Graft coronary artery disease is strongly related to the aetiology of heart failure and cellular rejections

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Aims To identify risk factors for the development of coronary artery disease after heart transplantation.

Methods and Results In consecutive heart transplanted patients, who underwent coronary angiography at the first year follow-up, the aetiology of heart failure in 113 was ischaemic heart disease or dilated cardiomyopathy. Development of clinically significant graft coronary artery disease was analysed vs recipient and donor pre- and post-transplantation variables. At 1, 5 and 9 years follow-up, coronary artery disease had developed in 4%, 16%, and 20% of the included patients, respectively. Among patients with ischaemic heart disease as the aetiology of heart failure, 38% developed graft coronary artery disease, while the corresponding figure for patients with dilated cardiomyopathy was 9% (P<0.001) during 9 years of follow-up. In multivariate regression analysis, the aetiology of ischaemic heart disease and the number of cellular rejections were independent predictors of developing graft coronary artery disease, with risk ratios of 5.8, (95% confidence interval of 2.2–14.8 (P=0.0003)) and 3.3, (95% confidence interval of 1.7–6.5 (P=0.0004)), respectively. Classical risk factors for coronary artery disease did not influence the development of graft coronary artery disease.

Conclusions Ischaemic heart disease as the aetiology of heart failure and the number of cellular rejections were powerful independent predictors of development of graft coronary artery disease following heart transplantation. The low incidence of graft coronary artery disease among patients with dilated cardiomyopathy implies that coronary angiography after heart transplantation can be made on a more selective basis.

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Key Words: Coronary artery disease, risk factor, heart transplantation, graft coronary artery disease, nitroglycerin.

Introduction

The development of graft coronary artery disease is a major limiting factor of long-term survival following heart transplantation[1–2]. The proportion of transplanted patients who develop graft coronary artery disease, as evaluated by coronary angiography, has previously been reported to be approximately 15% at 1 year and 45% at 5 years following heart transplantation[3]. A variety of factors have been associated with the development of graft coronary artery disease in previous, mainly cross-sectional, studies. Variables such as the aetiology of heart failure, recipient and donor age, recipient and donor gender match or mismatch, AB0 blood group match or mismatch, donor organ ischaemic time, immunosuppression induction therapy, number of rejection episodes, cytomegalovirus infection, cyclosporine-A treatment, and classical risk factors for ischaemic heart disease such as hypertension, diabetes, and hypercholesterolaemia have shown an occasional positive correlation to graft coronary artery disease in some studies[2,4–9], while other studies have shown a negative or a lack of correlation[10–15].

The aim of the present study was to analyse pre- and post-transplantation variables in order to identify risk factors for development of graft coronary artery disease, using the advantage of a longitudinal study design over 9 years following heart transplantation.

Methods

From January 1988 to December 1993, heart transplantation was performed in 147 patients at Sahlgrenska
Table 1 Pre-transplantation variables for all study patients and the subgroups IHD and DCMP, as defined in methods, respectively

<table>
<thead>
<tr>
<th>Variable</th>
<th>All study patients</th>
<th>IHD subgroup</th>
<th>DCMP subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>113</td>
<td>45</td>
<td>68</td>
</tr>
<tr>
<td>Recipient age (years)</td>
<td>44 ± 13</td>
<td>51 ± 6***</td>
<td>39 ± 15</td>
</tr>
<tr>
<td>Age range (years)</td>
<td>4–63</td>
<td>39–63</td>
<td>4–60</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>91 (81)</td>
<td>37 (82)</td>
<td>54 (79)</td>
</tr>
<tr>
<td>Donor age (years)</td>
<td>29 ± 11</td>
<td>33 ± 10**</td>
<td>27 ± 11</td>
</tr>
<tr>
<td>Donor gender, male n (%)</td>
<td>74 (65)</td>
<td>33 (73)</td>
<td>41 (60)</td>
</tr>
<tr>
<td>Gender mismatch, n (%)</td>
<td>41 (36)</td>
<td>18 (40)</td>
<td>23 (34)</td>
</tr>
<tr>
<td>Blood group mismatch, n (%)</td>
<td>26 (23)</td>
<td>9 (20)</td>
<td>17 (25)</td>
</tr>
<tr>
<td>Graft ischaemic time (min)</td>
<td>160 ± 42</td>
<td>159 ± 44</td>
<td>160 ± 41</td>
</tr>
<tr>
<td>Drug treated diabetes, n (%)</td>
<td>5 (4)</td>
<td>2 (4)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Triglycerides (mmol . l⁻¹)</td>
<td>1.5 ± 0.7</td>
<td>1.7 ± 0.8***</td>
<td>1.3 ± 0.6</td>
</tr>
<tr>
<td>Cyclosporine-A induction, n (%)</td>
<td>47 (42)</td>
<td>17 (38)</td>
<td>30 (44)</td>
</tr>
</tbody>
</table>

