CLINICAL RESEARCH

Chronic heart failure in heart transplant recipients: Presenting features and outcome

Insuffisance cardiaque chronique chez le greffé cardiaque : présentation initiale et devenir

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KEYWORDS
Heart transplantation; Heart failure; Rejection

Summary
Background. — The ageing graft frequently shows coronary lesions and a restrictive physiology.
Aims. — To determine the presenting features and outcome of chronic heart failure in heart transplant recipients.
Methods. — In this cohort study, we compared 44 consecutive heart transplant recipients who developed chronic heart failure more than 1 year after heart transplantation with 44 control heart transplant recipients who did not develop heart failure.
Results. — We found that patients who developed heart failure had more frequently a history of hypertension or diabetes before transplantation. During the 12 months after transplantation, significantly more patients had moderate-to-severe acute rejections (≥ grade 2R) in the heart failure group than in the control group. At the time of heart failure diagnosis, systolic left

Abbreviations: CAV, Cardiac allograft vasculopathy; HF, Heart failure; HTR, Heart transplant recipient; ISHLT, International Society for Heart and Lung transplantation; LV, Left ventricular; LVEF, Left ventricular ejection fraction.
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ventricular function was preserved in 50% of patients and coronary angiography was normal or near normal in 36% of patients. Half of the 44 patients in the heart failure group died within 2 years of heart failure diagnosis. Ascites and end-stage renal failure requiring dialysis were significantly more frequent during follow-up in the heart failure group than in the control group (respectively, 10/44 vs 0/44 [P = 0.001] and 18/44 vs 5/44 [P = 0.003]).

**Conclusion.** — In heart transplant recipients presenting with heart failure, systolic left ventricular function is frequently preserved and coronary angiography is frequently abnormal, but may be normal or near normal. During follow-up, the main features of these patients are a high mortality rate after heart failure diagnosis, a frequent need for renal dialysis and frequent ascites.

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**Background**

In the years after heart transplantation, the cardiac graft frequently deteriorates at an accelerated rate. The predominant features of the ageing graft at pathology are a diffuse thickening of the arterial intima, named cardiac allograft vasculopathy (CAV), and myocardial fibrosis [1,2]. Clinical manifestations are sudden death, ventricular and supraventricular arrhythmias, acute coronary syndromes and congestive heart failure (HF) [3]. The full spectrum of presenting features and the outcome of HF in these patients have not yet been fully described. The purpose of this study was to report the characteristics of HF in a cohort of heart transplant recipients (HTRs).

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**Methods**

In this cohort study, we included all the HTRs diagnosed with chronic HF after transplantation (HF group) at our institution between May 1994 and May 2014, who survived more than 1 year after heart transplantation. We compared these patients with HTRs who did not develop HF and survived more than 1 year after heart transplantation (control group). As the risk of developing HF is time dependent and may depend on the immunosuppressive era, each control was matched with one patient from the HF group with a close transplantation date. Each control was the next patient on the chronological list of transplanted patients at our centre who did not develop HF during the study period. Of the 164
HTRs followed at our institution during the study period, 44 met the inclusion criteria in the HF group and 44 controls were matched to these patients.

Criteria for the diagnosis of HF were symptoms associated with either left ventricular ejection fraction (LVEF) < 50% at rest echocardiography and/or elevated filling pressures at right-sided cardiac catheterisation (pulmonary capillary wedge pressure > 15 mmHg or mean right atrial pressure > 8 mmHg) [4]. Accepted symptoms were shortness of breath and/or signs of fluid retention, such as pulmonary congestion, ankle swelling or ascites. Exclusion criteria were as follows: age < 18 years at the time of the diagnosis of HF; chronic HF diagnosed less than 1 year after transplantation, as early graft failure may have different causes and outcome compared with late HF; acute heart rejection associated with transient symptoms of HF and subsequent recovery of normal ejection function and normal filling pressures on a modified immunosuppressive regimen.

