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The deleterious effects of smoking resumption after heart transplantation

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Abstract

Aims: Smoking is linked to disease and survival in the general and transplant population. We studied the smoking history, disease and survival of patients after heart transplantation.

Methods: A total of 130 patients who underwent heart transplantation between 1995 and 2019 received a questionnaire to document their smoking history. We assessed patient characteristics, comorbidities and survival.

Results: Sixty-five percent of patients were active or former smokers prior to heart transplantation. All patients stopped smoking; 26% of the former smokers resumed smoking after transplantation. Patients who resumed smoking were younger at the time of transplantation, used fewer statins and were more likely to be treated with azathioprine after transplantation. The mean follow-up for all patients was 11 ± 5.5 years. Patients who resumed smoking were more likely to develop solid organ cancers (45%) compared to those who remained abstinent (23%) and those who never smoked (13%) ($p 0.014$). A Cox proportional hazards regression analysis identified smoking resumption, with an RR of 2.31 (1.14-4.68, $p 0.02$), and age at transplantation, with an RR of 1.03 (1-1.06, $p 0.034$), as significant for survival. Patients resuming smoking after transplantation had a significantly higher risk of dying from solid organ cancer, with an RR of 2.54 (1.03, 6.28; $p 0.04$) with a short median survival time (25th-75th percentile) of (1 (0-5) months, $p 0.007$).

Conclusion: Patients who resume smoking after heart transplantation have worse survival and are at higher risk of dying from solid organ cancer. Implementing a smoking cessation plan throughout the post-transplant period is important.

Key words: smoking, survival, heart transplantation

Introduction

Tobacco use is deleterious to public health. In 2015, 11.5% of global deaths were attributable to smoking worldwide¹. In the US population, smokers lose at least one decade of life expectancy compared with those who have never smoked². Most of the excess mortality is due to neoplastic, vascular, respiratory, and other diseases that can be caused by smoking. Additionally, after organ transplantation, survival is impaired by smoking, and malignancies are a major cause of death > 5 years after heart transplantation³. After heart transplantation, smokers have worse survival, with an estimated 10-year survival of 62% versus 55% for those who never smoked⁴. Although quitting smoking is a prerequisite for being placed on the transplantation list, patients often resume smoking after transplantation. To better explore the issue of smoking and comorbidities after heart transplantation, an observational study was performed at Antwerp University Hospital. We will describe smokers and former smokers and assess the prognostic impact of smoking status on malignancies, the progression of arterial disease and survival.

Methods

This is a retrospective study of patients performed after heart transplantation during follow-up between 1995 and 2019 at Antwerp University Hospital, Belgium. The study was approved by the ethics committee. The medical records of the patients were used to obtain information on patient and transplant characteristics and comorbidities. The recorded patient data were age, gender, type of cardiomyopathy, body mass index, and malignancies prior to transplantation. The transplant data implied the time of survival after transplantation, cause of death, type of immunosuppression used for maintenance (double versus triple regimen and the drugs used) and the number of rejections that were treated. Data on comorbidities focused on malignancies and cardiovascular pathology. For malignancies, the type (biopsy-proven) and time to the first and second malignancy were assessed. Solid organ cancers were defined as all cancers except skin and haematological malignancies. For cardiovascular comorbidities, we recorded percutaneous coronary interventions, peripheral vascular

disease with complaints (cerebrovascular accident or claudication) or interventions for arterial disease. The smoking history of each patient was documented by a questionnaire. This questionnaire concerned past (consumption in pack years, stopping date, and use of stopping aids) and present smoking habits (consumption in pack years). Smoking was defined as tobacco use.

Statistical methods

Variables are expressed as the mean $\pm$ 1 SD and percentages. For smaller groups, the median (25th, 75th percentile) was assessed. A Chi-squared test was used for intergroup analysis. A Cox proportional hazards regression analysis was performed to analyse the independent predictors of long-term survival and the mortality of cancer. These were reported as the relative risk (RR) with the 95% confidence interval (CI). A p-value < 0.05 was considered statistically significant. Statistical analyses were performed with MedCalc, version 17.5.5 (MedCalc Software bvba, Ostend, Belgium).

