

DOI: 10.15825/1995-1191-2018-4-142-145

RATIONALE LIMITS OF ORGAN DONOR MAXIMIZATION FOR HEART TRANSPLANTATION

A. Zuckermann, G. Laufer

Medical University of Vienna, Austria

Cardiac transplantation is an established therapy for end-stage heart failure. The number of heart transplant procedures performed worldwide has remained relatively unchanged in recent years. Although mortality rates on the waiting list have improved due to improved ventricular assist devices and rhythm correction techniques, it remains imperative to maximize use of all potential donor hearts. The recipient now presents with multiple complexities. The continued divergence between the rising number of transplant candidates added to the transplant waiting list and the number of suitable organ donors has increased pressure on clinicians to maximize the use of available thoracic organs for transplantation.

Key words: heart transplantation, organ donation, extended-criteria donors.

ОБЪЕКТИВНЫЕ ОГРАНИЧЕНИЯ ПО УВЕЛИЧЕНИЮ КОЛИЧЕСТВА ДОНОРОВ ДЛЯ ТРАНСПЛАНТАЦИИ СЕРДЦА

A. Цукерманн, Г. Лауфер

Медицинский университет Вены, Австрия

Трансплантация сердца признана методом выбора лечения терминальной сердечной недостаточности. В последние годы число таких операций остается неизменным во всем мире. Несмотря на снижение смертности в листе ожидания, благодаря применению различных методов вспомогательного кровообращения остается актуальным максимальное использование всего донорского потенциала. Реципиенты донорского сердца имеют все больше сопутствующей патологии. Сохраняющаяся диспропорция между увеличением числа кандидатов на трансплантацию сердца и количеством доступных органов требует максимального использования торакальных органов для трансплантации.

Ключевые слова: трансплантация сердца, донорство органов, доноры с расширенными критериями.

Cardiac transplantation is an established therapy for end-stage heart failure. Since the first human heart transplantation in 1967, results have improved dramatically. One-year survival has increased to 85–90%. Within the first year, the early phase after transplantation is associated with the highest risk of death [1]. The number of heart transplant procedures performed worldwide has remained relatively unchanged in recent years [2]. But the growing number of patients wait-listed each year 2 creates an ever-expanding demand for transplantation [3].

Although mortality rates on the waiting list have improved due to improved ventricular assist devices and rhythm correction techniques, it remains imperative to maximize use of all potential donor hearts. However,

expansion of the donor pool must be balanced against the risk of adversely affecting outcomes [4].

The recipient now presents with multiple complexities, and there is increasing acceptance to tolerate these conditions, a reflection of the changing epidemiology of transplantation. In heart transplantation, age has increased significantly during the past 2 decades, with an ever-increasing proportion of recipients older than 60 years (24% of all recipients in 2006 up to 29% in 2016). Similarly, patients with complex congenital heart disease (CHD) and those with underlying chronic infections and conditions, such as cardiac amyloidosis, are now acceptable candidates for transplantation [5].

Not surprisingly, the burden of recipient comorbidities has increased in parallel, with increases in recipient weight, prior smoking history, hypertension, and

diabetes. Indeed, the prevalence of recipient diabetes mellitus, which was initially considered a contraindication to transplantation, has increased from 15% in the 1992 to 2003 era to 27% in the most recent era of 2009 to June 2017.

Adding to the complexity of finding an appropriate donor match and post-operative immunosuppression is the observation that the proportion of sensitized candidates (defined as panel reactive antibody >10%) has increased from 8% 15 to 20 years ago to >20% today. This partly reflects the increasing use of mechanical circulatory support as a bridge to transplantation. Currently, more than 50% of patients are bridged with one or more forms of mechanical support, including percutaneous and durable ventricular assist devices (VADs), total artificial heart, and extracorporeal membrane oxygenation (ECMO), such that conducting heart transplantation in a patient without a previous sternotomy has become quite unusual [6].

