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Heart transplant candidates at high risk can be identified at the time of initial evaluation

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Abstract The increasing discrepancy between the numbers of patients selected for cardiac transplantation and the available donor organs requires validation of markers of high risk at the time of initial evaluation that may help to determine which patients profit from aggressive therapy. We retrospectively examined the case records of 91 heart transplant candidates selected out of a total of 140 consecutive patients referred for evaluation. Of these 91 patients, 48 were transplanted during follow-up. Of the remaining 43 patients, 25 died after a mean survival time of 1.6 ± 2.5 months. The causes of death were pump failure in 18 (72 %) and sudden cardiac death in 7 (28 %). Multivariate analysis identified 4 out of 26 parameters at initial evaluation that distinguished the 25 nonsurvivors from the 18 survivors. These were: mean arterial pressure ($P = 0.03$), pulmonary capillary wedge pressure ($P = 0.002$), mean pulmonary artery pressure ($P = 0.001$), and fractional shortening ($P = 0.007$). The mode of death could not be predicted. We conclude that there are prognostic markers at initial evaluation that allow more restrictive selection of patients for cardiac transplantation and mechanical bridging.

Key words Heart transplantation, selection · Selection, heart transplantation

Introduction

As the gap between waiting lists for cardiac transplantation and the available donor organ pool widens, careful selection and restrictive listing of patients who are at highest risk becomes increasingly important [2, 17, 18, 62]. More than 60 % of patients initially referred for transplant evaluation may be stabilized by hemodynamically guided therapy tailored to individual needs of afterload and preload reduction [56–59]. In order to list only those patients who cannot be stabilized, it is necessary to apply appropriate selection criteria [27, 48]. A multitude of parameters have been proposed [8, 9, 12, 16, 19, 22, 31, 32, 36, 40, 64, 65, 67]; however, classical markers do not necessarily identify subgroups at high risk [14, 46, 62]. Functional [7, 42, 55, 59–61], hemodynamic [54], electrocardiographic [1, 5–8, 45, 54], neurohormonal [6, 8, 9, 47, 51, 52], and biochemical [7, 21, 35, 38, 52, 54] prognostic markers have been proposed. To identify potential markers, we have retrospectively analyzed the clinical data of patients selected as candidates for cardiac transplantation.

Materials and methods

Patients

The study group consisted of 91 heart transplant candidates selected from 140 consecutive patients who were referred for evaluation between January 1990 and September 1992. Case records were

retrospectively analyzed. The majority of patients were referred from regional hospitals and physicians because of progressive signs and symptoms of congestive heart failure.

Evaluation

All patients underwent a 5- to 10-day in-hospital evaluation including individual tailoring of inotropic, diuretic, and vasodilator therapy. Intravenous inotropes were administered if deemed clinically necessary. β-blockers were not used on a routine basis. After hemodynamic stability was achieved, cardiac and extracardiac function was assessed. The parameters analyzed in this paper reflect the situation after individually tailored medical therapy. They included resting ECG, chest x-ray, echocardiography, right and left heart catheterization, abdominal ultrasound, and laboratory tests. Myocardial thallium-scintigraphy, cranial computerized tomography, and upper and lower gastrointestinal endoscopy were included if clinically indicated. In addition, a psychosocial work-up was conducted. Functional testing by spiroergometry and neurohormonal assessment was not routinely performed.

Decision about placement on the waiting list

On the basis of this evaluation, a consensus decision was obtained within the interdisciplinary team that consisted of cardiac surgeons, transplant cardiologists, a psychologist, and a social worker. Of the 140 patients referred, 91 were selected for transplantation according to clinical criteria including severely impaired cardiac function with severe limitations in daily activities, a presumably markedly reduced life expectancy from the disease, and absence of contemporary contraindications [7, 27, 40, 48, 67]. Thirty-seven patients were not listed because they were considered stable. Within the group of 12 patients with contraindications, the following conditions were present: in two patients who suffered from cardiac amyloidosis associated with plasmocytoma, recurrence of amyloidosis in the allograft was suspected, in two patients who had pulmonary and urogenital manifestations of active tuberculosis, an unfavorable course of the infection following immunosuppression was anticipated, three patients were suffering from failure of more than two organs at the time of the listing decision; and five patients exhibited, according to the team opinion, behavior likely to lead to severe irregularities in intake of immunosuppressive medication and adherence to the post-transplant follow-up schedule.

Follow-up and transplant decision

Patients were followed by members of the team on a flexible outpatient or inpatient basis according to clinical requirements. Elective outpatient visit intervals ranged from weekly to once every 3 months. The decision for transplantation was, according to the rules of the Eurotransplant Foundation, based on blood group, size match, urgency, and waiting time. Within the Eurotransplant area, patients are either listed in the special urgency category (need for acute retransplantation because of primary graft failure) or in the urgency category (all other patients). For a small number of patients who deteriorate while on the waiting list and who cannot be bridged, a special urgency request may be activated (up to 15% of a center's transplant volume in the previous year). The vast majority of patients were placed in the general urgency category on the central Eurotransplant waiting list.

