Interactive CardioVascular and Thoracic Surgery

Cardiac allograft systolic function. Is the aetiology (ischaemic or idiopathic) a determinant of ventricular function in the heart transplant patient?

Manuel J. Antunes, Marta Biernat, Emília Sola, Luís Oliveira, David Prieto, Fátima Franco and Luís A. Providência

Interact CardioVasc Thorac Surg 2008;7:586-590; originally published online May 8, 2008;
DOI: 10.1510/icvts.2007.167924

doi:10.1510/icvts.2007.167924

INTERACTIVE CARDIOVASCULAR AND THORACIC SURGERY

Interactive CardioVascular and Thoracic Surgery 7 (2008) 586–590

www.icvts.org

Institutional report - Transplantation

Cardiac allograft systolic function. Is the aetiology (ischaemic or idiopathic) a determinant of ventricular function in the heart transplant patient?☆

Manuel J. Antunes*, Marta Biernat, Emília Sola, Luís Oliveira, David Prieto, Fátima Franco, Luís A. Providência

Program of Heart Transplantation, Centre of Cardiothoracic Surgery, University Hospital, Coimbra, Portugal

Received 14 September 2007; received in revised form 8 April 2008; accepted 8 April 2008

Abstract

The natural history of the LV systolic function (LV-SF) and functional capacity of survivors of heart transplantation (Htx) has not been defined. Some investigators suggest that SF may be different in recipients with different pre-transplant aetiologies: ischaemic or dilated, idiopathic disease. Routine transthoracic echocardiograms (TTE) were performed during a 1-year follow-up in 48 Htx recipients (total 864 examinations; mean 18/patient). Patients were divided into two groups based on pre-transplant diagnosis: ischaemic (CAD-CMP: $n=13$, age 54 ± 1.7 years, 23% females) and idiopathic dilated cardiomyopathy (ID-CMP: $n=35$, age 51 ± 2.3 years, 26% females). Patients with valvular and toxic aetiology were excluded. All patients underwent left ventriculography (VENT) 12–15 months after Htx. The majority of 1-year survivors of Htx maintained normal LV-SF: mean LVEF 65 ± 4% by echocardiography and 68 ± 3% by ventriculography, but in the ID-CMP group LVEF was significantly higher: 67 ± 4% vs. 62 ± 4% (TTE) and 77 ± 4% vs. 60 ± 4% (VENT), without significant differences in functional capacity (NYHA). 82.9% of ID-CMP patients had LVEF >65% vs. 39% in CAD-CMP. The incidence of acute cellular rejection, freedom from cardiac vasculopathy, renal failure, diabetes, hypertension and pre-transplant alloantibody level was similar. Our study shows a strong correlation between pre-transplant heart disease and the systolic function of the cardiac allograft at 1-year follow-up.

Keywords: Heart transplantation; LV function; Echocardiography

1. Introduction

Heart transplantation (Htx) has proven to be an effective treatment option for patients with end-stage heart disease [1]. However, even in the best situations, survival is limited, and variable with different pathologies. The two most common aetiologies leading to Htx, dilated and ischaemic cardiomyopathy, have a significantly different prognosis, far more unfavourable in the latter. The reasons for this different behaviour are largely unknown.

Besides routine transmyocardial biopsy, echocardiographic assessment of the left ventricular ejection fraction (LVEF) is now becoming a well established method of short and long-time evaluation of graft condition [2]. In clinically well Htx recipients, LVEF is usually normal. However, the natural history of systolic function in survivors has not been defined. Furthermore, little is known about potential differences in recipients with different pre-transplant aetiologies and its potential impact on survival.

In this work, we analyse a group of Htx patients, to determine the evolution of the systolic left ventricular function and attempt to correlate it with pre-transplantation aetiology.

2. Material and methods

Between November 2003 and December 2007, a total of 111 adult patients underwent primary orthotopic heart transplantation and constitute our total experience with this procedure.