Advances in reparative surgery for CHD have resulted in a higher number of CHD patients who achieve better quality of life and longer survival, yet many progress to requiring transplantation (e.g., «failing» Fontan physiology). Despite the increased risk of peri-transplant complications and early post-transplant mortality, CHD transplant recipients tend to have a very good prognosis in the long-term. These patients, who often have concomitant liver disease, may be evaluated for combined heart-liver transplantation.

The decision to perform such combined organ transplant procedures in patients with advanced CHD is never straightforward, and the indications, operative techniques, and post-operative care strategies are still being evaluated, debated, and revised. Progress in cancer therapy provides lasting remission to many patients, yet the cardiotoxicity of chemotherapeutic agents may lead to the need for heart transplantation, with its specific challenges for perioperative and long-term care. Increasingly, patients with prior cancer and a history of chest wall radiation present a unique complex group that requires better study for suitability [5]. The standard criteria for acceptability of a donor heart which were published in the mid 1990s stipulated a donor age <50 years, no segmental abnormalities or global hypokinesia, left ventricular ejection fraction (LVEF) >50%, normal valvular structure, normal ECG or only minor ST-T wave abnormalities, a short ischemic time (<4 hours), dopamine dose <15 µg/kg/min, donor-to-recipient weight ratio 0.7 ± 1.5 , and no donor infection including hepatitis B virus (HBV), hepatitis C virus (HCV) and HIV infection [7]. These strict criteria, however, severely restricted acceptance of potential donor hearts. A series of groups published evidence showing that the criteria could be expanded without compromising outcomes, leading to progressive acceptance of hearts from donors with longer ischemic times, wider 5 size mismatch, left ventricular

hypertrophy, significant coronary artery disease, HCV or HBV infection and non-heart-beating donors [8–10].

The continued divergence between the rising number of transplant candidates added to the transplant waiting list and the number of suitable organ donors has increased pressure on clinicians to maximize the use of available thoracic organs for transplantation. Donor age at acceptance is increasing, as are underlying comorbidities. Median donor age in 2016 was 32 years in adult heart and 38 years in adult lung transplantation. Transplantation of heart and lung allografts from well selected donors aged >60 years is no longer uncommon. A recent analysis of data from the Spanish Heart Transplantation Registry was cautiously reassuring, demonstrating no survival disadvantage in recipients of donor hearts aged more than 50 years. However, after multivariate adjustment, recipients of these older hearts did have a higher incidence of cardiac allograft vasculopathy at 5 years after transplant [11]. Based on the International Society for Heart and Lung Transplantation (ISHLT) registry, the rate of death from graft failure early after transplantation is 3–4%. However, more and more data are available that shows significant differences of the cardiac donor population and its management in the USA and Europe. In Europe, donors are significantly older and are treated with a different inotropic regime than in the USA. According to the ISHLT registry, the rate of donors who are >50 years of age has been constant at 10% over the last years. This is in sharp contrast to the donor population in this cohort, which comprises 50% of donor hearts aged 50 and above. Norepinephrine support in doses >0.3 mg kg⁻¹ min⁻¹ was used in >80% of donors. According to the definitions of marginal donors, this center has been using marginal donors in many cases. Over the last 10 years, using so-called «marginal donors» has become the routine in Europe's cardiac transplantation programs. If centers would only use standard donor hearts, they would have a significant reduction in transplant numbers [12].

Much interest has recently been given to donor hearts with left ventricular dysfunction, which is often caused by transient neurogenic injury. There is now convincing evidence that donor hearts with left ventricular dysfunction often improve during donor management and yield acceptable recipient outcomes after transplantation. In fact, even donor hearts that continue to have reduced function at the time of organ procurement may be safely transplanted [13, 14].

Deaths related to drug intoxication are on the rise, with opioid abuse reaching epidemic proportions in the United States. Consequently, drug overdose is an increasingly common donor cause of death. Illicit drug use is more frequent even in potential donors with other mechanisms of death – 12% of all donors have a history of cocaine use, 44% of whom are current users. Many potential donors dying of drug overdose are also hepatitis C virus positive. This pool of donors represents an

opportunity to increase thoracic transplant rates, given the recent availability of highly effective direct-acting antiviral therapy for hepatitis C virus [15–17].

