Defining an Extended Criteria Donor Heart in the Current Era

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Disclosure

I will not discuss off label use and/or investigational use of medications

Names of Companies with which relationships (research grants) exist:
Novartis, TransMedics, CareDx, Sanofi
Learning Objectives

• To learn what risk factors define an extended criteria donor heart.

• To understand why extended criteria donor hearts are not commonly used.

• To learn of the cumulative outcome effects of multiple risk factors in extended criteria donor hearts.
Background: Limited Donor Organ Supply

- The number of patients surviving to stage D heart failure has been increasing, while the supply of donor hearts has remained relatively stable.
  - Exacerbating this limited supply is a declining acceptance rate for donor heart offers
  - This is, in part, may be due to regulatory oversight for programs failing to meet outcome targets.
  - Therefore, some programs, especially low-volume centers, are reluctant to accept organ offers with perceived extended criteria.

Decreased Utilization in Donor Hearts is an Issue
National Decline in Donor Heart Utilization
with Regional Variability: 1995-2010

- US heart transplant (OPTN) data analyzed for all potential adult heart organ donors between 1995-2010
- Significant decrease in donor heart acceptance, from 44% in 1995 to 29% in 2006, then back up to 32% in 2010, with regional variation
- Most common predictors of heart non-acceptance were older donor age, female gender and medical co-morbidities
- Overall, the findings suggest research is needed at establishing a uniform, evidence-based donor utilization protocol.

Heart transplants performed vs waitlist candidates added, USA 1995-2014

From UNOS/SRTR data, available at https://optn.transplant.hrsa.gov/
Decreased utilization in donor hearts is an issue

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Marginal donors often aren’t used, but could be

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1,872 organ donors from the California Transplant Donor Network from 2001–2008

• Marginal donors are typically defined as those with perceived risk factors for poor subsequent outcome, typically:
  – Older age (>50)
  – History of drug abuse
  – Left ventricular hypertrophy
  – Borderline LVEF (<50%)
  – Donor comorbidity, e.g. diabetes, hypertension

• These are most common reasons for declining a donor heart

Debunking myths in donor selection

Key points for donor selection: debunking myths

- Oversizing is not necessarily needed for recipients with pulmonary hypertension, but undersizing should be avoided.
- Oversizing is not necessarily needed for female donors to male recipients and should be assessed on case-by-case basis.
- LV mass index should be considered in conjunction with height and weight.
- Younger donor age and good graft function should be prioritized above all other risk factors.
- There is no unacceptable length of CPR ("downtime") if echocardiographic function of the donor heart and other donor factors are favorable.
- Use of low-dose inotrope and vasopressors on the donor heart is acceptable to proceed to transplant; use of norepinephrine, epinephrine, and/or multiple inotropes should be viewed with caution.

CPR, cardiopulmonary resuscitation; LV, left ventricular.

Risk factors to be considered in donor selection, by tier of importance

<table>
<thead>
<tr>
<th>Donor risk factors</th>
<th>Recipient risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Most important</strong></td>
<td><strong>Most important</strong></td>
</tr>
<tr>
<td>• Older age</td>
<td>• Older age</td>
</tr>
<tr>
<td>• Left ventricular function</td>
<td>• Congenital heart disease as etiology of heart failure</td>
</tr>
<tr>
<td>• Presence of LVH</td>
<td>• Severe organ dysfunction (as reflected by elevated creatinine or total bilirubin)</td>
</tr>
<tr>
<td>• Cold ischemic time/ distance from transplanting center</td>
<td>• Pulmonary hypertension</td>
</tr>
<tr>
<td>• High inotrope use</td>
<td>• Temporary circulatory support (RVAD, Impella, ECMO), especially if complicated</td>
</tr>
<tr>
<td><strong>Important</strong></td>
<td>• Mechanical ventilation</td>
</tr>
<tr>
<td>• Sex mismatch (female to male)</td>
<td>• Amyloid Important</td>
</tr>
<tr>
<td>• Preexisting coronary artery disease</td>
<td>• Redo heart transplant</td>
</tr>
<tr>
<td>• Malignancy as cause of death</td>
<td>• Sensitization level of patient</td>
</tr>
</tbody>
</table>

ECMO, extracorporeal membrane oxygenation; LVH, left ventricular hypertrophy; RVAD, right ventricular assist device.

Left ventricular systolic dysfunction

- LV systolic dysfunction and regional wall motion abnormalities are common reasons for donor heart declines.
- Catecholamine release after brain death stuns the myocardium which is reversible with donor management.
- Even donor hearts LV systolic dysfunction not reversed by the time of procurement may be acceptable for transplant.
- Bombardini et al used stress echocardiography to screen donors with LV dysfunction and regional wall motion abnormalities yielding a 93% 1 year survival

Recent UNOS study of 30,993 HTx from 1996 to 2015
127 had EF < 40%
1 year survival comparable between normal EF and reduced EF groups
At 1 year the reduced EF group had a mean EF of 58% against 59% for matched normal group

Hepatitis C positive donors
Transplanting Hepatitis C Kidneys into Negative Kidney Recipients: THINKER Trial

- Open label, single center pilot study at U Penn (n = 10)
- HCV naïve patients received kidneys from donors with genotype 1 HCV
- 3 days post Tx all patients had detectable HCV RNA
- Elbasvir–grazoprevir was initiated in all patients
- A sustained virologic response was seen in all patients 12 weeks after Tx
Donors with hepatitis C infection

• The use of anti-HCV+, HCV-RNA- donor hearts are generally safe for transplantation but requires post-transplant HCV-RNA monitoring; anti-HCV+, HCV-RNA+ donor hearts should be limited to consented recipients with appropriate post-transplant treatment and monitoring.

