Lung Transplantation for Idiopathic Pulmonary Arterial Hypertension:
Steps in the Right Direction

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In the last decade, there have been remarkable advances in the medical management of patients with idiopathic pulmonary arterial hypertension (IPAH). These therapies have improved the quality of life, saved many lives and in some cases obviated the need for lung transplantation. However, the reality is that the majority of patients with IPAH, even with access to the best medical therapy, continue to progress and will require lifesaving lung transplantation.

Lung transplantation for PAH has traditionally been viewed as a higher up front surgical risk lung transplant to perform, but with excellent long term survival and quality of life. The concern in the current management strategy for patients with PAH is, that by virtue of the seriousness of the condition, they tend to have the highest mortality on the lung transplant wait list and then, with the practice of listing them after they begin to fail first, second and sometimes third line medical therapies, they are in even poorer medical condition and generally deteriorating very rapidly. With a limited supply of donor organs, one can see that this might exacerbate the problem of wait list mortality in this particular patient population that cannot afford to wait. One can also appreciate then, that when the UNOS Lung Allocation Score (LAS) was initially introduced, this caused some concern regarding the potential for disadvantaging IPAH patients on the list. The LAS score was designed with the intent to optimize utilization of the scarce resource – donor lungs – by allocation of lungs to patients who have the best potential for a good outcome after transplantation, balancing mortality on the waitlist with survival probability after transplant.

To optimally treat patients with IPAH, the treating physicians in the IPAH and lung transplant community need to: i) optimize medical care, ii) optimize timing of listing for transplant, and iii) optimize management on the lung transplant waitlist to maximize the likelihood of successful lifesaving lung transplantation in the context of available donor organs.
and current listing guidelines and practices.

i) **Optimizing medical care of IPAH patients:** this is a large and growing field in which major advances have been made with the development of intravenous infusion therapies of prostacyclin and related analogues and other vasoactive drugs. As further research is carried out into the fundamental pathophysiology and underlying mechanisms of IPAH, additional advances have been and continue to be made with the development of oral and inhaled therapeutic pharmacologic formulations. Advanced molecular therapies such as gene therapy and cell therapy directed at correcting the underlying defects are the hope on the horizon.

ii) **Optimize timing of listing for transplant:** Initially, after the introduction of effective medical therapy for PAH, many patients were taken off lung transplant wait lists (appropriately so) as their condition improved significantly. Many patients were never considered for transplant as they were effectively treated medically from the time of diagnosis. The honeymoon ended at it became evident that many patients would become refractory to medical therapy and begin to deteriorate much more rapidly such that they often could not make it to transplant. The effect of the prostaglandin analogues on platelet function, in combination with warfarin anticoagulation made these patients even higher risk surgical candidates as these lung transplants are done on cardiopulmonary bypass and the ensuing coagulopathy lead to significant issues with perioperative hemorrhage and primary graft dysfunction. Recognizing these issues lead to changes in anticoagulation management practice which has decreased the bleeding risks. Furthermore, it has become general practice in experienced centers to have PAH patients assessed for possible lung transplantation early on in their disease course so that they can be
promptly listed if they begin to deteriorate. This is especially important in those patients that present in a significantly symptomatic state or who do not demonstrate a prompt positive therapeutic response when medical therapy is initiated.

**iii) Optimize management on the lung transplant waitlist:** Medical therapy of course continues while waiting on the transplant list. Close communication between the IPAH pulmonary physicians and the lung transplant team is crucial. It is very important that these patients are monitored very closely for signs of decompensation. The improved waitlist mortality in the medium to large volume centers described in this paper indeed likely reflects increased experience and access to escalating therapies in the larger centers. In previous years, when PAH patients began to deteriorate they were urgently listed for transplant and had to wait their turn based on time accrued on the waitlist. The pre-LAS system did not take severity of illness into account, hence patients with IPAH that were rapidly deteriorating had few options and had an excessive wait list mortality.

