Editorial

Pulmonary transplantation—is it a long-term solution?

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The history of lung transplantation is a testament to the remarkable strides made in medicine. Through research, surgical innovation, and advancements in immunosuppression and immunomodulation, lung transplantation has evolved from a daring experiment to a life-saving procedure that offers hope to patients suffering from end stage lung diseases. While significant strides have been made in the field, improving long-term survival rates remains a key challenge.

It is interesting to note that while the first human to human heart transplant by Christiaan Barnard received international fame, the first human to human lung transplant did not garner as much attention. This was performed in 1963 by James Hardy at the University of Mississippi (1) in a patient diagnosed with advanced lung cancer. Despite the surgery itself being a success, this day in history was overshadowed by the tragic death of Medgar Evers, a prominent civil rights activist, who was shot on the driveway of his home and was brought to the University of Mississippi. Unfortunately, attempts at resuscitation were unsuccessful, and the first human lung transplant only found its way to the bottom corner of the morning newspaper's front page (2). While the patient's survival was short lived and only lasted eighteen days, this historic endeavor laid the foundation for subsequent efforts (3).

The first successful lung transplantation was reported in 1971 by Fritz Derom in Belgium (4). The patient was diagnosed with end stage silicosis and survived approximately 10 months post-transplant; however, he had spent most of his postoperative life in the hospital, making the palliative benefit of the transplant questionable (5). Lung transplants underwent another breakthrough in 1981 with double lung transplants with tracheal anastomoses.

Up until this time, all lung transplantations performed had been single lung transplants. Bruce Reitz and his team at Stanford University performed that first successful en bloc heart-lung transplant in a 45-year-old woman diagnosed with primary pulmonary hypertension (6). Five years later, Alexander Patterson and Joel Cooper performed the first successful double lung transplant in a 42-year-old woman with emphysema secondary to alpha1-antitrypsin deficiency (7). Despite the success, surgeons soon realized that en bloc lung transplantation with tracheal anastomosis had high rates of dehiscence. As a result, sequential double lung transplantation emerged with anastomosis being performed at the mainstem bronchus level. Interestingly, this technique, still used in practice today, was first described by Henri Metras in 1950 (8). Bilateral lung transplants have been recognized to show improved survival and lower incidence of bronchiolitis obliterans syndrome (BOS) (9-11).

While the advancements in surgical technique were key in contributing to better early survival, this gave rise to long term complications like chronic rejection. Perhaps nothing had a greater impact in this avenue than immunosuppression. The emergence and use of agents such as cyclosporine and tacrolimus, and induction therapy, were extrapolated from its benefits seen in patients who had undergone other solid organ transplants (12).

As the field of lung transplantation has continued to evolve past its nascent stages, we have now reached an era

where we are not limited by the technical aspect of this operation, but rather other factors. Patients who underwent lung transplantation before 2010 had a one- and five-year survival of 85% and 59%, respectively (11). Historically, most efforts focused on improving survival in the first post-transplant year. While there have been some significant milestones which have contributed to improving survival like the implementation of the Lung Allocation Score, utilizing donation after circulatory death (DCD) donors and using ex-vivo lung perfusion (EVLP), decline in survival after year one points out that chronic lung allograft dysfunction (CLAD) remains a major barrier in the field. An analysis of the recipient, donor, and operative characteristics in a cohort of multiple decade survivors is key in helping us understand factors associated with sustained long term graft function.

The current study by Miggins *et al.* is the first to explore these factors in transplant recipients who have survived multiple decades (13). Their results have redemonstrated what we know thus far regarding single versus bilateral lung transplants. Although there are no significant differences in postoperative complications between the two cohorts, there have been a plethora of recent studies that have associated better long-term survival and postoperative lung function in bilateral recipients (14). BOS, a subtype of CLAD, continues to be the leading cause of late mortality and morbidity in recipients, and bilateral recipients have shown to have a lower incidence compared to single recipients (15). Interestingly, the authors demonstrated a significant drop in single lung transplant survival in the 20 plus year group.

Perhaps the most important contribution of this study are the findings which raise several immunological questions and beg for further investigation. Minimal human leukocyte antigen (HLA) mismatch and female-to-female gender match was associated with increased likelihood of multiple decade survival. While the literature regarding HLA mismatch's association with CLAD is well documented (16), female-to-female donor-recipient matching in lung transplantation remains controversial. Prior observations have shown female recipients to have significantly improved survival. This study identifies female-to-female gender match associated with increased likelihood of 20 plus year survival. The development of antibodies against human minor histocompatibility antigens encoded on the Y chromosome (H-Y antibodies) has been studied in recipients of other organ transplants which showed a correlation with acute rejection, however, the Y chromosome influence will require further investigation on its role in lung transplantation (17,18).

The molecular mechanism by which donor smoking affects long term survival in recipients is another venue worth investigating. It is interesting note that retrospective studies have shown donor lungs with a >20-pack-year smoking history having no significant effect on the incidence of BOS (19). However, donor smoking history has been associated with decreased recipient survival (20). This study has identified donor cigarette use as a moderate long-term risk factor independent of its short-term effect (13), suggesting that carbon black from smoking may have a hand in the CLAD.

The pursuit of improving lung transplant survival rates requires a multifaceted approach that encompasses advancements in immunosuppressive strategies, precision medicine, donor-recipient matching, and collaborative care. Collaboration ensures a comprehensive evaluation to select candidates with the best chances of long-term success. This also helps strive toward a future where lung transplantation becomes an increasingly successful and transformative therapy, offering renewed hope and improved quality of life for individuals in need.

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