Increasing use of organs from donation after circulatory death (DCD) also provides promise for expansion of the donor pool for thoracic transplantation. Although this approach adds complexity to the transplant process, DCD heart transplant has now been shown to have long-term outcomes similar to lung transplant with allograft [18].

Yet, clinical implementation of DCD heart transplantation remains relatively slow, partly due to ethical and regulatory considerations and partly to the concern for high susceptibility of the myocardium to ischemia. Ex vivo organ perfusion techniques, recently tested for clinical application in organ transplantation, may enhance the feasibility of DCD organ donation. This has also ushered in the era of reconditioning of donated organs not immediately suitable for transplantation, especially for lung transplantation [19].

Recent changes in treatment of advanced heart and lung disease and changes in donor demographics have put a strain on existing organ allocation systems. Many countries have re-examined how well their allocation algorithms ensure that organ allocation is equitable. The implementation of the Lung Allocation Score in the United States, Germany, and the Netherlands was intended to strengthen utilitarian features of the allocation algorithm by considering the risk of death on the waiting list and in the first year after transplant [20].

In contrast, cardiac allocation is still mainly «urgency» driven, based mostly on the assessment of mortality risk on the waiting list. The United States heart allocation policy will soon undergo a major change, implementing new urgency tiers and expanding regional organ sharing [21]. In Europe, efforts are underway to create a heart allocation score via integration of information from existing heart failure survival scores, post-transplant outcome scores, and public registries [22]. Decision-making about acceptance or non acceptance of a «marginal» donor heart, however, is complex. Additionally, the risk profile of the potential recipient must also be taken into account, for example when the donor is aged over 55 years or has a low ejection fraction. Combined donor and recipient risk profiling can help to predict post-transplant survival rates and is useful in general terms but when faced with a specific donor an individualized assessment of that particular donor and heart – and the candidate recipient – is required. This decision-making progress is largely unsupported by rigorous evidence and depends to a large extent on the experience of the clinician. Refining this process is difficult because data on the outcomes for donor hearts transplanted elsewhere after non-acceptance are not readily available [23].

What is remarkable in the context of what could be seen as the «perfect storm» at the intersection of a higher risk donor, a more complicated transplant recipient, and

the ever changing regulatory environment, is that the volume of thoracic transplantation continues to increase and that contemporary survival after heart, lung and heart-lung transplant continues to improve. Perhaps one of the greatest drivers of this change is the irrepressible urge to continue to explore the limits of what is possible, and our collective contributors to the International Society of Heart and Lung Transplantation International Thoracic Organ Transplant Registry deserve gratitude for pushing the boundaries for patients worldwide.

The authors declare no conflict of interest.

REFERENCES

1. D'Allesandro C, Golmard JL, Barreda E, Laali M, Makris CE, Leprince P et al. Predictive risk factors for primary graft failure requiring temporary extracorporeal membrane oxygenation support after cardiac transplantation in adults. *Eur J Cardiothorac Surg*. 2011; 40: 962–969.
2. Lund LH, Edwards LB, Kucheryavaya AY et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-first Official Adult Heart Transplant Report-2014; focus theme: retransplantation. *J Heart Lung Transplant*. 2014; 33: 996–1008.
3. Organ Procurement and Transplantation Network. <https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#> Accessed 6 August 2017.
4. Colvin-Adams M, Smithy JM, Heubner BM et al. OPTN/SRTR 2012 Annual Data Report: heart. *Am J Transplant*. 2014; 14 (Suppl 1): 113–138.
5. Mehra MR, Canter CE, Hannan MM et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. *J Heart Lung Transplant*. 2016; 35: 1–23.
6. Khush K, Cherikh WS, Chambers DC et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-fifth adult heart transplantation report – 2018; focus theme: multiorgan transplant. *J Heart Lung Transplant*. 2018; 37: 1155–1168.
7. Laks H. Only optimal donors should be accepted for heart transplantation: antagonist. *J Heart Lung Transplant*. 1995; 14: 1043–1046.
8. Roig E, Almenar L, Crespo-Leiro M et al. Heart transplantation using allografts from older donors: multicenter study results. *J Heart Lung Transplant*. 2015; 34: 790–796.
9. Stehlik J, Edwards LB, Kucheryavaya AY, Aurora P, Christie JD, Kirk R, Dobbels F, Rahmel AO, Hertz MI. The Registry of the International Society for Heart and Lung Transplantation: twenty-seventh official adult heart transplant report – 2010. *J Heart Lung Transplant*. 2010; 29: 1089–1103.
10. Chen CW, Sprys MH, Gaffey AC et al. Low ejection fraction in donor hearts is not directly associated with increased recipient mortality. *J Heart Lung Transplant*. 2017; 36: 611–615.
11. Madan S, Saeed O, Vlismas P et al. Outcomes after transplantation of donor hearts with improving left ven-