We observed prospectively 48 consecutive Htx survivors during the first year of follow-up following transplantation performed in 2005 and 2006. The indication for Htx during the study period was ischaemic cardiomyopathy in 13 (CAD-CMP group, age 54 ± 3.7 years, 23% females), idiopathic or familiar dilated cardiomyopathy in 35 (ID-CMP group, age 51 ± 4.3 years, 26% females). Four patients who had valvular, toxic or hypertrophic cardiomyopathy were excluded from this study.

All patients were in NYHA functional class III or IV at the time of transplantation. Other pre-operative clinical data are presented in Table 1. CAD-CMP patients had a higher incidence of hypertension. Otherwise, there were no differences between the two groups.

☆ Presented at the 21st Annual Meeting of the European Association for Cardio-thoracic Surgery, Geneva, Switzerland, September 16–19, 2007.

*Corresponding author. Centro de Cirurgia Cardiotorácica, Hospitais da Universidade, 3000-075 Coimbra, Portugal. Tel.: +351-239400418; fax: +351-239829674.

E-mail address: antunes.cct.huc@sapo.pt (M.J. Antunes).

Table 1
Pre-transplant clinical data

	CAD-CMP	ID-CMP	*P*-value
Recipients			
n	13	35	
Age (years)	54.0±3.7	51.1±4.3	0.04
Females	23%	25%	0.82
NYHA III	68%	72%	0.93
NYHA IV	32%	28%	0.93
Creatinine >1.4	15%	17%	0.78
Diabetes	23%	14%	0.76
Hypertension	54%	17%	0.029
Previous sternotomy	15%	0	0.14
Donors			
Age (years)	23.4±4.8	21.9±6.1	0.42
% Females	15%	13%	0.78
Recipient M/donor F	31%	31%	0.73
Cause of death/trauma	61%	68%	0.91
Cause of death/stroke	39%	32%	0.91

Demographic data of donors were identical in both groups. As far as possible, size mismatches between donors and recipients were limited to a maximum of 20% of body weight, and there were no differences between the two groups of patients in this respect. All patients received ABO compatible allografts. None of the donors were known to have significant co-morbid disease. Local and distant procurement were 39% and 61%, respectively, identical for both groups. Transthoracic echocardiographic examinations (TTE) were performed in all donors prior to transplantation and none had a structural abnormality.

Total (bicaval) transplantation was performed in all patients. Reperfusion was initiated immediately after the pulmonary veins and aortic anastomoses were completed. There were no significant differences between the two groups with regards to graft ischaemic time (mean 82 vs. 84 min) and extra-corporeal circulation time (101 vs. 98 min), and length of ventilation (5.0 vs. 4.5 h) and of hospital stay (13 vs. 12 days).

All recipients received immunosuppression, with cyclosporine or tacrolymus, mycophenolate mofetil and corticosteroids, following generally accepted protocols. All patients were followed at a dedicated outpatient clinic by the transplantation group of physicians.

2.1. Echocardiographic data

All patients were assessed by two-dimensional trans-thoracic echocardiography (TTE) using a standard institutional protocol (all admissions for endomyocardial biopsy and intermediate outpatient visits), between 7 days and 12 months after Htx. Eight hundred and sixty-four routine TTE (mean, 18 per patient) were performed during a 1-year follow-up in the 48 Htx recipients. Left ventricular ejection fraction was calculated by the biplane Simpson's method [3].

2.2. Haemodynamic data and graft rejection

Endomyocardial biopsies were performed according to classical, internationally accepted protocols. Full right and left catheterisation with ventriculography and coronary angiography were performed one year after Htx procedure using standard techniques. An average of 13 biopsies per patient were performed during the follow-up period. Biopsy specimens were graded for acute cellular rejection using the revised International Society of Heart and Lung Transplantation grading system [4].

2.3. Data analysis

The data were collected prospectively in a dedicated data base (spreadsheet) and analysed at the end of follow-up. Means and standard deviations were automatically calculated.

Normally distributed continuous variables are represented as mean±standard deviation (S.D.) or as the percentage of the sample. The χ^2-test and Fisher's exact test were used to determine differences in patient characteristics and events. Continuous variables (EF) were compared by the Student *t*-test.

