RISK FACTORS OF SMOKING AFTER HEART TRANSPLANTATION

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Abstract

While cessation of smoking is a requirement for cardiac transplantation prior to listing, some patients return to smoking after recovery. Since 1993, we have covertly tested the smoking habits of our recipients of cardiac transplants (with ethical approval) by calculating urinary cotinine: a level of > 500 ng / mL suggesting continuing tobacco use. Survival, causes of death and the occurrence of graft coronary artery disease (GCAD) were retrospectively analyzed in terms of the amount of positive and negative levels of cotinine. At some point after transplantation, one hundred and four out of 380 (27.4 percent) patients tested positive for active smoking, and 57 (15.0 percent) tested positive repeatedly. Because of GCAD (21.2 percent vs. 12.3 percent, p<0.05), and because of malignancy (16.3 percent vs. 5.8 percent, p<0.001), smokers experienced slightly more deaths. Smoking after heart transplantation reduced median survival from 16.28 years to 11.89 years in the univariate study. After accounting for the impact of pretransplant smoking in a time-dependent multivariate study, the most relevant determinant of total mortality remained posttransplant smoking (p < 0.00001). We conclude that by accelerating the production of graft vasculopathy and malignancy, cigarette smoking after cardiac transplantation has a substantial effect on survival. We hope that this information will prevent recipients of cardiac transplants from relapsing and will intensify efforts to increase the rate of cessation.

Keywords: heart transplantation, Cardiac allograft vasculopathy, smoking, malignancy

Introduction:

In the developing world, cigarette smoking is the single biggest modifiable risk factor for death from ischemic heart disease (IHD) and malignancy. Smoking accelerates coronary vascular atherothrombosis by inducing endothelial dysfunction, leukocyte and platelet activation, lipid peroxidation, smooth muscle proliferation and a prothrombotic hematomal environment through free radical mediated endothelial harm.1 The end result of persistent limitation of myocardial blood flow in those who survive the acute effects of atherosclerotic plaque rupture and myocardial ischemia is ischemic cardiomyopathy. A history of previous smoking is also not unusual in patients with idiopathic dilated cardiomyopathy.2 When end-stage cardiac failure occurs, heart transplantation remains the treatment method of choice for all these patient groups and provides substantially superior survival over full medical therapy.3 While survival benefits are well known from smoking cessation following a diagnosis of heart failure or coronary artery disease, compliance rates with cessation measures remain weak. It has been shown that only comprehensive therapy and effective medical care for nicotine withdrawal have increased compliance rates.4-5-6 Tobacco recurrence is normal even after surviving heart failure of a degree that involves heart transplantation. Previous estimates of the risk of smoking after transplantation have been restricted by self-reported smoking assessment and risk quantification based on the population smoking prevalence stage. Over a span of 13 years, we have covertly evaluated smoking behaviors in cardiac transplant recipients at our clinic. In an effort to...
provide outcome evidence to promote smoking cessation or sustained abstinence in cardiac transplant patients, we aimed to compare this evaluation with survival data and growth of graft vasculopathy and malignancy.⁷

Methods:
Since 1993, the smoking habits of cardiac transplant patients attending follow-up at our facility have been covertly analyzed. The study procedure was approved by the local ethics review board, and waived the need for individual patient consent. At the time of the annual angiography or myocardial perfusion scan, a random urine sample from each patient was obtained and urinary cotinine was determined by immunoassay.⁸ Using a direct cotinine enzyme-linked immunosorbent assay (ELISA) kit (Bio-quant, San Diego, CA) in samples that were stored at 40°C, urinary cotinine levels were calculated in batches. In previous studies, urinary levels of cotinine ranged from 0.3 ng/mL to 392 ng/mL in 131 non-smokers exposed to passive smoke.⁹ Therefore, an amount of cotinine greater than 500 ng/mL was taken to denote active smoking in order to reduce false positives. Although the specimens were collected at the time of routine angiography or perfusion scanning, all patients included in the study survived at least 1 year after transplantation. The number of positive tests were used for logistic regression analyses to summarize individual patient smoking behaviors over the study period, and a time-dependent covariate was modelled for the analysis of Cox survival.

As previously mentioned in the analysis of such results, the time-dependent covariate was modelled on the percentage of time a patient had smoked post transplants.¹⁰ Patients were listed as non-smokers from the date of transplantation until their first measurement of cotinine and as smokers or non-smokers according to their last cotinine level for the duration after each cotinine level up to the next / end of follow-up. Prospectively, patient demographics, data on survival and causes of death were collected. In addition, there was a separate record of the need for percutaneous coronary intervention for graft coronary artery disease (GCAD) or death from GCAD. Heart transplant recipients dying unexpectedly were included in this category, where GCAD was established as a major contributing cause of death. As the calculated endpoint, death from posttransplant malignancy was used for study of the impact of smoking on posttransplant malignancy.