- tricular systolic dysfunction. *J Am Coll Cardiol.* 2017; 70: 1248–1245.
12. Mehra MR, Jarcho JA, Cherikh W et al. The drug-intoxication epidemic and solid-organ transplantation. *N Engl J Med.* 2018; 378: 1943–1945.
 13. Jayarajan S, Taghavi S, Komaroff E et al. Long-term outcomes in heart transplantation using donors with a history of past and present cocaine use. *Eur J Cardiothorac Surg.* 2015; 47: 146–150.
 14. Schlendorf KH, Zalawadiya S, Shah AS et al. Early outcomes using hepatitis C-positive donors for cardiac transplantation in the era of effective direct-acting anti-viral therapies. *J Heart Lung Transplant.* 2018; 37: 763–769.
 15. Tenderich G, Koerner MM, Stuetzgen B et al. Extended donor criteria: hemodynamic follow-up of heart transplant recipients receiving a cardiac allograft from donors > or = 60 years of age. *Transplantation.* 1998; 66: 1109–1113.
 16. Forni A, Luciani GB, Chiominto B, Pizzuti M, Mazzucco A, Faggian G. Results with expanded donor acceptance criteria in heart transplantation. *Transplant Proc.* 2011; 43: 953–959.
 17. Wittwer R, Wahlers T. Marginal donor grafts in heart transplantation: lessons learned from 25 years of experience. *Transplant Int.* 2008; 21: 113–125.
 18. Messer SJ, Axell RG, Colah S et al. Functional assessment and transplantation of the donor heart after circulatory death. *J Heart Lung Transplant.* 2016; 35: 1443–1452.
 19. Mehra MR. Challenges, diligence, and a breakthrough in donation after circulatory death in heart transplantation. *J Heart Lung Transplant.* 2017; 36: 1319–1321.
 20. Keller CA, Gonwa TA, White LJ et al. Utilization and cost analysis of lung transplantation and survival after 10 years of adopting the lung allocation score (LAS) [e-pub ahead of print]. *Transplantation* 2018. <https://doi.org/10.1097/TP.0000000000002227>, accessed September 6, 2018.
 21. Davies RR, Farr M, Silvestry S et al. The new United States heart allocation policy: progress through collaborative revision. *J Heart Lung Transplant.* 2017; 36: 595–596.
 22. Smits JM, de Vries E, De Pauw M et al. Is it time for a cardiac allocation score? First results from the Euro-transplant pilot study on a survival benefit-based heart allocation. *J Heart Lung Transplant.* 2013; 32: 873–880.
 23. Trivedi JR, Cheng A, Ising M, Lenneman A, Birks E, Slaughter MS. Heart transplant survival based on recipient and donor risk scoring: A UNOS database analysis. *ASAIO J.* 2016; 62: 297–301.

Статья поступила в редакцию 28.09.2018 г.
The article was submitted to the journal on 28.09.2018