IHD=aetiology of ischaemic heart disease; DCMP=aetiology of dilated cardiomyopathy. **P<0.01, ***P<0.001, ischaemic heart disease vs dilated cardiomyopathy.

University Hospital in Göteborg, Sweden. Only patients with ischaemic heart disease and dilated cardiomyopathy were included in the study to avoid interpretation bias from heart failure of other aetiologies. The study patients had completed a follow-up of at least a year, which included coronary angiography, and were followed until December 1997. The end-point was graft failure (mortality and re-transplantation). Ischaemic heart disease was defined as previous myocardial infarction, according to the criteria of the World Health Organisation, previous coronary bypass grafting, significant coronary artery disease on coronary angiography or findings at autopsy that the condition of the recipient heart corresponded to ischaemic heart disease. Dilated cardiomyopathy was defined as ventricular dilation with impaired systolic function without significant coronary artery disease on coronary angiography or autopsy. If the findings were inconsistent, a cardiologist, radiologist and pathologist made a joint decision on the diagnosis. A reconsideration regarding 13 patients resulted in a change of aetiology in three patients: the condition of two was attributed to ischaemic heart disease and one to dilated cardiomyopathy. Among the 147 patients the following 34 were excluded: seven with congenital heart disease, one with hypertrophic cardiomyopathy, three with an aetiology of dilated cardiomyopathy who had a re-transplantation performed before the first year follow-up (one patient because of vascular rejection and two because of cellular rejection), and 23 transplanted patients who died before the first year follow-up (three patients from cellular rejection, one from vascular rejection, four from infection, six from per-operative graft failure, four from per-operative bleeding, one from cerebral bleeding, three from malignancy, and one from pancreatitis). Among the excluded transplanted patients alive, three patients developed graft coronary artery disease (one after re-transplantation, one with hypertrophic cardiomyopathy, and one with congenital heart disease). Among the 23 transplanted patients who died during the first postoperative year, the aetiology was ischaemic heart disease in 11 and dilated cardiomyopathy in 12 patients. Autopsies were performed in nine ischaemic heart disease and eight dilated cardiomyopathy patients, respectively. The results showed that six ischaemic heart disease (55%) and three dilated cardiomyopathy (25%) patients, had minor changes in their coronary vessels except for one ischaemic heart disease patient, who had moderate graft coronary artery disease. The remaining 113 patients constituted two subgroups: 45 with ischaemic heart disease and 68 with dilated cardiomyopathy as the aetiology of heart failure. Baseline data are presented in Table 1.

