Smoking After Cardiac Transplantation

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Introduction

- Cigarette smoking \( \rightarrow \) ↑ death form ischemic heart disease (IHD) and malignancy
- Free radical-mediated endothelial damage \( \rightarrow \) accelerates coronary vascular atherothrombosis

Heart transplantation remains the treatment option of choice for ischemic cardiomyopathy and idiopathic dilated cardiomyopathy

Smoking cessation
- Benefit from cardiac failure or coronary vascular disease
- Compliance rates remain poor
- Intensive counseling, appropriate medical treatment of nicotine withdrawal

Even after surviving heart failure of a severity requiring cardiac transplantation, tobacco relapse is common

Limitation of previous reports of the risks of smoking after transplantation
- Self-reported assessment of smoking

This study
- Covertly assessed smoking habits in cardiac transplant recipients there center over a period of 13 years
- Aimed at: Smoking V.S. Survival data, Graft vasculopathy and malignancy

Methods

- From 1993, covertly assessed the smoking habits of cardiac transplant recipients attending follow-up at our center.
- Local ethics review board approved the study protocol, and waived the need for individual patient consent.
Detected smoking
- A random urine sample was collected from each patient at the time of annual angiography or myocardial perfusion scan.
- Urinary cotinine levels were measured in batches using a direct cotinine ELISA kit (Bio-quant, San Diego, CA).
- Urinary cotinine levels in nonsmokers exposed to passive smoke: 0.3 ng/mL ~ 392 ng/mL.
- >500 ng/mL → Active smoking.

All patients had survived >1 years post transplantation.
- Number of positive tests was used for logistic regression analyses, and a time-dependent covariate was modeled for Cox survival analysis.
- Time-dependent covariate: the percentage of time a patient had smoked posttransplant.

Patient demographics, survival data and causes of death were collected prospectively.
- Separately record:
  - The need for percutaneous coronary intervention for graft coronary artery disease (GCAD).
  - Death from GCAD.
  - Death from posttransplant malignancy.

Results

Patients
- From January 1993 to August 2005,
- 526 adult (>16 years of age) patients
- At least one urinary cotinine level measured: 380
- Mean follow-up: 10.1±4.4 years

Analyzed in univariate survival models by the Kaplan-Meier method using log-rank tests for significance.
- Those factors showing significant effects were further entered into multivariate analysis.
- All analyses were performed using SPSS version 14.0 for Windows (SPSS, Inc., Chicago, IL).

Table 1: Patient demographics

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at transplant (years)</td>
<td>47 ± 12</td>
<td></td>
</tr>
<tr>
<td>Gender (male)</td>
<td>323</td>
<td>85.0%</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>219</td>
<td>57.8%</td>
</tr>
<tr>
<td>Diabetic cardiomyopathy</td>
<td>138</td>
<td>36.3%</td>
</tr>
<tr>
<td>Congenital</td>
<td>18</td>
<td>4.7%</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>1.3%</td>
</tr>
<tr>
<td>Urgent list status pretransplant</td>
<td>93</td>
<td>24.5%</td>
</tr>
<tr>
<td>Pretransplant smoking history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>152</td>
<td>41.4%</td>
</tr>
<tr>
<td>Other</td>
<td>60</td>
<td>14.4%</td>
</tr>
<tr>
<td>Era of transplantation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1985–1989</td>
<td>59</td>
<td>15.5%</td>
</tr>
<tr>
<td>1989–1994</td>
<td>149</td>
<td>39.2%</td>
</tr>
<tr>
<td>1994–1999</td>
<td>129</td>
<td>33.9%</td>
</tr>
<tr>
<td>1999–2004</td>
<td>43</td>
<td>11.3%</td>
</tr>
</tbody>
</table>
Smoking: Incidence and risk factors

- Urine cotinine specimens: mean 3 times/person (rank: 0~13)
  - 104 (27.4%) Positive at least once test
  - 27 (7.4%) Positive at > one test
  - 47 (12.4%) Positive only at one test
  - 30 Has tested repeatly

- Median urinary cotinine level
  - In those testing positive: 2139 ng/mL (504~8000ng/mL)
    - >5000 ng/ml: 6.4%
    - 5000~1000 ng/ml: 73.3%
    - 1000~500 ng/ml: 23.3%
  - In those testing negative: 46 ng/ml
    - 0~50 ng/ml: 52.9%
    - 50~200 ng/ml: 33.8%
    - 200~500 ng/ml: 13.2%

- Logistic regression analysis demonstrated the predictor of predictors of smoking posttransplantation
  - Smoking within 6 months prior to transplantation (RR: 7.635, 95% CI: 2.890~20.169, p < 0.0001)
  - Pretransplant diagnosis of IHD (RR 2.239, 95% CI: 0.911~5.504, p = 0.079)
  - Pretransplant urgent list status, gender and era of transplantation

Graft coronary artery disease (GCAD)