All patients had routine follow-up visits at our institution at least every 4 months, including physical examination, laboratory evaluation, electrocardiography, echocardiography and chest X-ray. From 1992 to 1998, most patients were treated using a protocol comprising cyclosporine and prednisolone, with or without additional azathioprine. In 1999, mycophenolate mofetil was introduced to replace azathioprine. In addition, tacrolimus was used instead of cyclosporine in patients with significant rejection or severe side effects. Since 2004, tacrolimus has been used as the calcineurin inhibitor of choice.

At presentation with HF symptoms, the patients had a clinical evaluation, laboratory measurements, standard 12 lead electrocardiography and echocardiography, and were referred, in the absence of contra-indication, for right cardiac catheterization and coronary angiography. Chronic microvoltage was defined as maximum QRS amplitude < 0.5 mV in each limb lead, observed in more than three consecutive electrocardiograms. All Doppler echocardiography studies were performed by an experienced cardiologist (P.A. or G.H.). LVEF was measured using the Simpson’s biplane method or by a visual estimate associated with the Teicholz method. Systolic dysfunction was defined as LVEF < 55%. Significant valve regurgitation was defined as moderate or severe mitral or tricuspid regurgitation. Conventional coronary angiography was performed using either the femoral or radial approach. Right catheterization and endomyocardial biopsies were performed using the femoral approach with the Judkins technique with local anaesthesia. Right ventricular pressures were measured using a 4F National Institute of Health catheter. Coronary angiographies were interpreted by two independent reviewers; if the reviewers disagreed, a third reviewer was consulted and consensus was achieved. Abnormalities at coronary angiography were classified according to the International Society for heart and lung transplantation (ISHLT) classification from CAV0 (no detectable angiographic lesion) to CAV3 [5]. Cardiac allograft rejection was classified according to the revised ISHLT consensus [6].

Statistical analysis

Intergroup comparisons were made using the unpaired Student’s t test or χ² analysis. Multivariable logistic regression analysis was applied to determine independent predictors of HF. We analysed mortality using the Kaplan-Meier model. The log-rank test was used to compare subgroup survival. Statistical analyses were performed using Statview, version 5.0 (SAS Institute Inc., Cary, NC, USA). A value of P < 0.05 was considered as statistically significant in all analyses.

Results

Table 1 shows the baseline characteristics of the 44 HTRs with HF and the 44 controls. Patients who subsequently developed HF had more frequently a history of hypertension or diabetes before transplantation. In a multivariable logistic regression model, including sex, age, hypertension, diabetes and primary cardiac disease, hypertension remained the only significant predictor of HF (P = 0.02). The major primary heart disease was dilated cardiomyopathy in both groups. During the 12 months after transplantation, significantly more patients had moderate to severe acute rejections (≥ grade 2R) in the HF group than in the control group (23% vs 7%; P = 0.03). Body mass index measured 1 year after transplantation did not differ significantly between the HF and control groups (23.8 ± 3.6 vs 24.4 ± 3.2 kg/m²; P = 0.4).

Table 2 shows the presenting features in the HF group at the time of HF diagnosis. The first symptoms of chronic HF were noted as early as 1 year in some cases. However, time since transplantation was 7 years or more in most patients. Ankle oedema and exertional dyspnoea were the more frequent symptoms, and were both present in 15 patients. The type of presentation was progressive HF in 38 patients and acute pulmonary oedema or cardiogenic shock in six patients. In four of these six patients, acute HF was associated with an acute coronary syndrome.

