brain death has a clinically relevant, deleterious impact on organ survival, as is demonstrated in the most recent 2004 kidney graft adjusted survival data from the Scientific Registry of Transplant Recipients, with a 1-year graft survival of $90 \pm 0.3\%$ for a deceased donor vs. $95 \pm 0.3\%$ for a living donor.[7] The same has been shown in experimental liver transplantation.[8] Moreover, it was experimentally shown that hearts from brain dead donors are rejected at an increased rate.[9]

Usually brain death is due to a sudden or gradual increase in intracranial pressure and herniation of the brain stem. This causes progressive ischaemia in the pons, the medulla oblongata and cranial parts of the spinal cord. This has profound effects on the cardiovascular, pulmonary and endocrine states.

The mixed vagal and sympathetic stimulation caused by pontine ischaemia causes the Cushing response, which consists of bradycardia, hypertension and irregular breathing. As the ischaemia expands in a caudal direction in the medulla, this Cushing response gives way to unopposed sympathetic stimulation with tachycardia and hypertension. Later a progressive loss of spinal sympathetic pathways occurs and total sympathetic denervation ensues.[10] The incidence and severity of these changes depends on the rate of development of intracranial hypertension and the exact location of the insult.[11]

The intense sympathetic outflow that occurs during the brain death process leads to an up to 800% increase in the levels of the circulating catecholamines dopamine, epinephrine and norepinephrine, both in experimental models and in clinical observations.[11–14] This probably is still an underestimation of the concentrations found at the synapses, especially for norepinephrine.[15] This 'sympathetic storm' during the brain death process causes intense vasoconstriction. In Table 1, organ blood flows and