Results

A total of 130 patients were studied after heart transplantation between 1995 and 2019 in Antwerp. The mean follow-up was 11 $\pm$ 5.5 years. Additional details on the patient characteristics are given in Table 1. As shown, 65% of our study population had a history of tobacco use before transplantation. All patients stopped smoking before transplantation as requested by the programme. However, 26% of the previous smokers resumed smoking after transplantation. No difference in consumption in pack years was noted between the two groups, with a mean of 28 $\pm$ 18 pack years for those who remained abstinent versus 25 $\pm$ 8 pack years for those who resumed smoking. Patients who resumed smoking were significantly younger at the time of transplantation, used fewer statins and were more likely to be treated with azathioprine after transplantation. In Table 2, we describe the development of comorbidities after heart transplantation in view of the smoking history. Solid organ cancers, particularly lung cancer, but not vascular disease, were of major concern. Thirty cases of solid organ cancers were noted, including 15 cases of lung, 2 cases of prostate, 2 cases of larynx, 2 cases of bladder and 9 cases of other cancers. The mean survival time after the diagnosis of solid organ

cancer was 26±40 months for all patients. Solid organ cancers, and in particular lung cancer, were more prevalent in smokers, especially in those who resumed smoking. For skin cancer, smoking status was not significant.

A Cox proportional hazards regression analysis of the age at transplantation, BMI, consumption in pack years, smoking history, number of treated rejections after transplantation and gender identified smoking resumption, with a RR of 2.31 (1.14-4.68) (p 0.02), and age at transplantation, with a RR of 1.03 (1-1.06) (p 0.034), as significant determinants for long-term survival (see Figure 1). The determinants studied for their association with the development of solid organ cancer included age at transplantation, BMI, consumption in pack years, smoking history, number of treated rejections after transplantation and gender. Patients resuming smoking after transplantation had a significantly higher risk of dying of solid organ cancer, with a RR of 2.54 (1.03, 6.28) (p 0.04). The median survival time of these patients was short (1 (0-5) months (Table 2)). In 38% of patients, metastases were already present at the time of solid organ cancer diagnosis, which was not linked to their smoking history.

Discussion

This study was performed to evaluate the outcome after heart transplantation in Antwerp to identify risk factors for poor survival and to improve post-transplant follow-up. The smoking habits of our patients in particular were a neglected problem.

Long-term survival in patients after solid organ transplantation is hampered by the development of cancer. Malignancies are the cause of death > 5 years after heart transplantation in 20% of patients⁴. A thorough pre-transplant work-up can lead to the detection of 15% of asymptomatic carcinomas⁵. Screening for malignancies every 1-2 years post-transplant is standard care⁶. Despite the intensive follow-up, 22-67% of transplant patients died of malignancies. Their survival time was very short. Thirty-eight percent of solid organ cancers in our cohort and 79% of lung cancers in a Spanish registry were disseminated at the time of diagnosis, illustrating the devastating course of this

disease⁷. In addition to screening strategies for the early detection of malignancies, the management of the immunosuppressive regimen and the prevention of dangerous behaviour, such as tobacco use, deserve equal attention.

The immunosuppressive drugs used to prevent allograft rejection are associated with a risk of malignancy⁸. Minimizing the doses and the number of these drugs is standard care during the first year after heart transplantation (CARE). Additionally, the type of immunosuppressive drug is important. Patients who resumed smoking were, in our cohort, more likely to be treated with azathioprine instead of mycophenolate mofetil (MMF) due to historical use or side effects. Switching from azathioprine to MMF has been shown to reduce the incidence of squamous cell carcinoma in lung transplant recipients⁹. Patients who resume smoking are also less likely to use statins, although statins are part of standard immunosuppressive therapy⁶. Statins are associated with increased cancer-free survival after heart transplantation¹⁰.

