Organ regeneration: with perfusion and purification, a turning point in the world of transplantation

Over ten years of work for the first human study on lung transplantability and patient survival after the perfusion and purification of the lungs. Significantly increasing the number of organs suitable for transplantation is possible thanks to "perfusion and purification" methods, which allow recovering a significant part of those that would otherwise be discarded.

The results are solid in terms of the percentage of the number of organs that could be transplanted and the fewer post-transplant complications, but also in terms of survival one year after transplantation. This was attested to – for the first time worldwide – by the Boffini et al. study published in August in *Transplant international*. The study deals with lung transplantation, but is also consistent with early clinical findings related to other organs such as kidneys and livers. The study also confirms the value and prospects of the application of systems for "cytokine removal" during the perfusion of organs for transplantation, implicitly confirming the results seen in many other clinical areas such as sepsis and septic shock, among others.

The medical staff involved work in the Department of Thoracic Surgery of the Turin City of Health and Sciences led by Professor Mauro Rinaldi. The method and system used refer to Aferetica (Biomedical SME of San Giovanni in Persiceto), in partnership with CytoSorbents (USA), world leader in life-saving systems.

San Giovanni in Persiceto (BO), 15 December 2023 – Press release

The Boffini et al. study (*Cytokines Removal During Ex-Vivo Lung Perfusion: Initial Clinical Experience*) published last August is unique in the world, both because it is the first study carried out with this method on lungs destined for transplantation, and because of the topics and numbers involved. Lasting 10 years (from 2011 to 2020), it demonstrated for the first time – on an unparalleled large case series of 54 lung treatments intended for transplantation – that the removal of "cytokines during Ex-Vivo Lung Perfusion1 (EVLP)" allows for a significant increase in the number of transplantable organs, reducing postoperative complications and significantly improving survival:100% of patients who received an organ treated with cytokine adsorption were alive one year after transplantation, compared to 64% of the group not treated with adsorption.

Lung transplantation is the best treatment for patients with terminal lung failure. It is a very delicate and complex organ failure to manage, as there are no applicable "replacement" therapies, such as dialysis for kidneys. In Italy there are currently more than 300 patients on the list waiting for a lung. The average waiting time is 2.5 years. These waiting times, combined with the complexity of the patients' clinical pictures, lead to high mortality on the waiting list. In 2021, of the 319 patients on the list, 58 deteriorated or died (approximately 18-20%). In 2022 a total of 138 transplants were performed in Italy (including 17 in Turin, an international centre of excellence). The underlying reason for the long waiting times and the great imbalance between supply and demand for lungs lies in the fact that only 20% of available lungs are considered optimal and are used for transplantation.

The low number of usable lungs is determined by many factors, some of them positive, such as the increasing average age of potential donors. Added to this are advanced age, smoking habits, days spent in intensive care and possible artificial respiration, and the presence of infections, all of which have a decisive impact on the quality of available lungs, and therefore on the possibility of using them for transplants. With this in mind "organ perfusion" techniques were born, the aim of which is to recover organs that were otherwise considered untransplantable. Organ perfusion makes it possible to keep the organ "active" after removal and before transplantation in order to assess its vitality and functionality, and if necessary to apply specific

treatments to further improve its quality. In the Boffini et al. study, the therapeutic treatment applied was cytokine removal using the CytoSorb® device. Fifty-four organ perfusion treatments were included in the study, 21 of which with Cytosorb®. This is an impressive number of cases, a total never been seen before in this sector. Note that the results of the study – limited to isolated organs – are also consistent with what has already been widely found with respect to the application of cytokine adsorption in other scenarios, such as in the treatment of critical patients (e.g. with inflammatory complications, patients with sepsis, septic shock, organ failure, etc.), i.e. what has already been observed with more than 200,000 treatments carried out with CytoSorb® and in more than 900 publications on experiences of use in a wide variety of clinical settings.

"The study leaves no doubt about the improved clinical outcomes, both in the immediate post-transplant period (reduced post-surgery complications) and in terms of survival one year after transplantation, which was significantly higher in the group treated with Cytosorb®. It is shown that the concentration of cytokines in the organ is a highly representative indicator of its actual quality for transplantation. Just as their removal has been proven to be effective in the recovery of organs that are defined as "marginal", i.e. barely and in many cases not at all suitable for transplantation. We have been working on this idea and this solution since the birth of Aferetica, which not coincidentally is about to turn ten years old. It is a solution that was made possible thanks to targeted research in collaboration with the most accredited transplant centres in Italy, and we thank them all for their efforts and cooperation. The Turin City of Science and Health is an excellent example. We began our adventure in the world of transplants by partnering with them nine years ago, and today we are seeing public – and highly acclaimed – results. We are proud of these collaborations with Italian and European clinics, just as we are proud of our partnership with CytoSorbents, which has opened up new frontiers, not only in transplantation but also in intensive care, cardiac surgery and many other clinical areas. We can absolutely say that a breakthrough has been made in the field of transplantation and organ availability, the beginning of a new era in Italy and the rest of the world", remarked ***Mauro Atti, CEO Aferetica***