A pre-transplantation evaluation, including coronary angiography where applicable, and evaluation of variables as listed in the introduction, was performed. Post-transplantation, the tests were repeated at yearly follow-ups and complications were registered continuously. During coronary angiography, 5 mg of sub-buccal nitroglycerin was routinely given to prevent coronary artery spasm. Graft coronary artery disease was defined as significant coronary artery stenosis on coronary angiography i.e. ≥50% reduction in lumen diameter in at least one coronary vessel. A 50% reduction in diameter in non-transplanted patients is the common limit for a coronary intervention. This is according to ‘the gold standard’ introduced by Gould et al., who showed that a reduction of 50% in lumen diameter is the point at which flow reserve becomes compromised during exercise[16]. As a consequence of this, we evaluated the angiograms according to routine standard radiology. All angiograms in patients with significant stenosis, according to the referral answer, and the most recent angiograms performed in patients without significant stenosis were re-evaluated by a single radiologist, blinded to the aetiology of the heart failure. In total, 221 angiograms were re-evaluated. A total of 666 angiograms may have been performed in our study patients, but 79 angiograms were missing. Of these,
angioograms were later performed in 41, and demonstrated the same pattern as before, therefore not affecting the results of the study. The remaining 38 missing angiograms (6·8% in the ischaemic heart disease group and 5·0% in the dilated cardiomyopathy group) reduced the follow-up time. Coronary interventions, e.g. percutaneous transluminal coronary angioplasty, were recorded. Intravascular ultrasound was not used routinely in our institution. Endomyocardial biopsies were performed during the first post-transplantation year, and thereafter only when rejection was suspected. Cellular rejection was defined as an abnormal histopathological endomyocardial biopsy findings that required augmented treatment. The number of biopsy occasions with inflammatory cells affecting the graft vessels were also recorded. The results of 2156 biopsy occasions during the first year were evaluated. Hypertension was defined as a diastolic blood pressure repeatedly exceeding 90 mmHg. Diabetes was defined as a fasting blood glucose ≥6·7 mmol.1⁻¹ on repeated measurements. Hypercholesterolaemia was defined as serum cholesterol ≥6 mmol.1⁻¹. Patients with drug treatment for hypertension, diabetes, or hypercholesterolaemia were registered at the first and last year of follow-up. Lipid levels were also registered at the first and last year of follow-up. Cytomegalovirus infection was defined as immunoglobulin-G/immunoglobulin-M titre switch, or positive findings by polymerase chain reaction technique during the first follow-up year. Immunosuppression induction therapy comprised cyclosporine-A (Sandimmun®, Sandoz Pharma Ltd, Basel, Switzerland) or anti-thymocyte-globulin (Thymoglobulin®, Pasteur-Merieux, Lyon, Cedex, France). The serum cyclosporine-A concentration (µg.1⁻¹), which was registered at every follow-up, was analysed by the EMIT® method (Behring Diagnostika, Stockholm, Sweden). The reason for re-transplantation and death were registered. The study was approved by the Ethical Committee at the University of Göteborg.

Statistics

The log rank test was used to test the statistical significance of the univariate association between the development of graft coronary artery disease and patient characteristics. The development of graft coronary artery disease and graft survival during follow-up were estimated by the Kaplan–Meier method. Cox’s multivariate stepwise regression model was used to identify independent predictors of development of graft coronary artery disease. All variables with a univariate P-value <0·05 that correlated with the outcome were included. Differences in pre- and post-transplantation characteristics between ischaemic heart disease and dilated cardiomyopathy patients were tested using Fisher’s exact test for dichotomous variables and the Mann–Whitney U test for continuous/ordered variables. All P-values are two-tailed and nominal. A P value <0·05 was considered statistically significant.

Results

All study patients

Among the 113 patients included in the study, graft coronary artery disease developed in 23 patients (20%) during a maximum of 9 years follow-up. The incidence of graft coronary artery disease development at 1 year was 4%, at 3 years 5%, at 5 years 2%, at 7 years 2%, and at 9 years 0%. During the study 22 patients died and two had a re-transplantation during the follow-up.

Univariate analysis of pre-transplantation variables showed that ischaemic heart disease as an aetiology of heart failure and donor age correlated significantly with graft coronary artery disease development. Post-transplantation, the number of treated cellular rejections and the number of biopsy occasions with vascular inflammation affecting the graft vessels also correlated significantly with the development of graft coronary artery disease. Other pre- and postoperative variables, as listed in the introduction and methods section (recipient age, match or mismatch of recipient and donor gender, match or mismatch of ABO blood group, donor organ ischaemic time, choice of immunosuppression induction therapy, cytomegalovirus infection, cyclosporine-A concentrations, and classical risk factors for ischaemic heart disease such as hypertension, diabetes, and hypercholesterolaemia), did not significantly correlate with the development of graft coronary artery disease. In the multivariate analysis, an aetiology of ischaemic heart disease and the number of treated cellular rejections were independent predictors of graft coronary artery disease development (Table 2).