- GCAD, requiring percutaneous coronary intervention: 34 (8.9%)
- Died (GCAD related): 56 (14.7%)
- Smokers suffered significantly more deaths due to GCAD (21.2% vs. 12.3%, p < 0.05)

| Table 2: Risk factors for percutaneous coronary intervention or death due to GCAD |
|-----------------------------|----------|---------|-------|
| Covariate                  | Odds ratio | 95% CI  | p-Value |
| Number of positive cotinine tests | 1.280     | 1.073~1.527 | 0.006  |
| Donor age (decades)        | 1.293     | 1.001~1.671 | 0.049  |
| Acute rejection             | 0.250     |          | 0.250  |
| Diagnosis IHD              | 0.333     |          | 0.333  |
| CMV reinfactor              | 0.229     |          | 0.229  |
| Pretransplant smoking       | 0.806     |          | 0.806  |

Multivariate logistic regression analysis for the combined endpoint of death due to GCAD or percutaneous coronary intervention, IHD = ischemic heart disease; CMV reinfactor = recipient cytomegalovirus IgG negative pretransplant, donor IgG positive.
Malignancy
- Died from malignancy posttransplant: 33 (8.7%)
- Tumor origin
  - Lymphopoietic: 11
  - Pulmonary: 5
  - Gastrointestinal: 6
  - Dermatological: 4
  - Rarer origins: 7

Returned to smoking posttransplant ➔ ↑ death due to malignant
(16.3% vs. 5.8%, p < 0.001)

Table 3: Risk factors for fatal malignancy

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of positive cotinine tests</td>
<td>1.283</td>
<td>1.049–1.570</td>
<td>0.015</td>
</tr>
<tr>
<td>Diagnosis IHD</td>
<td>2.950</td>
<td>1.165–7.473</td>
<td>0.023</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>0.684</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretransplant smoking</td>
<td>0.987</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipient age (decades)</td>
<td>0.686</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Multivariate logistic regression analysis for the development of fatal malignancy.

Survival
- Median survival for all patients: 15.4 years (95% CI: 13.4–17.4)

Table 4: Overall mortality

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posttransplant smoking</td>
<td>1.018</td>
<td>1.010–1.027</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Pretransplant smoking</td>
<td>2.589</td>
<td>1.134–5.866</td>
<td>0.0240</td>
</tr>
<tr>
<td>Donor gender</td>
<td>0.5700</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor age (decades)</td>
<td>0.6170</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urgent status pretransplant</td>
<td>0.2470</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipient age (decades)</td>
<td>0.2960</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cox multivariate survival analysis.

- Posttransplant smoking analyzed as a time-dependent covariate using the percentage of time smoked posttransplant—odds ratio, therefore, reflects increased odds ratio for death per percentage of time smoked.
- IHD = ischemic heart disease.

Discussion

- Previous studies of smoking habits in heart transplant recipients
  - Rate: 12–26%
  - In patients smoked pretransplant: 32.5%
- Smoking detection in these studies:
  - Self-reporting, Carboxyhemoglobin assay, Urinary cotinine assay
- Limitation:
  - Point prevalence of smoking based on a single self-report or assay
  - Dichotomous scoring as smokers or nonsmokers
Urinary cotinine levels

- In a study of 49 smokers and 184 nonsmokers
  - Smoker: 1623 ng/mL
  - Nonsmoker: 0.1 ng/mL

- In smokers: 126 ng/mL / day
- In nonsmokers reporting passive smoke exposure:
  - Cotinine level: 0.3 ng/mL to 392 ng/mL
- Urinary cotinine ↑ 44% / 10h exposure

Urinary IHD in predicting the development of malignancy after transplantation.

- Higher incidence of fatal allograft vasculopathy in recent smokers before transplantation.
- Posttransplant smoking has been shown to significantly accelerate the development of cardiac allograft vasculopathy (this risk has not been quantified).

Testing positive for active smoking ➔ continue to smoke indefinitely

- Repeated testing ➔ assess the effects of this variable duration of active smoking.
- Smoking is the single greatest determinant of the development of GCAD of a severity requiring PCI or causing death (OR: 1.280/positive cotinine level).

Cardiac allograft vasculopathy

- Most significant factor limiting long-term graft survival after heart transplantation.
- Mediate the development of this condition.
  - Early endothelial injury during ischemia-reperfusion.
  - Disturbances in lipid and glucose homeostasis.
  - Viral infections (especially CMV).
  - Smoking.

Transplantation, and subsequent immunosuppression is a known risk factor for the development of malignancy.

- Primary pulmonary malignancy is more frequently in heart transplant recipients than in a nontransplant population.
- A study of 22 posttransplant smokers: posttransplant malignancy ↑

In this study:

- Posttransplant smoking to be the most significant predictor of the development of fatal malignancy.
- Pretransplant IHD in predicting the development of fatal malignancy ➔ may implied heavy or prolonged smoking in predicting the development of malignancy after transplantation.
Decreasing incidence of smoking over the course of the study period
- Increasing public awareness of the risks of smoking
- The more recent availability of a multidisciplinary smoking cessation program
- The adverse effects of nicotine replacement therapy (BP and glucose tolerance) may be less in newer therapies

History of smoking within 6 months is a risk factor for smoking
- Obligatory 6-month period of abstinence from smoking before acceptance onto the waiting list
- They feel patients that have an enforced period of abstinence during hospitalization or mechanical support are at high risk for relapse after transplantation
- Early counseling and intervention

Significant reduction in posttransplant life expectancy → a powerful deterrent to patients from returning to smoking

Thank you for your attention