| Table 1 | Characteristics of the heart failure and control groups at the time of transplantation. |
|---------|---------------------------------|-----------------|-------|
|         | Heart failure (n = 44) | Controls (n = 44) | P     |
| Men     | 33 (75) | 38 (86) | 0.3   |
| Age (years) | 45.8 ± 16 | 49.6 ± 14 | 0.2   |
| Primary cardiac disease | | | |
| Ischaemic | | | |
| Idiopathic dilated cardiomyopathy | 15 (34) | 14 (32) | 0.8   |
| Other | 22 (50) | 26 (59) | 0.4   |
| History of hypertension | | | |
| Diabetes | 7 (16) | 4 (9) | 0.3   |
| History of alcohol abuse | 10 (23) | 3 (7) | 0.04  |
| History of smoking | | | |
| Chronic obstructive pulmonary disease | | | |
| Heart/kidney transplantation | 24 (55) | 24 (55) | 0.9   |
| Chronic obstructive pulmonary disease | 2 (5) | 3 (7) | 0.7   |
| Heart/kidney transplantation | 2 (5) | 2 (5) | 0.9   |

Data are expressed as number (%) or mean ± standard deviation.
In the HF group, all patients had a coronary angiography after HF diagnosis. Coronary angiography showed normal arteries (CAV0) in 12 patients, CAV1 in 17 patients (four had only mild coronary irregularities), CAV2 in one patient and CAV3 in 14 patients. All these patients except four had a right cardiac catheterization after HF diagnosis. Pulmonary capillary wedge pressure was >15 mmHg in 31 patients and mean right atrial pressure was >8 mmHg in 25 patients. Endomyocardial biopsies were available from 40 patients at the time of HF diagnosis, and showed mild rejection grade 1R in 12 patients and moderate rejection grade 2R in one patient.

All patients had regular routine echocardiograms during follow-up. In the HF group, LVEF was ≥55% in all patients except one during the first year after transplantation. At the time of HF diagnosis, the end-diastolic left ventricular (LV) diameter was >55 mm in nine patients and LVEF was preserved (≥55%) in half of the patients (n = 22). Five patients had moderate-to-severe tricuspid regurgitation at the time of HF diagnosis.

Mean follow-up was 13.4 ± 5.5 years since transplantation; none of the patients was lost to this follow-up. Thirty-three patients (75%) died in the HF group versus 20 (45%) in the control group (P = 0.009; Fig. 1). Half of the patients in the HF group (n = 22) died within 2 years after the diagnosis of HF. In the HF group, 37 of 44 patients (84%) had a cardiac event during follow-up: cardiac death, retransplantation, hospitalization for HF or supraventricular arrhythmias (Table 3). The last echocardiogram before death showed an LVEF ≥ 55% in 15 of the 33 patients in the HF group. Ten of 33 deaths in the HF group and 3 of 18 deaths in the control group presented in the form of sudden death. Only three patients had an implantable cardioverter defibrillator, all in the HF group. Ascites and end-stage renal failure requiring dialysis were significantly more frequent during follow-up in the HF group than in the control group (Table 3). Mean survival was shorter in the group with impaired LVEF at presentation than in the group with preserved LVEF, but the difference was not statistically significant (29 ± 31 vs 52 ± 44 months; log-rank P = 0.08; Fig. 2).

### Discussion

#### Risk factors for developing HF

We found that patients who subsequently developed HF had more frequently a history of hypertension or diabetes before...
transplantation, and that, in a multivariable analysis, hypertension remained the only predictor of HF among baseline characteristics. During the 12 months after transplantation, significantly more patients had moderate-to-severe acute rejections (> grade 2R) in the HF group than in the control group. Thus, as expected, HF shares several risk factors with CAV in HTRs [2].