Subgroups of patients with ischaemic heart disease and dilated cardiomyopathy as the aetiology of heart failure

Among the ischaemic heart disease patients, 17 (38%) developed graft coronary artery disease during follow-up, as compared to six (9%) of the dilated cardiomyopathy patients. The development of graft coronary artery disease over time differed significantly between the subgroups (Fig. 1). There were significant differences in pre-transplantation variables between ischaemic heart disease and dilated cardiomyopathy patients; ischaemic heart disease patients had a higher recipient age, a higher donor age, and higher blood lipid values than the dilated cardiomyopathy patients (Table 1). Post-transplantation, ischaemic heart disease patients had a higher proportion of patients with drug treatment for hypercholesterolaemia, although the actual blood lipid values were similar in the two subgroups at 1 year and at the last year of follow-up (Table 3). Late (>5 years) graft survival was significantly lower in ischaemic heart disease as compared to dilated cardiomyopathy patients (P=0·02) (Fig. 2), but after correction for age, the significant difference between the two graft survival
curves was lost ($P=0.23$). Among the ischaemic heart disease patients, one had a re-transplantation (because of vascular rejection) and 12 (29%) died (one from myocardial infarction, one from cellular rejection, one from heart failure, two from infection, two from cerebral events, four from malignancy, and one from peptic ulcer). Among the dilated cardiomyopathy patients, one had a re-transplantation (due to myofibrosis) and 10 (16%) died (three from cellular rejection, one from vascular rejection, two from infection, two from malignancy and two were suicides). Percutaneous transluminal coronary angioplasty was performed in four patients (three ischaemic heart disease and one dilated cardiomyopathy).

The influence of rejection on graft coronary artery disease development

Both ischaemic heart disease and dilated cardiomyopathy patients with graft coronary artery disease had twice as many treated cellular rejections as those without graft coronary artery disease (Fig. 3). Only the dilated cardiomyopathy patients showed a significant difference in the number of biopsy occasions, with vascular inflammation affecting the graft vessels, between those who developed graft coronary artery disease compared to those who did not (Table 4).

<p>| Table 2 Uni- and multivariate predictors of graft coronary artery disease development |</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate $P$</th>
<th>RR</th>
<th>95% CI</th>
<th>Multivariate $P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHD aetiology</td>
<td>0·0002</td>
<td>5·8</td>
<td>2·2-14·8</td>
<td>0·0003</td>
</tr>
<tr>
<td>Donor age</td>
<td>0·02</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cellular rejection</td>
<td>0·001</td>
<td>3·3</td>
<td>1·7-6·5</td>
<td>0·0004</td>
</tr>
<tr>
<td>Vascular inflammation</td>
<td>0·001</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

$P=level$ of significance; $RR=risk$ ratio; $95\% CI=95\% confidence$ interval; IHD aetiology=aetiology of ischaemic heart disease; cellular rejection=number of treated cellular rejections during the first year; vascular inflammation=number of biopsy occasions with vascular inflammation affecting the graft vessels during the first year.

Patients who developed graft coronary artery disease vs those who did not

A comparison of data between patients who developed significant graft coronary artery disease vs those who did not, only revealed significant differences in donor age, number of treated rejections and number of biopsy occasions with vascular inflammation. The recipient age among patients with graft coronary artery disease was 46±10, and 43±14 years among those without ($P=0.605$). Among the 23 patients with graft coronary artery disease, eight reached an end-point (one had a re-transplantation and seven died) during follow-up. Five of these eight patients had an autopsy performed (three ischaemic heart disease and two dilated cardiomyopathy patients). In the three ischaemic heart disease patients, autopsy verified atherosclerotic coronary artery disease of the same type as that seen in non-transplanted patients with ischaemic heart disease. The two dilated cardiomyopathy patients had graft coronary artery disease according to angiography but autopsy revealed normal coronary vessels (Fig. 4). All angiograms in the first dilated cardiomyopathy patient were performed with simultaneous nitroglycerin treatment, but they nevertheless showed progressive pathological changes over 3 years. In the most recent angiogram, this patient had seven short stenoses, three long stenoses, and seven distal occlusions. This last angiogram was performed 3 months before the patient died from cellular rejection. The second dilated cardiomyopathy patient had two short stenoses and two long stenoses, which were also progressive over 5 years, despite nitroglycerin treatment. This patient died from pneumonia, 14 months after the last angiogram. Both patients had vascular inflammation on their endomyocardial biopsies. In another eight patients without graft coronary artery disease (five ischaemic heart disease and three dilated cardiomyopathy patients), autopsies verified normal coronary arteries.
Patients without significant graft coronary artery disease