The results of cotinine assays and scoring were collated with clinical outcome data and evaluated by the Kaplan-Meier system using log-rank tests for significance in univariate survival models. Furthermore, certain factors with major effects and those considered to be of particular clinical significance were included in the multivariate study, with the incremental backward exclusion of those factors not contributing significantly to the model (at the level of 0.1). All parametric data is presented as mean ± standard deviation and the independent t-test samples are used to make comparisons. Categorical data is viewed as an absolute value, followed by a percentage in parentheses, and the chi-square test is used to make comparisons. SPSS version 14.0 for Windows (SPSS, Inc., Chicago, IL) was used to conduct all the analyses.

Results:
Patients
During the period from January 1993 to August 2005, 526 adult patients (> 16 years of age) underwent heart transplant follow-up at our hospital. Of these, at least one urinary level of cotinine was assessed in 380 patients and included in further studies. The mean follow-up duration was 10.1 ± 4.4 years in this patient category. Demographics for patients are specified in Table 1.

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<th>Table 1: Patient demographics</th>
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Smoking: Incidence and risk factors
During the period from January 1993 to August 2005, 526 adult patients (> 16 years of age) underwent heart transplant follow-up at our hospital. Of these, at least one urinary level of cotinine was assessed in 380 patients and included in further studies. The mean follow-up duration was 10.1 ± 4.4 years in this patient category. Demographics for patients are specified in Table 1.¹¹

Graft coronary artery disease (GCAD)
Thirty-four (8.9%) patients developed GCAD, requiring percutaneous coronary intervention. Fifty-six patients (14.7%) died during follow-up, with GCAD determined as a major contributing cause of death at postmortem examination. Smokers suffered significantly more deaths due to GCAD (21.2% vs. 12.3%, p < 0.05). A combined endpoint of percutaneous coronary intervention or death from GCAD was used in multivariate analysis. Donor age (odds ratio [OR] 1.293 per decade, 95% CI: 1.001–1.5671, p = 0.049) and posttransplant smoking (OR 1.280 per positive cotinine test, 95% CI: 1.073–1.527, p = 0.006) were the only factors significantly predictive of the development of the combined endpoint for GCAD in multivariate analysis (Table 2).¹²
Malignancy

Thirty-three (8.7%) patients died from malignancy posttransplant. The origin of the tumor was lymphopoietic in 11, pulmonary in 5, gastrointestinal in 6 and dermatological in 4, and the unusual origin of 7 primaries was diverse. Owing to malignancy, patients who returned to smoking after transplantation experienced substantially more deaths (16.3 percent vs. 5.8 percent, p < 0.001). Only the post-transplantation smoking habit (OR 1.283 per positive cotinine test, 95 percent CI: 1.049-1.570, p < 0.001) and pre-transplantation diagnosis of IHD (OR 2.950, 95 percent CI: 1.165-7.473, p = 0.023) were important predictors of the occurrence of fatal malignancy when adjusted for pre-transplantation smoking history in multivariate analysis (Table 3).

Survival

The median survival was 15.4 years (95 percent CI: 13.4–17.4) for all patients screened for smoking. Cumulative survival was slightly lower for those with a single positive cotinine measurement (log-rank, p = 0.0013) and those with more than one positive cotinine measurement (log-rank, p = 0.0006) than for non-smokers after transplantation. Smoking after transplantation substantially shortened median survival in univariate research from 16.28 years (95 % CI: 15.2–21.6) to 11.89 years (95 % CI: 10.4–14.1) (Figure 2). Multivariate survival analysis showed effects on survival as a time-dependent variable for pre-transplant smoking history and, most importantly, for post-transplant smoking (Table 4).

