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Heart Transplantation after a Prolonged Series of Cardiac Arrest: a Matter of Ischaemic Preconditioning?

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Highlights

We present the case of a successful heart transplantation from a donor that suffe ed an out of hospital cardiac arrest lasting approximately one hour.

Keywords: transplantation; preconditioning; reperfusion

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The recipient, a 27-year-old female nurse, was diagnosed with arrhythmogenic right ventricular cardiomyopathy in 2012. Echocardiography demonstrated a severely dilated right atrium and an aneurysmal, hypocontractile right ventricle. The left ventricle (LV) appeared small and compressed. Moderate tricuspid regurgitation was present with a mean pulmonary pressure of 25mmHg. She underwent an implantation of a triple-chamber cardioverter-defibrillator in 2013. Repeated electrocardiogram (ECG) recordings showed that the patient was in sinus rhythm with persistent T-wave inversions across pre-cordial leads V1 to V5.

The donor was a 24-year-old male from France, holidaying in Malta during the popular summer season. He had no past medical history of note. After consuming an unknown quantity of alcohol and cocaine aboard a yacht berthed about 100 metres from the shoreline, bystanders saw him floating face-down in the sea and dragged him onto the sandy shore. When he failed to respond, emergency services were called. No cardiopulmonary resuscitation (CPR) was performed at this point and an ambulance took approximately 7 minutes to arrive.

Upon arrival at the scene, paramedics found the patient to be pulseless and started CPR. The length of time that he spent in the sea was unknown, being spotted floating by onlookers from another vessel. Sea temperature was around 23°C. Return of spontaneous circulation (ROSC) occurred after 20 minutes of CPR on site. However, the patient arrested again in the ambulance and CPR was performed until he arrived at Mater Dei Hospital, still in cardiac arrest. ROSC was achieved after a further 23 minutes of CPR in the Emergency Department but the patient arrested three more times before achieving a stable circulation (Figure 1). He was transferred to the intensive care unit on high doses of Noradrenaline and Adrenaline to maintain an adequate mean arterial blood pressure. An initial echocardiogram (ECHO) revealed a hypocontractile left ventricle (LV) with an estimated ejection fraction (EF) of 30%.

Over the following 3 days the patient's cardiac function improved. He was weaned off inotropic support and a repeat ECHO showed a normal LV with an EF of 70%. A brain MRI showed diffuse swelling consistent with global hypoxic injury with wide areas of cortical and basal ganglia infarction. He remained ventilated and failed to recover spontaneous respirations. He was confirmed brain dead on two separate brain death tests. The patient's parents gave their consent and he was offe ed for organ transplantation on day 6. The operation was successful, with the recipient making an uneventful recovery. She received immunosuppressive treatment with cyclosporine, prednisolone and azathioprine and experienced one episode of early mild rejection with full resolution. She remains well 15 months later.

Discussion

Ischaemia-reperfusion injury (IRI) describes the cellular damage caused by an interruption to a tissue's blood supply and the subsequent return of blood flo . Certain tissues develop a

Figure 1. The patient's transport to the Accident and Emergency Department with episodes of cardiac arrest illustrated by red circles. Markings represent 5 minute intervals.

protective mechanism against IRI if first subjected to short episodes of ischaemia before the final, prolonged arrest of blood flo . Murry et al. first described Ischaemic Preconditioning (IPC) in 1986[1]. The authors noted that intermittent episodes of ischaemia slowed down the depletion of Adenosine Triphosphate (ATP) from cells during a subsequent, sustained period of ischaemia. Two windows of cardio-protection following IPC were identified. The first window, which occurs after 20 minutes is mediated by cellular signalling pathways and their concerted effect on the mitochondrial permeability transition pore (mPTP). The second window, which occurs after 24 hours, is due to genetic transcription, with the production of protective enzymes such as induced nitric oxide synthase [2]. The various molecular pathways are complex and beyond the scope of this article. They are tabulated in Table 1 and summarised in Figure 2.

Since its first description, surgeons and clinicians have been keen to test the therapeutic implications of IPC in patients. Various clinical trials in coronary bypass and valvular heart surgery were undertaken, each simulating a preconditioning stimulus by means of aortic cross-clamping and de-clamping and using diffe ent parameters of cardiac injury, from myocardial ATP levels [3] and blood markers of myocardial necrosis (CK-MB and troponin) [4] to ventricular arrhythmias and LV contractile function [5]. In 2008, a meta-analysis of 22 randomized controlled trials that involved 933 patients over a 10-year period concluded that ICP of this nature reduced post-operative arrhythmias, inotropic support and duration of intensive care unit stay for cardiac surgical patients [6].