Patients with IPAH tend to die of progressive right heart failure or sudden cardiac death from secondary related arrhythmias when the heart just cannot pump any more against the high resistance of the diseased pulmonary vascular bed. An historical option used to palliate patients was the use of an atrial septostomy. Creating an atrial septostomy would decompress the pressure on the right heart for a period of time, but eventually led to death from biventricular failure secondary to hypoxic perfusion (right to left shunting) of the coronary circulation of the already failing heart. Another option that was sometimes used was extracorporeal lung support (ECLS) instituted in a veno-arterial perfusion conformation – usually femoral vein to femoral artery. This has the benefit of supporting the circulation of the severely decompensated patient,
but often is not successful in that it does not effectively address the right heart failure and the
very high pulmonary vascular resistance faced by the heart of a patient with end stage PAH.

We described the use of extracorporeal lung support in a unique fashion for PAH
patients\textsuperscript{1}. We placed the Novalung\textsuperscript{R} (Novalung, Germany) membrane in parallel to the
pulmonary circulation, canulating the pulmonary artery and the left atrium (right superior vein or
left atrial appendage) to effectively create a PA-LA shunt. The right ventricle provides the
pumping action and hence this membrane is used in a pumpless fashion to effectively create a
shunt which also oxygenates the blood while offloading the RV by providing a low resistance (6
mmHg at 1.5L/min flow across the membrane) path for ejection of blood from the right heart.
Since the introduction of this technology, we have decreased the lung transplant wait list
mortality for IPAH patients in the Toronto Lung Transplant Program from 22% to 0\%\textsuperscript{2}. ECLS
bridging to lung transplantation is an effective therapeutic option that will likely play an
increasing role in successfully managing patients on the lung transplant list, to decrease not only
wait list mortality, but also post lung transplant survival. These patients can be extubated and
ambulatory on ECLS and as such with successful PA-LA bridging come to surgery in far better
condition with a recovered right ventricle and recovery of hepatic and renal congestion/failure\textsuperscript{2}.

Mallidi and colleagues have studied in a competing outcomes analysis, the cumulative
incidence of lung transplant and mortality for waitlisted patients in the period preceding and post
the introduction of the UNOS Lung Allocation Score (LAS).\textsuperscript{3} The authors have duly
acknowledged the limitations of inferences made from the study of registry data. The most
important bottom line is that in this analysis, the LAS system does not appear to have
specifically disadvantaged patients with IPAH. In fact, to the contrary, this analysis reports that
despite of the fact that IPAH patients in the post–LAS era had worse comorbidities (reflected in
higher LAS scores), at two years the incidence of lung transplant as a competing outcome was higher (39% vs. 18%), the incidence of death on the waitlist was lower (23% vs. 31%), and furthermore the post-transplant survival was improved (80% vs. 65% at two years). All encouraging statistics supporting the contention that the LAS is functioning as intended to prioritize sicker patients for transplant and get these patients to transplant sooner. While LTx incidence doubled but post-LTx survival did not increase likely reflects that the patients are still very sick, or sicker, when they get to transplant.

This registry analysis however is not able to account for significant changes in practice that have occurred over the same time period. Importantly, the UNOS registry data does not collect data related to ECLS bridging to lung transplant. The finding that IPAH patients on the waitlist fare better in medium to large centers potentially alludes to this. Specialized centers with increased experience likely have knowledge of and access to progressive IPAH medical therapies and ECLS technologies for bridging patients. The LAS scoring system was intended to be a modifiable scoring system based on analysis of real data over time. Clearly this analysis and adjustment needs to be done to increase the fidelity of the scoring system. The authors have raised provocative questions regarding the role of cardiac index and donor - recipient gender matching that need to be evaluated in more detail. We will also need to look at how to allocate LAS points to patients on a ventilator vs. on extracorporeal lung support.

Conclusions

Major advances have been made in the treatment of patients with IPAH. While tremendous improvements have been achieved with medical therapy, the majority of patients will require lung transplantation. Our goal should be to continue to study underlying mechanisms of this
disease to develop therapies to prevent or treat IPAH and also maximize the access of all patients to donor lungs. Thankfully, the implementation of the LAS system appears to have improved the incidence of LTx and the waitlist mortality overall is also reduced. The association of improved outcomes in higher volume centers in dealing with complex patients is once again borne out. While this study is reassuring in that it appears that the LAS is doing what it was intended to do, the improvements in the parameters reported in this study clearly cannot all be attributed to the impact of implementation of the LAS system. As outlined, it is possible that the major advances in care that have occurred have had a significant effect and that the impact of the LAS itself may not be as large.

**Conflict of Interest Disclosures:** None.

**References:**


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