Among the 90 patients without significant graft coronary artery disease, as defined in the methods section, 12 patients had minor lesions. Of these 12, six had an aetiology of ischaemic heart disease (13%) and six an aetiology of dilated cardiomyopathy (9%). Among the ischaemic heart disease patients, four had wall irregularities in one vessel and two had one short stenosis. Among the dilated cardiomyopathy patients, four had one short stenosis, one had one short and one long stenosis, one had a combination of one ectasia, one short, and one long stenosis, respectively. These 12 patients were not included among the patients with graft coronary artery disease as their coronary changes did not fulfil the definition of disease as put forward in this study. The remaining 78 patients were free of changes on coronary angiography, 22 of them had ischaemic heart disease as an aetiology (49%) and 56 had dilated cardiomyopathy (82%).

Discussion

In the present study, ischaemic heart disease as the aetiology of heart failure was identified as a strong independent predictor of the development of graft coronary artery disease, whereas conventional risk factors for coronary artery disease were not. We decided to omit aetiologies other than ischaemic heart disease and dilated cardiomyopathy to achieve sufficiently large groups for analysis. The long-term follow-up made it possible to detect the development of graft coronary artery disease over time. Probably, partly due to the study design, we were able to find highly significant predictors for the development of graft coronary artery disease.
Donor age significantly correlated with the development of graft coronary artery disease, hence, pre-existing coronary artery disease in donor hearts might explain a higher incidence of graft coronary artery disease in the ischaemic heart disease patients\(^{[17]}\). However, the donors for ischaemic heart disease patients were relatively young (mean age of 33 years, range 14–50) and preoperative coronary angiograms were regularly performed in older donors to exclude coronary artery disease. Furthermore, palpation during organ explantation did not reveal any signs of coronary calcification, and there was no difference in the incidence of graft coronary artery disease at the first year follow-up between ischaemic heart disease and dilated cardiomyopathy patients (Fig. 1). Therefore, factors other than pre-existing coronary artery disease in the donor heart were more likely to explain the difference in the development of graft coronary artery disease between the two groups. Neither the incidence of hypertension nor diabetes differed between ischaemic heart disease and dilated cardiomyopathy patients, consequently, these factors are probably without influence on the result. Pre-transplantation, ischaemic heart disease patients had higher blood lipid levels than dilated cardiomyopathy patients. There were, however, no differences during follow-up, possibly due to treatment with statins in 60% of ischaemic heart disease vs 19% of dilated cardiomyopathy patients at the time of the first year follow-up. Therefore, high blood lipid values per se probably did not influence the observed difference in graft coronary artery disease between the ischaemic heart disease and dilated cardiomyopathy group. However, the overall low prevalence of graft coronary artery disease might partly be explained by the frequent treatment with statins, which has been shown to reduce the number of patients who develop graft coronary artery disease\(^{[18]}\). Hence,
conventional risk factors for developing coronary artery disease among non-transplanted patients do not seem to influence the development of graft coronary artery disease.

Despite a longer follow-up, our study showed a considerably lower incidence of graft coronary artery disease than earlier studies where the same technique was applied[3-5]. According to our experience, false coronary obstructions due to coronary spasm commonly occurred before routine use of nitroglycerin at coronary angiography. In our first patients, multivessel disease was sometimes suspected, but the coronary angiograms were often completely normalized after nitroglycerin administration. Therefore, coronary spasm may account for the previously reported higher incidences of graft coronary artery disease, as it has not been stated whether nitroglycerin was given or not. The use of nitroglycerin has reduced the bias of false graft coronary artery disease in our study and in that way perhaps also contributed to our findings of highly significant predictors.