A *P*-value <0.05 was considered significant for all tests.

3. Results

Operative and in-hospital mortality for the 106 patients was 2.8% (3 patients) and late mortality was 8%. Three-year actuarial survival was 86%.

The clinical data at 1-year are shown in Table 2. The incidence and frequency of acute cellular rejection was similar in both groups [3 in the CAD-CMP group (23%) and 6 in the ID-CMP group (17%)]. All rejection episodes observed in the study group were subclinical ($\geq$ grade 2R of the ISHLT classification). No relationship was found between echo findings and rejection episodes. Freedom from cardiac vasculopathy (no case identified by coronary angiography in either group), incidence of CMV positive serology and renal failure were also similar.

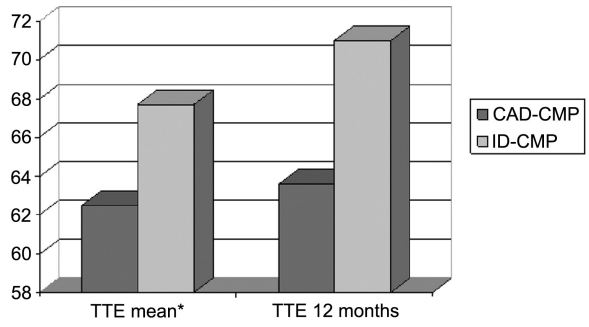
At 1 year, diabetes, hypertension and obesity rates were significantly higher in the CAD-CMP group.

The values of LVEF measured during the follow-up by TTE are represented in Fig. 1 and those measured by left ventriculography (VENT) at 1 year are shown in Fig. 2. The majority of 1-year survivors of Htx maintained normal left ventricular ejection fraction: mean LVEF 65±4% by TTE and 68±3% by VENT, but in the ID-CMP group the LVEF was higher: 67±2% vs. 62±2% by TTE in the CAD-CMP, and 77±2% vs. 60±2% by VENT ($P<0.01$).

Twenty-nine patients (83%) in the ID-CMP group had LVEF $\geq$65% vs. only five (39%) in the CAD-CMP group (Fig. 3). At the end of the follow-up period, none of the patients with ID-CMP had LVEF $\leq$40%, vs. 3 (23%) of the CAD-CMP group (Fig. 4).

Table 2
Patients' clinical data at 1-year follow-up

	CAD-CMP	ID-CMP	*P*-value
Rejection ≥3A	3 (23%)	6 (17%)	0.69
CMV+	9 (69%)	28 (80%)	0.46
Renal failure	1 (8%)	4 (11%)	1.0
Diabetes	3 (23%)	2 (6%)	0.11
Hypertension	10 (78%)	19 (54%)	0.2
BMI <25	2 (15%)	20 (57%)	0.021
BMI=25–29.9	9 (70%)	13 (37%)	0.059
BMI ≥30	2 (15%)	2 (6%)	0.29



*Mean of LVEF measured by TTE during the 1st year post-transplant

Fig. 1. LVEF by transthoracic echocardiography (TTE).

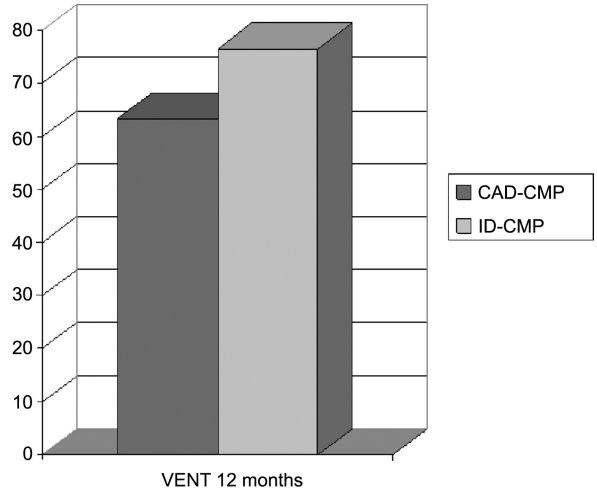


Fig. 2. LVEF by ventriculography (VENT).