In 1995 Manché et al investigated the effects of IPC on beating donor rat hearts perfused with oxygenated blood from a support rat in order to characterize the relations between the duration of ischaemia and the extents of early and late recoveries of function.[7] Hearts were subjected to graded intervals of ischaemia ranging from 10 minutes to 80 minutes before allowing 60 minutes of reperfusion. Longer recovery times were noted for those hearts that experienced a preconditioning stimulus longer than 30 minutes, suggesting that ischaemic times longer than this are harmful rather than cardio-protective. A subsequent double-blind randomized controlled trial on the cardioprotective effect of remote IPC on donor hearts in patients undergoing heart transplantation was published in April, 2019 with favourable results [8].

The authors cannot in any way be certain of the reasons for the favorable outcome of this heart transplantation following

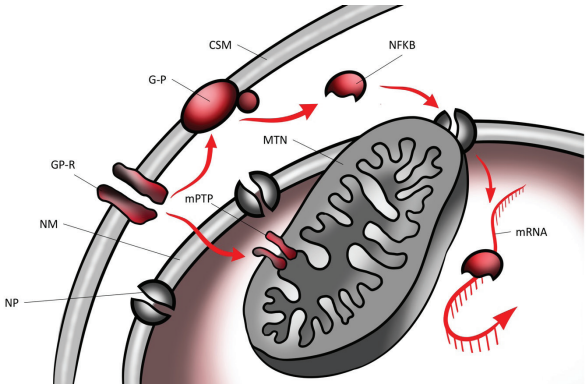

Figure 2. The molecular pathways involved in the two 'windows' of cardio-protection following ischaemic preconditioning. CSM cell surface membrane; GP G-protein; GP-R G-protein coupled receptor; NM nuclear membrane; NP nuclear pore; mPTP mitochondrial permeability transition pore; MTN mitochondrion; NFKB nuclear factor kappa beta; mRNA messenger RNA

Table I. An outline of molecular pathways involved in Myocardial Conditioning

Triggers	Signal transducers	End-effectors
IPC First Window		
Adenosine, bradykinin, opioids	Protein kinases, phosphorylases, proteinases	Ion channels, mitochondrial enzymes
G-protein + cGMP + NO	PKG	mPTP
G-protein + RISK	PKB, ERK, GSK 3 Beta	Cytochrome C
SAFE + TNF-alpha	JAK, STAT 3	Caspases
IPC second window		
	JAK, NFK- B, activator protein-1 hypoxia inducible factor-1	iNOS, Cox-2, aldose reductase, mSOD, HSPs

IPC ischaemic preconditioning; cGMP cyclic guanosine monophosphate; NO nitric oxide; PKG protein kinase G; RISK reperfusion injury salvage kinase; PKB protein kinase B; ERK extracellular regulated kinase; GSK glucose synthase kinase; SAFE survival activating factor enhancement; TNF tumour necrosis factor alpha; JAK janus kinase signal transducer; STAT-3 signal transducer and activator of transcription; mPTP mitochondrial permeability transition pore; NFK-B nuclear factor kappa B; iNOS induced nitric oxide synthase; COX-2 cyclo-oxygenase type-2; mSOD mitochondrial superoxide dismutase; HSPs heat shock proteins

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cardiac arrest. It is interesting to speculate whether the repeated episodes of cardiac arrest led to sub-lethal cardiac ischaemia and resulted in ischaemic preconditioning of the donor heart. The 9 episodes of cardiac arrest, each ranging from 3 to 23 minutes, are supported by experimental evidence on IPC, where longer periods of ischemia preceding an index ischaemic event were found to significantly affect cardiac function.[8] Donor hearts are increasingly being harvested following circulatory deaths in an effort to broaden the donor pool. More focused studies on the effects of ischaemic preconditioning in the course of cardiac transplantations such as the one described here may shed more light on the clinical significance of this phenomenon. They might include an endomyocardial biopsy after a period of IPC, as well as metabolomic profiling and troponin assays. Such studies might have supported the authors' impression that IPC was at least partly responsible for the dramatic increase in LV ejection fraction from 30% to 70% and we therefore recommend that they should be undertaken in similar cardiac transplantation scenarios.

Declarations of interest

The authors declare no conflicts of inte est.

Acknowledgements

The authors state that they abide by the "Requirements for Ethical Publishing in Biomedical Journals" [10].

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