The number of treated cellular rejections during the first post-transplantation year was an independent predictor of graft coronary artery disease. The number of treated cellular rejections and biopsy occasions with vascular inflammation also differed between those who developed graft coronary artery disease and those who did not. However, the results were complex and the variation among individual patients was large. Moreover, the majority of patients had \( \leq 2 \) treated rejections (Fig. 3). Immunoreactive injury to the endothelium is considered to be a potential cause of graft coronary artery disease[1,19,20]. The time of rejection has also been shown to correlate with the development of graft coronary artery disease in short-term follow-up[21]. Furthermore, circulating immunoreactive proteins are known to vary with coronary artery disease in both transplanted and non-transplanted patients[22–23]. This was perhaps demonstrated by the two dilated cardiomyopathy patients who were classified as having graft coronary artery disease according to their angiograms (Fig. 4) but autopsy revealed normal coronary vessels. Another patient had a re-transplantation because of vascular rejection and autopsy of the first graft showed normal coronary arteries filled with macrophages. Therefore, apart from the possibility of coronary spasm, false graft coronary artery disease might be caused by immunological deposits. Treated cellular rejections were more frequent in patients who developed graft coronary artery disease, regardless of heart failure aetiology. However, only the dilated cardiomyopathy patients with graft coronary artery disease seemed to have more frequent biopsy occasions with vascular inflammation affecting the graft vessels. As only six dilated cardiomyopathy patients developed graft coronary artery disease and at least two of them did not actually have graft coronary artery disease according to autopsy, any conclusion is questionable. The finding may indicate a difference, depending on aetiology, in the mechanisms for development of graft coronary artery disease.
Our definition of graft coronary artery disease, which is commonly used in clinical practice, clearly underestimates the number of cases with any degree of coronary artery disease. If non-significant lesions had also been included, the incidence of graft coronary artery disease would have been higher among our study patients. However, this would involve an additional uncertainty due to the shortcomings of the angiographic method used to distinguish minor lesions from normal vessels. Intra-coronary ultrasound has been advocated as the method of choice as it can detect atherosclerotic changes at an earlier stage\cite{17}, although the risk of endothelial damage in heart transplanted patients from the procedure itself is unclear. Moreover, graft coronary artery disease also affects the distal parts of the coronary vessels where the ultrasound probe can not reach, and the heart transplanted patients in our study have frequently reacted with coronary artery spasm, which are other limitations for intracoronary ultrasound. Nevertheless, the current angiographic criteria used in our study, based on the findings by Gould et al.\cite{16}, were clinically relevant since the patients without graft coronary artery disease, including those with non-significant lesions, had excellent long-term survival. Coronary angiography is also relevant for clinical use when an intervention is considered. Discrete atherosclerotic obstructions can often be treated with percutaneous transluminal coronary angioplasty in contrast to diffuse multiple lesions\cite{24}. Among our patients, percutaneous transluminal coronary angioplasty was successfully performed in four patients (three of them with ischaemic heart disease) which may have had a positive influence on the survival of the ischaemic heart disease patients.

The reasons for a high incidence of graft coronary artery disease among the ischaemic heart disease patients have not been explained, but it is suggested that hitherto poorly understood factors in patients with ischaemic heart disease could exert a negative influence on the coronary arteries of the donor heart. Also, among patients with minor lesions on coronary angiography, but without significant graft coronary artery disease, ischaemic heart disease was more frequent than dilated cardiomyopathy as the aetiology of heart failure. Patients without any angiographic changes predominantly had dilated cardiomyopathy as the aetiology. This finding may help us to further understand the development of graft coronary artery disease and has implications for future research on the development of coronary artery disease, also among non-transplanted patients.

Conclusions

Ischaemic heart disease as the aetiology of heart failure was a powerful independent predictor for the development of graft coronary artery disease following heart transplantation. The number of cellular rejections during the first post-transplantation year was also an independent predictor of graft coronary artery disease development. The presence of hypertension, diabetes mellitus, or high blood lipid levels did not influence the development of graft coronary artery disease.

Our findings imply that annual coronary angiographies after heart transplantation may be performed more selectively, mainly in patients with ischaemic heart disease the aetiology of heart failure and in those with frequent cellular rejections. We strongly recommend the routine use of nitroglycerin to prevent coronary spasm at coronary angiography after heart transplantation.

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References