There were no significant differences in functional capacity (NYHA) between the two groups. All patients but 3 are in NYHA class I.

4. Discussion

According to the most recent data of the Registry of the International Society of Heart and Lung Transplantation, the current survival rates for cardiac transplantation are around 80% at 1 year, 65% at 5 years and 50% at 10 years [5]. The majority of long-term survivors of Htx maintain normal left ventricular ejection fraction [6]. In the experience of Lietz et al., left ventricular dysfunction (defined as LVEF $\leq$40%) developed in 15.8% recipients at 10 years and increased the risk of cardiac death (OR=2.7) [7].

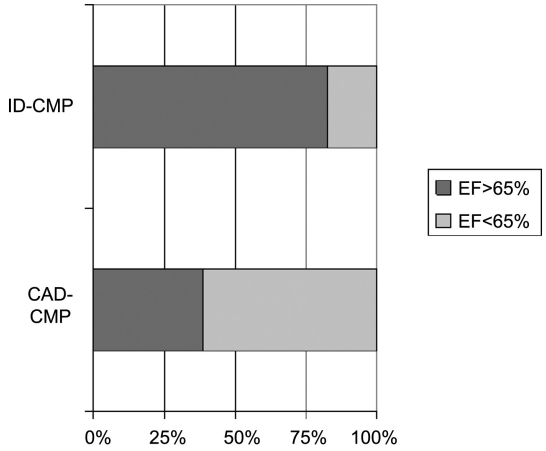


Fig. 3. Percentage of patients with LVEF $\geq$65% (VENT).

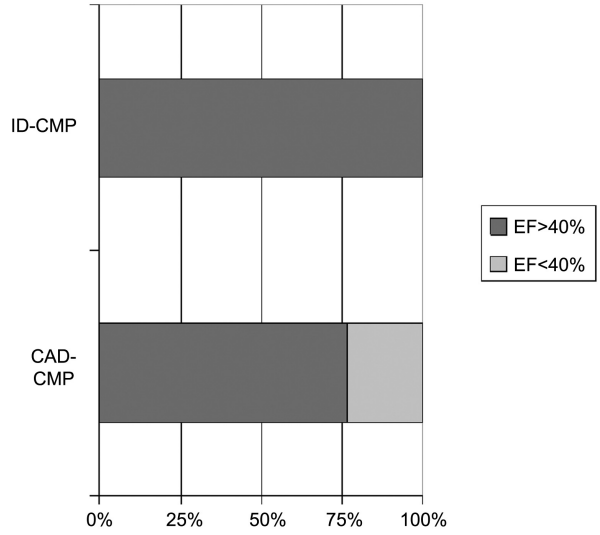


Fig. 4. Percentage of patients with LVEF $\leq$40%.

However, survival varies widely between different groups of aetiology. It is well known that it is lower in patients with ischaemic cardiomyopathy, especially when compared to dilated cardiomyopathy. This is especially true for one-year survivors [5]. But the time-frame and causes for these differences remain largely unknown. The evolution of systolic ventricular function may reveal some clues about this different behaviour. New-onset or evolution of ischaemic heart disease in transplanted patients with known risk factors for this pathology is likely to occur, but this is usually a relatively chronic and delayed process and diagnosis of the disease by common methods does not occur until late.

The impact of a history of ischaemic heart disease on the long-term survival of Htx patients has been demonstrated by some authors. Shiba et al. [8] compared two groups of Htx patients: one group consisted of patients who survived $<$10 years and the other of patients who survived $>$10 years. A history of ischaemic heart disease was found to have a negative impact on survival. A similar conclusion was derived by Stoica and co-workers [9].

Routine evaluation of heart transplant recipients is usually based on right heart catheterisation with biopsy, but the invasive nature of these diagnostic procedures have led to the search for less invasive, also less expensive, methods. Non-invasive assessment of cardiac structure and function is typically done by 2-D trans-thoracic echocardiography. Other authors have demonstrated the usefulness of TTE in some subgroups of patients as an additional method to monitor for rejection in a non-invasive and frequent manner [10]. Advances in echocardiographic techniques indicate a potential important role for the reliable detection of rejection by this modality in the future. Appreciation of typical

alterations from 'normal' may allow to identify clinically significant changes and to avoid unnecessary invasive procedures based on misinterpretation of these differences [2].

