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Editorial

Extrapolating novel techniques utilised in solid organ transplantation to the microsurgical and vascularised composite allograft arena

Under ideal circumstances, autologous free tissue transfer is performed with short ischemic times. However, in some cases the ischaemic period is extended: for example, when communication between teams is poor; when there are problems with inset; or when the donor or recipient vessels are in a suboptimal state due to atherosclerosis, radiotherapy, or trauma and more challenging for anastomosis.[1] In these cases, there may be a role for plastic surgeons to adopt some of the anti-ischaemia reperfusion injury (IRI) practices used in solid organ transplantation (SOT). In allogeneic solid organ, or composite free tissue transfer/vascularised composite allografts (VCA) such as limb transplant, IRI is inevitable and methods to reduce the IRI are more closely studied. Modalities that have been utilised include cold storage; flushing out the blood within the organ with preservation solutions such as University of Wisconsin solution[2] combined with hypothermia in static cold storage[3]; heterotopic temporary re-vascularisation[4]; pharmacological manipulation[5] such as administering steroids, dextran, anti-oxidants, and most recently dynamic machine perfusion preservation, either hypo- or normothermic.[6,7]

Knowledge of current trends in SOT IRI reduction should be discussed by plastic surgeons to assess whether certain facets can be extrapolated into the plastic and reconstructive armamentarium. Three important approaches are discussed below:

Cold flush: it is standard SOT practice to flush blood from the organ (to remove potential toxic metabolites).[2,8] It is unclear why this technique has not been adopted in free flap (or replantation) practice, and there is minimal data in the literature to explain this paucity. Flushing of vessel ends to remove clot prior to performing anastomosis is not associated with increased flap survival[9] but formal thorough large volume flushing (i.e. through the artery and out of the vein) has not been adopted by microvascular surgeons, perhaps for fear of "separating/damaging endothelial layer of artery"[10], although there is no evidence for this to be the case.[11] The effect of flushing in SOT is to eliminate what would be static prothrombotic and proinflammatory blood mediators stagnant in the microvasculature and infuse the organ parenchyma with preservation solutions designed to limit cellular ischaemic injury. Such flushing is practiced in VCA transplantation and benefit of this simple manoeuvre in this setting has been reported in an experimental porcine limb model.[12] Hypothermia is induced (by flushing of cold preservation solution through the organ) in the SOT prior to and during transport and fastidiously maintained until the point of reperfusion. Hypothermia reduces cellular metabolism via van't Hoff's equation[8,13], allowing time for transport, and preparation of the recipient.

Machine perfusion: This can be hypothermic or normothermic. Hypothermic machine perfusion (HMP; controlled re-circulation of preservation solution through the target organ at hypothermic temperatures) is rapidly becoming the preferred preservation modality in abdominal organ preservation. Recently, experimental models of machine preservation of in-situ porcine abdominal wall flaps have highlighted improved tissue viability, and opportunities for flap pharmacological manipulation[14], particularly targeting thrombosis in the context of prevention or salvage of a thrombosed graft. This may certainly lend benefits in tissue transplantation in high risk groups. Furthermore with recent advances in novel normo-and subnormothermic organ preservation[15] the potential opportunities for wider use of ex-vivo machine perfusion strategies in clinical practice may become a reality.

Pharmacology: traditional protocols using systemic anticoagulation to minimise thrombosis-related complications have been adopted when required, but risk significant perioperative bleeding due to the nature of their systemic ad-

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ministration.[16] The role of coagulation cascades in IRI and their interface with the inflammatory response has only recently started to be appreciated.[17] Novel cytotopic endothelial localising proteins that target the coagulation cascade and complement system, such as thrombolexin administered into the target organ bed, have been described in animal and pre-clinical human models. They have the potential to target the free flap itself, limiting local detrimental IRI-related injury, whilst ameliorating systemic bleeding risks and associated complications.[18,19] Using a HMP thrombolexin delivery model in porcine kidney grafts achieved a 50% improvement in micro- and macrovascular tissue blood flow with less coagulopathy than controls during subsequent normothermic haemo-reperfusion. Thus, specifically targeting the flap and delivering therapeutics locally to its microvasculature prior to re-anastomosis, is both an ideal and potentially a more effective strategy than systemic post-transplantation (or re-plantation) pharmacotherapy. Furthermore as machine perfusion protocols for VCAs are developed there will likely be a renewed interest in interventions to therapeutically target other pathways involved in IRI [20,21] pre-treating grafts before transplantation.[20]

Addressing IRI related sequelae using novel approaches from the SOT arena has the potential to ameliorate some of its effects in high-risk, prolonged and complex free flap, replant and VCA surgery. Ongoing research will need to study the safety of and impact these potential interventions will have on acute complications but also in which subset of patients they would be most beneficial. This area is novel, dynamic and interesting, but cautious implementation is advised with scrutiny of future data.

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