Discussion

Previous studies of smoking habits in heart transplant recipients have shown a relapse rate of approximately 12 to 26 percent after transplantation (7,11,12), or 32.5 percent in post-transplantation recipients. To assess the prevalence, some of these studies have used self-reporting and have possibly underestimated the true incidence of smoking in these patients. A 12 percent prevalence of smoking (17.6 percent in posttransplant smokers) in cardiac transplant recipients by self-reporting was shown by Basile and colleagues. A important indicator of recurrence in this study was recent cessation (within 1 year of transplantation). Using the carboxyhemoglobin assay, higher concentrations of about 26 percent, demonstrating the relative underestimation of the true incidence of smoking by self-reporting. More recently, in 86 post-transplantation smokers by urinary cotinine assay. The point prevalence of smoking based on a single self-report or assay, or a dichotomous scoring as smokers or non-smokers were both used in these tests, neglecting the impact of smoking length and severity. The smoking habits of cardiac transplant recipients at our center were identified in our research over a span of 13 years through annual testing of urinary cotinine levels. This measure has been shown to be substantially associated with the average daily intake of cigarettes in smokers and also with the average period of passive smoke exposure in non-smokers. The median urinal level of cotinine was 1623 ng / mL in smokers and 6.1 ng / mL in non-smokers in a sample of 49 smokers and 184 non-smokers. Each additional cigarette smoked per day has increased the amount of urinary cotinine by an estimated 126 ng / mL in smokers. Cotinine levels ranged from 0.3 ng / mL to 392 ng / mL for nonsmokers reporting passive smoke exposure, with urinary cotinine rising by 44 percent (95 percent CI: 23–67 percent) per 10 hours of recorded exposure. To remove those likely to have been exposed to passive smoking only, we used a cutoff of 500 ng / mL. In line with previous studies, we found the overall incidence of smoking to be 27.4% in our sample population over the study period.
The most critical factor limiting long-term graft survival after heart transplantation is cardiac allograft vasculopathy. Several factors, including early endothelial injury during ischemia-reperfusion, lipid and glucose homeostasis disorders, viral infections, especially those with cytomegalovirus (CMV), and smoking, have been shown to mediate the development of this disease. A diffuse, tapering distal vessel disease is the usual lesion in cardiac graft vasculopathy, as opposed to isolated, proximal plaques in areas of elevated vessel wall shear-stress seen in non-transplant coronary atherosclerosis. Previous studies have shown a higher incidence of fatal allograft vasculopathy in young post-transplant smokers. Similarly, the development of cardiac allograft vasculopathy has been shown to substantially accelerate post-transplant smoking. although this risk has not been quantified. Crucial determinant of the occurrence of coronary artery disease in a non-transplant population is the length and severity of exposure to cigarette smoke. It cannot be concluded that all patients testing positive for active smoking will continue to smoke forever at some stage after transplantation. The use of repeated research has therefore allowed us to evaluate the effects of this variable period of active smoking in recipients of heart transplants. Smoking has been shown to be the single greatest determinant of GCAD development of a severity requiring PCI or causing death by univariate and multivariate studies. The OR for developing this combined GCAD endpoint was 1,280 per positive amount of cotinine.

A recognized risk factor for malignancy development is transplantation and subsequent immunosuppression. However, primary pulmonary malignancy has been shown to occur no more often in recipients of heart transplantation than in a population matched for age and smoking background in a nontransplant population. An analysis of 22 posttransplant smokers diagnosed by self-reporting and measurement of carboxyhemoglobin showed a substantial rise in malignancy after transplantation in this population.

The short half-life of carboxy-hemoglobin and the documented self-reporting underestimation of tobacco use by 8 to 25 percent of patients could still have resulted in an underestimation of the true danger. Our research showed that the most important indicator of the development of fatal malignancy was posttransplant smoking. The effects of the history of posttransplant smoking were examined using a dichotomous classification because a large proportion of patients in the sample were unable to obtain accurate quantitative smoking history data. This method made it difficult to determine the impact of the magnitude of previous exposure, likely contributing to this effect being underestimatated in our studies. In predicting the development of fatal malignancy, the importance of a posttransplant diagnosis of IHD may indicate the importance of heavy or prolonged smoking in predicting the development of malignancy after transplantation.

**Conclusion:**

To conclude, over the course of the study period, we noticed a declining incidence of smoking. There are many potential reasons for this finding, in particular the growing public perception of the dangers of smoking and, likely, the more recent availability in the British National Health Service of a multidisciplinary smoking cessation service. Concerns regarding the adverse blood pressure and glucose tolerance effects of nicotine replacement therapy are well known, but the benefits of a potential doubling of compliance outweigh these relatively minor risks. In this respect, newer therapies will potentially prove safer and further improve compliance rates. A history of smoking within 6 months of transplant was identified as the most significant in our study of risk factors for smoking relapse after transplantation. While the common practice is a mandatory 6-month period of abstinence from smoking until admission to the waiting list, we agree that patients with an enforced abstinence period during hospitalization or mechanical assistance should be classified as at high risk of relapse after transplantation. To avoid relapse, this encourages early therapy and intervention. In view of their enhanced post-transplant longevity, it is open to discussion whether this time of abstinence is the only ethical way of granting nonsmokers the ‘priority’ waiting list. A good deterrent to patients from returning to the posttransplant smoking habit should be our finding of a substantial decrease in posttransplant life expectancy. We hope that this result will, before and after transplantation, benefit these therapy patients by providing the evidence to support the continued abstinence argument.

**References**