An important but often neglected factor in post-transplant management is the prevention of dangerous behaviour, particularly tobacco use. The listing criteria for heart transplantation of the ISHLT recommend education on the importance of tobacco cessation before transplantation (Class I) and state that it is reasonable to consider active tobacco smoking, especially during the previous 6 months, as a relative contraindication for heart transplantation (Class IIa)¹¹. We noted a rate of 65% of tobacco use, including that of former and active smokers, in our transplant population. In Belgium, 19% of the general population were active smokers in 2018 versus 30% in 1997¹². Considering this shift in tobacco use, the rate of smoking can be high in a historical cohort. Heart transplantation is also reserved for end-stage heart failure, with coronary artery disease as the major underlying cause. A review of the literature reveals that approximately 24% of heart transplant recipients return to tobacco abuse after transplantation, despite adhering to the policy of cessation before surgery¹³. Rates of smoking recurrence between 11 and 40% after solid organ transplantation are reported¹⁴. The underlying diagnosis leading to heart or lung disease but not

gender or age is a risk factor that increases the likelihood of tobacco resumption after transplantation¹⁵. Additionally, a short period of abstinence before transplantation and exposure to second-hand smoking are risk factors. Given the high rate of smoking recurrence after transplantation, it comes as a surprise that the issue was not covered in the 2010 International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients (CARE). Guidelines for the general population offer only scarce advice on how to handle patients who resume smoking after a life-saving event. Research concerning smoking cessation strategies and their safety, tolerance and effectiveness in thoracic organ transplantation patients is lacking. Counselling and encouragement remain important throughout the whole post-transplant period. Implementing a smoking cessation plan after heart transplantation should be considered, not only for patients but also for smoking relatives¹⁶. A standardized questionnaire and repeated cotinine testing can be applied.

Our results must be interpreted with caution. This was an observational study, and questionnaires were used. Measurement of urinary cotinine or carbon monoxide in exhaled air is more reliable for monitoring smoking. Because of the small number of patients and rigorous definition of vascular complications used in this study, we were not able to document the progression of arterial disease. Despite these limitations, our results are in line with those of earlier reports on the subject.

In conclusion, we could state that patients who resume smoking after transplantation have worse long-term survival and are at higher risk of dying from solid organ cancer. Their survival time after diagnosis is short. Decreasing the doses and numbers of immunosuppressive drugs and early screening for cancer are insufficient to improve survival. The follow-up and guidance of patients in terms of smoking habits after heart transplantation is important. Implementing a smoking cessation plan throughout the post-transplant period is mandatory.

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Table 1: Patient characteristics

Before heart transplantation	Non-smokers	Smokers		p-value
After heart transplantation		Abstinent	Resume smoking	
n	46	62	22	
Female	11 (24%)	12 (19%)	5 (23%)	ns
BMI	25 ($\pm$ 3)	25 ($\pm$ 4)	26 ($\pm$ 3)	ns
Age at transplantation (years)	52 ($\pm$ 11)	56 ($\pm$ 10)	50 ($\pm$ 9)	0.044
Primary ischemic cardiac disease	24 (53%)	24 (39%)	8 (36%)	ns
On statins after transplant	43 (96%)	60 (97%)	18 (82%)	0.037
Azathioprine after transplantation	9 (20%)	8 (13%)	9 (41%)	0.019
Triple immunosuppressive regimen	40 (87%)	53 (86%)	20 (91%)	ns
Treated rejections after transplant (%)	15 (32%)	23 (37%)	10 (46%)	ns

Table 2: Comorbidities after transplantation and smoking history

Before heart transplantation	Non-smokers	Smokers	p- value	
After heart transplantation		Abstinent	Resume smoking	
n	46	62	22	
Any malignancy after transplantation	13 (29%)	26 (42%)	13 (59%)	ns
Skin cancer	11 (24%)	19 (30%)	6 (27%)	ns
Lung cancer	1 (2%)	8 (13%)	6 (27%)	0.01
Solid organ malignancy	6 (13%)	14 (23%)	10 (45%)	0.014
Survival time (months) after solid organ cancer diagnosis (median, (25 th , 75 th percentile))	16 (6-99)	11 (4-52)	1 (0-5)	0.007
Time to solid organ malignancy (months)	88±57	93±32	24±66	0.005
Time to first malignancy (all) (months)	82±43	75±33	114±60	0.03
Death due to malignancy	4 (22%)	10 (48%)	10 (67%)	0.045
Any arterial disease	7 (16%)	13 (21%)	8 (36%)	ns
coronary	2 (4%)	2 (3%)	3 (14%)	ns
other	5 (11%)	11 (18%)	5 (23%)	ns

Figure 1: Overall survival after heart transplantation