Our findings demonstrate a moderate agreement between left heart catheterisation and echocardiography in the assessment of LVEF. Although echocardiography is very load sensitive, the relative homogeneity of the measurements in an average of 18 echocardiograms in each patient permits a reasonable degree of confidence in the results. The slightly and almost uniformly lower LVEF obtained by echocardiography, as compared to catheterisation data, most likely reflects limitations resulting from geometric assumptions, as well as inadequate visualisation of the left ventricular outflow tract and potential foreshortening of the left ventricular apex, as previously demonstrated by Chuang et al. using two- and three-dimensional echocardiography and magnetic resonance imaging [11].

A surprising finding of our study was the strong correlation between pre-transplant heart disease and the evolution of the systolic function of the cardiac allograft after only 1 year of follow-up, in the absence of significant differences in functional capacity between the two groups.

We have observed a decrease of the LVEF in patients of the ischaemic cardiomyopathy group, significantly different from that observed in the dilated cardiomyopathy group, which remained relatively constant during this first year of follow-up, in the absence of differences between the two groups with regards to preoperative patient characteristics and of those of the donors and transplanted organs. Furthermore, a significant percentage of patients in the ischaemic group had significant LV dysfunction ($EF \leq 40\%$). Nonetheless, some authors have found that low EF after HT, especially with later onset, is not associated with poor survival and is not related to haemodynamically significant rejection [12]. Others have found a better sensitivity of the myocardial performance index that combines both systolic and diastolic performances, which seems to be a useful adjunct in the follow-up of cardiac transplant patients.

The leading risk factors for left ventricular dysfunction (cardiac allograft vasculopathy, renal failure, acute rejection and age <40 years) were not different in both groups of our study. Hypertension was three times more common in the ischaemic patients before surgery (suggesting the probability of a raised systemic vascular resistance). This may be one of the causes for the deteriorating LV function in ischaemic patients, but it does not invalidate the conclusions of the study. On the other hand, there are suggestions that severe cardiac dysfunction in heart recipients is associated with neurocognitive dysfunction, which is evident among patients with cardiac diseases associated with poor health behaviours (i.e. coronary artery disease) when compared to individuals with congenital, viral or unknown (idiopathic) aetiology [13]. A generalised vascular factor is, probably, the common factor.

After infection and rejection, graft vasculopathy is one of the leading causes of death, in the first year after Htx and the first leading cause in the following years [3]. Obesity and dyslipidemia act as predictors for the development of graft vasculopathy and, therefore, as risk factors for survival [14]. In our patients, the pre-transplant incidence of overweight or obesity, hypertension and diabetes appeared higher, although not reaching statistical significance, in the ischaemic cardiomyopathy group and this became even more notorious in the postoperative period. This should constitute a motivation for tighter control of these risk factors.

The gold standard in the diagnosis of cardiac allograft vasculopathy is coronary angiography and intra-vascular ultra-sonography (IVUS). But recent evidence demonstrates that CAV can be identified using information on donor age, wall motion score at rest and AT-III staining late after HTx. Hence, coronary angiography may eventually become limited to patients with a high probability score and may not be necessary routinely for surveillance of CAV [15].

In conclusion, we have identified a very early deterioration of systolic function in patients with pre-transplant diagnosis of ischaemic cardiomyopathy. To our knowledge, this has not been reported before. Identification of patients with faster deterioration of the LVEF may help treat these patients, especially by implementing measures to reduce risk factors for the development of graft vasculopathy. Further work is required to correlate these echocardiographic changes with vascular changes.

References

[1] Mudge GH, Goldstein S, Addonizio LJ, Caplan A, Mancini D, Levine TB, Ritsch ME Jr, Stevenson LW. 24th Bethesda Conference: cardiac transplantation. Task Force 3: recipient guidelines/priorisation. J Am Coll Cardiol 1993;22:21–31.