*"We conducted a clinical trial, also thanks to the collaboration with Aferetica, applying perfusion techniques to make the organ breathe outside the body and sorbents to cleanse it of toxic substances before transplantation into the recipient. This was the first concrete example of the use of ex-vivo perfusion as a platform not only for organ preservation and assessment, but also for active manipulation through cytokine removal aimed at limiting damage and improving organ function. We're talking about a true reconditioning of the organ aimed at a further leap in quality in the transplantation process that we hope will help reduce the discrepancy between the availability of suitable lungs and the number of patients on the waiting list. Currently the perfusion technique alone has enabled us to increase the number of lung transplants performed by 20-30%, recovering organs that were initially discarded, with results that are comparable to if not better than those of standard organs. The experience reported in this study shows how with active interventions such as purifying the organ of cytokines and other toxic molecules these numbers can be further increased, both in terms of the number of organs available and in terms of better postoperative outcomes and post-surgery survival***." Prof. Massimo Boffini, Cardiac Surgery division Città della Salute e della Scienza Torino"***

"We applaud Professor Boffini and colleagues on the publication of their landmark study on the use of CytoSorb with ex vivo lung perfusion (EVLP) to improve in-hospital and 1-year survival in patients undergoing lung transplant. In the largest published human case series to date in this application, they were able recondition lungs using CytoSorb and EVLP driving excellent clinical outcomes. The ability to improve the quality and number of usable organs has broad implications in the transplant field for both patients and surgeons alike, potentially alleviating the chronic shortage of suitable organs for transplant.

We also congratulate our long-term partner, Aferetica, for their pioneering work and vision in the field of ex vivo organ perfusion, including the development of the PerLife® and PerLungs®

platforms, for liver and kidneys, and lungs, respectively. We are honored to be the exclusive supplier of their PerSorb® cytokine adsorbing cartridge internationally, which is specifically E.U. approved for ex vivo organ perfusion. Together, we hope to make the organ transplant waiting list a thing of the past." ***Phillip Chan, CEO of CytoSorbents,***

Starting from its experience and know-how in extracorporeal purification and dialysis in particular developed in the Mirandola area, Aferetica's insights have led to the deployment of Therapeutic Apheresis (purification seen as therapy) in a wide variety of clinical applications, in new worlds such as the treatment of organs for transplantation, an area in which Aferetica intends to position itself as a front runner both in Italy and abroad. CytoSorbents, a US company and leader in life-saving systems for the removal of inflammatory mediators for very serious diseases such as Sepsis – the leading cause of death in intensive care – and Covid-19, has chosen Aferetica as its exclusive global partner for Transplantation. This partnership also demonstrates Aferetica's ability to identify novel applications, where the synergy between the two technologies (Aferetica, Made in Italy and CytoSorbents, Made in the USA) promises to dramatically expand the availability of organs for transplantation.

Aferetica was born in November 2013 as an innovative start-up registered in the national register (Law 221/2012), within the incubator of the Mirandola Science and Technology Park. Since 2019, Aferetica has become an innovative SME. The area of intervention is that of THERAPEUTIC APHERESIS, the 'depuration/purification' seen as THERAPY. And it is precisely from this area that Aferetica positions itself on the national and international scene by offering innovative and integrated solutions for transplantation. In addition to transplantation, it is possible to intervene effectively and innovatively in vast and diversified clinical fields, such as: Neurology, Nephrology, Cardiac Surgery, Intensive Care. Aferetica's intuitions and know-how come from Aferetica's founders' decades-long experience in Medical Devices. The fabric of knowledge and experiences starts from what is historically specific to the Mirandola area, to open new frontiers, thanks to 'collaborative research'. Among the most important industrial partnerships is the one with CytoSorbents for the development of sorbent systems dedicated to its therapies. CEO: Mauro Atti (formerly Scientific Director of Bellco); Stefano Rimondi (Past president of Assobiomedica) is Chairman and founding partner of Aferetica; William Pulga (formerly head of Bellco's Intensive care sector) is a founding member and Sales Manager.

For more information: http://www.aferetica.com

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