• The risk of coronary artery endothelial dysfunction must be disclosed to the recipients.

Blumberg E. et al. NEJM 2019;380:1669-70.
Marginal donors often aren’t used, but could be

1,872 organ donors from the California Transplant Donor Network from 2001–2008

- Retrospective analyses demonstrate that when these hearts are transplanted, do not result in worse outcomes
- Suggests that more liberal use of donor hearts with relative contraindications may increase donor pool without compromising outcomes
- “The enemy of good is perfect”

Expanding the Donor Pool

• Despite concerns over these perceived extended criteria, there has been an effort to utilize marginal donors and expand the donor pool

• A UNOS study found comparable 30-day to 3-year survival for HT patients receiving donors with mild-moderate LVH (1.1–1.3cm) and even severe LVH (≥1.4cm)¹
  o However, further analysis revealed LVH in combination with age >55yrs and ischemic time >4h led to decreased survival

• It has not been well established whether the number of extended criteria in donor hearts have a cumulative effect on outcomes after heart transplantation.

Cumulative Adverse Effects of Extended Criteria Donor Hearts After Heart Transplant

• 626 consecutive heart transplant recipients who underwent a transplant between 2012 and 2017 at our center were assessed.

• We reviewed donor information for commonly defined extended criteria, which included:
  1) Donor age >50 yrs
  2) Left ventricular (LV) hypertrophy >1.2cm
  3) LV ejection fraction (LVEF) <50%
  4) Ischemic time >4 hours
  5) Donor-transmitted coronary artery disease (CAD)
  6) Female-to-male gender mismatch
  7) Donor:recipient weight <0.80

Olymbios M, Kobashigawa J, presented at ATC 2019
The recipients were divided into four groups according to the number of criteria present:

1) 0 criteria \( (n=350) \)
2) 1 criterion \( (n=220) \)
3) 2 criteria \( (n=76) \)
4) \( \geq 3 \) criteria \( (n=15) \)

We assessed each group for:

- 3-year actuarial survival
- Freedom from cardiac allograft vasculopathy (CAV)
- Freedom from any-treated rejection
- Freedom from non-fatal major adverse cardiac events (NF-MACE: MI, CHF, stroke, and need for angioplasty or pacemaker/ICD).

Olymbios M, Kobashigawa J, presented at ATC 2019
### Cumulative Adverse Effects of Extended Criteria Donor Hearts After Heart Transplant: Results

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>0 Extended Criteria (n=315)</th>
<th>1 Extended Criterion (n=220)</th>
<th>2 Extended Criteria (n=76)</th>
<th>≥3 Extended Criteria (n=15)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-Year Survival</td>
<td>82.4</td>
<td>86.0</td>
<td>94.5</td>
<td>78.6</td>
<td>0.136</td>
</tr>
<tr>
<td>3-Year Freedom from NF-MACE</td>
<td>82.5</td>
<td>74.8</td>
<td>59.3</td>
<td>54.6</td>
<td>0.035</td>
</tr>
<tr>
<td>3-Year Freedom from CAV</td>
<td>93.8</td>
<td>85.1</td>
<td>83.5</td>
<td>92.9</td>
<td>0.081</td>
</tr>
<tr>
<td>3-Year Freedom from Any-Treated Rejection</td>
<td>83.0</td>
<td>77.0</td>
<td>75.1</td>
<td>75.7</td>
<td>0.583</td>
</tr>
</tbody>
</table>
The most common extended criterion or combination of criteria for the groups were:

- Group 2: Older donor age (n=56/220)
- Group 3: Older donor age and CAD (n=19/76)
- Group 4: LV hypertrophy, gender mismatch and CAD (n=4/15)
Cumulative Adverse Effects of Extended Criteria Donor Hearts After Heart Transplant: Conclusion

- There was comparable survival for heart transplant recipients receiving donor organs with one or more commonly defined extended criteria.
- The most common extended criterion were: Donor age, CAD, LV hypertrophy and gender mismatch.
- The risk of NF-MACE incrementally increased with the number of risk factor criteria.

Olymbios M, Kobashigawa J, presented at ATC 2019
Summary

- As more patients are added to the heart transplants waitlist in the US, the shortage of donor hearts looms larger.

- Donor heart usage in the US has not increased over the past 2 decades for various reasons which may, in part, be due to regulatory oversight.

- Extended criteria donor hearts have acceptable outcome to enlarge the donor pool and increase heart transplantation.

- Multiple donor heart risk factors appear acceptable but may have less than optimal outcomes.
Thank You