[2] Thorn EM, de Filippi CR. Echocardiography in the cardiac transplant recipient. Heart Fail Clin 2007;3:51–67.

[3] Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise J, Solomon S, Spencer KT, St John Sutton M, Stewart W. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed with conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–1463.

[4] Stewart S, Winters GL, Fishbein MC, Tazelaar HD, Kobashigawa J, Abrams J, Andersen CB, Angelini A, Berry GJ, Burke MM, Demetris AJ, Hammond E, Itescu S, Marboe CC, McManus B, Reed EF, Reinsmoen NL, Rodriguez ER, Rose AG, Rose M, Suciu-Focia N, Zeevi A, Billingham ME. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. J Heart Lung Transplant 2005;24:1710–1720.

[5] Taylor DO, Edwards LB, Boucek MM, Trulock ElP, Aurora P, Christie J, Dobbels F, Rahmel AO, Keck BM, Hertz MI. Registry of the International Society for Heart and Lung Transplantation: Twenty-fourth Official Adult Heart Transplant Report—2007. J Heart Lung Transplant 2007;246:769–781.

[6] Gorcsan J 3rd, Snow FR, Paulsen W, Arrowood JA, Thompson JA, Nixon JV. Echocardiographic profile of the transplanted human heart in clinically well recipients. J Heart Lung Transplant 1992;11:80–89.

[7] Lietz K, Herre JM, John R, Miller LW. The natural history of cardiac allograft systolic function and determinant of functional capacity in the US population of heart transplant recipients (abstract). J Heart Lung Transplant 2006;25:S44.

[8] Shiba N, Chan MC, Valantine HA, Gao SZ, Robbins RC, Hunt SA. Longer-term risks associated with 10-year survival after heart transplantation in the cyclosporine era. J Heart Lung Transplant 2003;22:1098–1106.

[9] Stoica SC, Cafferty F, Pauriah M, Taylor CJ, Sharples LD, Wallwork J, Large SR, Parameshwar J. The cumulative effect of acute rejection on development of cardiac allograft vasculopathy. J Heart Lung Transplant 2006;25:420–425.

[10] Leonard GT, Fricker FJ, Pruett D, Harker K, Williams B, Schowengerdt KO. Increased myocardial performance index correlates with biopsy-proven rejection in pediatric heart transplant recipients. J Heart Lung Transplant 2006;25:61–66.
[11] Chuang ML, Hibberd MG, Salton CJ, Beaudin RA, Riley MF, Parker RA, Douglas PS, Manning WJ. Importance of imaging method over imaging modality in non-invasive determination of left ventricular volumes and rejection fraction: assessment by two- and three-dimensional echocardiography and magnetic resonance imaging. J Am Coll Cardiol 2000; 35:477–484.
[12] Radovancevic B, Radovancevic R, Vrtovec B, Thomas CD, Frazier OH. Outcomes in patients with low left ventricular ejection fraction after heart transplantation. Eur J Cardiothorac Surg 2003;23:743–747.
[13] Madan A, White-Williams C, Thurstin AH, Bush BA, Rayburn BK. Neurocognitive dysfunction and end stage heart disease: differences among aetiologies (abstract). J Heart Lung Transplant 2006;25:S153.
[14] Vassalli G, Gallino A, Weis M, von Scheidt W, Kappenberger L, von Segesser LK, Goy JJ, Working Group Microcirculation of the Eurpean Society of Cardiology. Alloimmunity and nonimmunologic risk factors in cardiac allograft vasculopathy. Eur Heart J 2003;24:1180–1188.
[15] Störk S, Behr TM, Birk M, Uberfuhr P, Klauss V, Spes CH, Angermann CE. Assessment of cardiac allograft vasculopathy late after heart transplantation: when Is coronary angiography necessary? J Heart Lung Transplant 2006;25:1103–1108.

Conference discussion

Dr. A. Poncelet (*Brussels, Belgium*): I thought that there was a couple of 3A rejection during the first year of follow-up, and we know that it (rejection) can be correlated to an impaired left ventricular function. So, I would just ask you: did the echo data that are included in your analysis exclude the time period within which it could have been related to rejection?

