

Machine Perfusion: The Paradigm Shift in Transplantation Technology

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Organ transplantation has been repeatedly referred to as the *medical miracle* of the 20th century [1]. End-stage single-organ failure has been finally eradicated as an irreversible condition [2], and a new generation of therapeutic modalities has been incorporated into our daily clinical and surgical practices under the large umbrella of transplantation technology [3-5].

Transplantation became a clinical reality following the initial consolidation of the practices involved in organ preservation [6]. Hypothermia was initially seen as an effective way to decrease the metabolic rate and preservation solutions were conceived as potent buffers against the inexorable metabolic acidosis fostered under anoxic conditions [7-9]. Osmolality and cell membrane integrity were initially sustained by major advances in the composition of these preservation solutions, which unfortunately experienced very limited changes from their initial inception over three decades ago [10, 11].

Organ preservation became synonymous with static cold storage and the field spent several years working around ways to maximize the unavoidable cold ischemia time (CIT) [12, 13]. The strategic *time gap* built by this technology allowed the subsequent development of new protocols and practices that involved tissue matching among several additional peri-operative logistics related to organ procurement and allocation [13]. For several years, CIT remained as the benchmark for organ function after allograft implantation [14]. The warm ischemia time (WIT) experienced during organ implantation would be followed by reperfusion and treated as an unavoidable additional delay for oxygenation in the transplantation process, where the combination of both the cold and warm ischemia times would then lead to a predictable cycle of ischemia/reperfusion (IR) injuries [15]. The combination of several donor and recipient factors were further implicated in the etiology of primary non function (PNF) and/or delayed graft function (DGF), where organ preservation seemed to play a seminal role in the magnitude of this induced inflammatory process [16]. Avoidable situations that led to PNF were progressively recognized and subsequently minimized. The long-term implications of DGF related to suboptimal features of organ preservation remain a significant problem in the field and still translate into unacceptable morbidity and mortality rates [17, 18].

Live donation revolutionized the field and fostered an effective reduction of the feared CIT, which created a new set of outcome expectations regarding short- and long-term graft function [19]. The impact of this new reality was so important that several concepts regarding the importance of tissue matching were explored [20]. The absolute reduction of IR injuries would go a long way when plotted against more extensive features of long-term allograft function. Could we minimize, even further, the deleterious effects of prolonged CIT?

Machine perfusion, as an alternative for organ preservation, was conceived even before the modern era of organ transplantation. It was initially used as the only effective method for organ preservation even before the inception of the modern preservation solutions [21-24]. The idea of having a perfusion system capable of sustaining circulation appeared to be physiologically sound. New devices were developed and the kidneys became the first organ to incorporate machine perfusion as a part of its routine post-recovery preparation [25, 26]. This was a big leap for transplantation technology which began to move beyond the strict medical and surgical arenas.

The Organ Procurement Organizations (OPOs) were the initial driving forces behind this new technological milieu. They were responsible for organ procurement and allocation and the natural site for an intended *ex-vivo* therapy aimed initially to extend preservation time and maximize organ utilization. The maximum number of organs potentially recoverable from a cadaveric donor is thought to be eight but the current organ utilization average is unfortunately around three in most regions [27]. Organ donation achieved a great milestone as a public initiative but continued to be eroded by a significant discard rate. The standard features of cold static preservation were unable to supply the ever-increasing market demand for additional organs with proven functionality. The unacceptable hourly mortality rate continued to be witnessed nationwide by patients already placed on the transplant waiting list [28].

As every biological mechanism aiming to emulate nature, the new devices faced additional questions regarding flow, pressure, and temperature [29]. The idea of extending the time of preservation itself was initially the biggest driving force behind the development of more efficient devices. Hypothermia remained sacred as a seminal condition to be sustained during the CIT and some minor changes in preservation solutions were witnessed [30]. Machine preservation gained momentum away from the foundation built for kidney transplantation and continued to move forward. The liver became the next targeted organ, and new devices were created along the way [31, 32]. The first clinical application for livers came finally in 2010 using a modified Belzer preservation solution within an adapted device capable of simultaneously perfusing the hepatic artery and portal vein vascular beds. The initial results were rather promising but were still seen with some residual skepticism [33].

Hypothermic machine perfusion continued to be extensively studied in spite of the additional claims regarding normothermic perfusion as an effective way to rescue otherwise unsuitable donors after cardiac death (DCD) [34]. Temperatures were increased and oxygenation was brought in as a way to fully support the metabolic needs during the *ex-vivo* stage [35-38]. Even blood was utilized in some models as an effective oxygen carrier, in spite of the clear limitation of this approach in daily clinical practice [37].

The search for the ideal preservation solution for machine perfusion remains elusive, but the literature seems to converge on the alternatives of using sub-normothermic conditions in combination with solutions with oxygen-carrier capabilities [39].

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The most striking clinical developments were led by the lung transplant group headed by Keshavjee in Toronto with a new device and a new solution that has generated a revolution in the clinical application of this technology [40]. The concept of *ex-vivo* therapy was fully introduced—from new supportive chemical optimization to striking genetically engineered applications [41]. *Ex-vivo* therapy finally reached the ability to promote immunomodulation through advanced vector technology and the precise ability to down regulate class I antigens. Machine perfusion created a new way to assess true organ function by promoting full oxygenation under a strict circulation protocol, where lungs were able to show for the first time their ability to function before the critical stage of organ implantation. Machine preservation had finally achieved a new degree of maturity, by allowing a safe “test drive” before organ implantation [42].

This revolutionary work brought up a rather interesting issue regarding the site of this complex activity—the hospitals were now capable of conducting advanced “organ rescue therapy protocols”, which would be a change from the traditional kidney model where the OPO was the center of this activity. Hospitals could now play the role of advanced organ rescue centers and this would eventually bring additional implications to the current system of organ allocation. Organs previously discarded in a systematic fashion were now capable of being safely utilized with this sophisticated *ex-vivo* therapy. The impact on effective organ utilization regarding lung transplantation in Canada has been nothing short of extraordinary as they were able to significantly increase their initial transplant volume based solely on the organs deemed initially as unsuitable.

Transplantation technology through effective translational research continuous to move at a very fast pace and we might be witnessing a major paradigm shift towards the new horizons for organ preservation.

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