Clinical presentation

Our study shows that HF presentation is usually gradual in HTRs, and that the more frequent symptoms of HF are ankle oedema and/or exertional dyspnoea. Attribution of these symptoms to HF raises frequent difficulties, and this may delay an appropriate diagnosis, referral and treatment. For instance, the cardiac origin of dyspnoea may be ambiguous because, on the one hand, many patients concomitantly have anaemia or chronic obstructive pulmonary disease, and, on the other hand, undirected echocardiography reporting normal systolic LV function may be confusing [7]. Similarly, ankle oedema could be related to frequent associated conditions, such as calcium inhibitor or everolimus treatment, and renal failure [8,9]. We can affirm that the patients in the HF group had HF, because: all had impaired systolic LV function and/or elevated filling pressures at cardiac catheterization; ankle oedema was usually associated with exertional dyspnoea or other signs of right HF; survival did not differ in the HF group between patients with or without ankle oedema at presentation (data not shown); most of the patients developed severe HF during follow-up and 84% had a cardiac event during follow-up. Thus, ankle oedema and/or exertional dyspnoea in HTR, although non-specific, warrant extensive evaluation, including echocardiography and right-sided cardiac catheterization.

Systolic ventricular function

A main result of our study is that LV systolic function was preserved in half of the patients at the time of the diagnosis of HF. LV systolic function was frequently still preserved at the last echocardiogram in patients in the HF group who died during follow-up. This result is in agreement with previous demonstrations of the restrictive physiology of the ageing graft [10]. There are several potential reasons for this physiology: frequent LV hypertrophy, myocardial fibrosis due to previous acute rejection or chronic rejection, and coronary artery disease are the more likely explanations [1,11,12].

Coronary angiography

Another important finding of our study is that coronary angiography may be normal or near normal at the time of HF diagnosis. Coronary angiography may miss moderate intimal thickening and intravascular ultrasound is the best examination to demonstrate the absence of CAV [2]. However, coronary angiography ruled out advanced CAV in about one third of the HF group. This suggests that HF in HTR can be related to mechanisms other than CAV. Myocardial fibrosis may be a direct consequence of acute or chronic rejection, through inflammation and scars [11,13]. Other factors have been proposed as participants in allograft fibrogenesis: early ischaemic stress during transplantation; calcineurin inhibitor toxicity; activation of the renin-angiotensin-aldosterone system; hypertension; and chronic renal impairment [11].

![Figure 2. Kaplan-Meier survival graph of 44 heart transplant recipients who developed heart failure, according to left ventricular ejection fraction (LVEF) at heart failure diagnosis (open circles: patients with preserved LVEF; solid circles: patients with impaired LVEF).](image-url)
Follow-up

Our study shows that overall survival was poor in the HF group, as more than half of the patients died within 2 years after the diagnosis of HF. As LV systolic function is frequently preserved, and as sudden death represents about one third of the deaths, the question arises whether conventional thresholds for implantable cardioverter defibrillator indications are suitable for HTRs. Very small series have evaluated implantable cardioverter defibrillator in HTRs [14,15]. In our study, only three patients had an implantable cardioverter defibrillator, because of a global poor prognosis or because most of the patients did not meet current standards for implantation. There is a need for prospective multicentre studies to define implantable cardioverter defibrillator indications in these patients [16].

We found high incidences of ascites and end-stage renal failure during the evolution of HF in HTRs. The two probable main explanations for ascites are renal failure and high venous pressures, as shown by our results. The proportion of patients in the HF group requiring dialysis (41%) was markedly higher than in the control group and other non-selected populations of HTRs (about 4%) [17,18]. Cardiorenal syndrome is a likely explanation for this finding, in association with the factors usually involved in HTR renal failure, such as calcineurin inhibitor toxicity and arterial hypertension [19].

Study limitations

Due to the small size of the population, our study was not powered sufficiently for a more precise determination of the risk factors for HF in HTRs. Moreover, donor-specific antibody levels were not available for most patients, because many of them presented with HF before the era of easy determination of donor-specific antibodies.

Conclusion

The main features of HF in HTRs are the frequent preservation of systolic LV function, even in the months preceding death, a significant prevalence of ascites during follow-up and a frequent need for renal dialysis. Coronary angiography is often abnormal at the time of diagnosis, but may be normal or near normal.

Disclosure of interest

The authors declare that they have no competing interest.

References