Dr. Antunes: Well, rejection Grade 3A, none clinical, just by biopsy, was observed in about 20% of the patients. These results are at 1-year for ventriculography. So, at least from that time of the study, it was no coincidence. But if it was, it was one of the cases.

The results of echocardiography were the mean for those 18 observations during the year because we thought that it was better. But they were compared to the immediate postoperative, 7-day postoperative, ejection fraction which was within normal range in all patients.

We all know that survival is worse in ischemic patients and what we notice is that these changes can already be confirmed by echocardiography, at one year. There is no change in the patient's functional class. It's probably too early. But this change is in the ejection fraction, probably reflecting the late survival. And what we want to do now is to make sure that we have identified a group of patients who have this small ejection fraction and perhaps we can change our immunosuppression protocol or give these patients medical treatment, vasodilators and beta blockers, to prevent an accelerated deterioration of the systolic function.

Dr. D. Tixier (*Paris, France*): I'd like to know what is your hypothesis about this difference between the cardiomyopathy group and the cardiac ischemic group?

Dr. Antunes: As you will see in the manuscript, none of the coronary angiographies was abnormal, at least by macroscopic evidence. But we feel that maybe echocardiography can help us at least to detect early systolic dysfunction which can predict deterioration at a later stage. I don't have any other hypothesis for this. It's just that it probably confirms that ischemic cardiomyopathy is an entity with worse prognosis. Our experience is only of three years. We're learning from our own experience as well as from that of others, but perhaps we should single out our patients with ischemic cardiomyopathy and treat them differently from day 1, because some modifications are evident by 1-year post transplant.

If you have any explanation, I would welcome it. Do you treat patients, your patients, ischemic and dilated cardiomyopathy, differently?

Dr. Tixier: No, we don't, but perhaps we should. I don't know. I don't have any explanation for that.

Dr. G. Laufer (*Innsbruck, Austria*): It's well known for patients with general atherosclerotic and vascular disease that there is endothelial dysfunction. And after transplantation, I would submit that the endothelial dysfunction risk factor causing this endothelial dysfunction are still persistent. A lot of people are smoking after transplantation, hypercholesterolemia, diabetes and all these kind of risk factors are persistent, so could you speculate that maybe it's a microvascular problem that is reflected as depressed LV function in some of these patients?

Dr. Antunes: Naturally in the manuscript we discuss all those possibilities. The only reason for presentation of these data is the fact that we could not find a similar report indicating that echocardiography, which is increasingly used as a non-invasive method, could detect these changes in the ischemic group so early after transplantation. And we're using the same modern protocols of immunosuppression as everybody else uses. All our patients, in fact, are on MMF and we have not withdrawn steroids in any of them and most are on cyclosporin, although we have used tacrolimus in some, but maybe ischemic patients should be treated differently.

Dr. G. Dellgren (*Stockholm, Sweden*): To me it seems hard, anyway, to believe that it's the etiology of the disease that gives this outcome. Have you looked into the, I mean, for instance, the donor hearts? I mean, it's not only the coronary angiograms pre-transplant but the echos on the pre-transplant. And for instance, is there a difference in how they have been managed postoperatively in terms of afterload reduction? And that could also give different results in these.

Dr. Antunes: We did routine echocardiograms in all our donors. Our system permits that. And in any analysis that we made of the characteristics of the donor hearts, we couldn't find any differences. Of course, it's only 48 patients. We may increase this group for a bigger analysis and see if we can find something. But we have so far not sensed any difference in the whole group of over 100 patients.

We were puzzled by the fact that 1 year after surgery we saw such evident changes in one group as compared to the other group, which prompted us to query whether we should not be treating them from the beginning differently.

In terms of cardio-active agents, we're only using diltiazem in every single patient as a routine. But these ischemic patients were preoperative smokers hypertensive patients more frequently. They were postoperatively hypertensive also a little bit more frequently, although there were no statistical differences. I don't know if doing a different treatment will influence the outcome, but certainly we should investigate and try to do this differently.