Parameters analyzed

The following 26 parameters were assessed and entered into the statistical analysis: age, sex, underlying cardiac disorder, medication (dose of digoxin, diuretics, ACE-inhibitors), functional class according to the New York Heart Association (NYHA), mean blood pressure, heart rate, cardiac index, systemic vascular resistance, mean pulmonary artery pressure, pulmonary capillary wedge pressure, pulmonary vascular resistance, right atrial pressure, ejection fraction, left ventricular end-diastolic diameter (m-mode echo), left ventricular end-systolic diameter (m-mode echo), fractional shortening (m-mode echo), serum sodium, serum bilirubin, serum creatinine, cardiac rhythm (sinus rhythm vs atrial fibrillation), left bundle branch block, right bundle branch block, and diffuse intraventricular conduction disturbance (defined as intraventricular conduction disturbance in at least three leads not associated with infarct signs with or without QRS > 0.11 s in the absence of left bundle branch block or right bundle branch block).

Retrospective analysis

Patients were analyzed by groups as clinically defined (stable, contraindications, listed; within the group listed: transplanted, dying on waiting list and alive on waiting list) with regard to the described clinical parameters. End points for survival statistics were date of transplantation or date of death.

Classification of deaths

In all patients who died before transplantation, the mode of death, i.e., sudden cardiac death versus nonsudden cardiac death (progressive pump failure) versus noncardiac death, was assessed by review of chart information as well as oral information from next of kin and physicians in charge. Within an independent expert committee, the decision was reached by consensus based on clinical criteria [24]. Death was assumed to be sudden if it occurred within 1 h after the onset of symptoms or if the arrhythmic event caused an unstable hemodynamic situation from which the patient eventually died. Noncardiac death was assumed to have taken place if no cardiac cause could be identified retrospectively. Nonsudden cardiac death was assumed to have taken place for all other situations.

Statistical analysis

Qualitative items were analyzed using the chi-square test. Fischer's exact test was applied if parameters expressed were less than $n = 5$. The Kaplan-Meier life table analysis [30] was used to calculate event-free survival. Follow-up started at the time of the listing decision according to the principle of intention to treat. Quantitative items were analyzed using the Mann-Whitney U-test for independent samples. Parameters that were significant by univariate analysis were entered into multivariate analysis [13]. For all statistical analyses, P values below 0.05 were considered significant and P values between 0.05 and 0.10 as trend. The SPSS statistical software package was used for all statistical analyses.

Table 1 Clinical data at the time of initial evaluation of 140 patients referred for transplantation [*n* number of patients in each category, *M/F* male/female, *DCM* dilated cardiomyopathy/other cardiomyopathies, *ICM* ischemic cardiomyopathy, *Dig* digitalis (%), *Furo* furosemide (mg), *Capto* captopril (mg), *F-up* follow-up (months), *1-y-m* 1-year mortality (%), *NYHA IV* NYHA-class IV (%)]

	Total group referred	Stable	Contra indications	Total group listed	Transplanted	Waiting list	
						Alive	Dead
N	140	37	12	91	48	18	25
Age	51.0 ± 14.6	49.6 ± 12.2	55.1 ± 13.4	51.0 ± 15.7	51.6 ± 14.4	53 ± 6	48.4 ± 21
M/F	120/20	31/6	10/2	79/12	39/9	17/1	23/2
ICM	63 (45 %)	13 (35 %)	6 (50 %)	44 (48 %)	26 (54 %)	6 (33 %)	12 (46 %)
DCM	77 (55 %)	24 (65 %)	6 (50 %)	47 (52 %)	22 (46 %)	12 (67 %)	13 (54 %)
Dig	74	68	67	78	75	81	81
Furo	127 ± 123	87 ± 65	140 ± 128	137 ± 123	147 ± 164	123 ± 69	125 ± 92
Capto	31.5 ± 18	30.6 ± 16	28.8 ± 17	32.1 ± 19	31.8 ± 18	28.8 ± 17	34.4 ± 23
F-up	10.0 ± 9.4	13.6 ± 10.3	9.8 ± 10.2	8.5 ± 8.1	12.3 ± 4.3	8.1 ± 6.9	1.6 ± 2.5
1-y-m	28	0	50	35	17	0	100
NYHA IV	45	8	50	60	77	42	44

Table 2 Hemodynamic, echocardiographic, laboratory, and electrocardiographic profiles at the time of initial evaluation of 140 patients referred for transplantation [*A-fib* atrial fibrillation (%), *Bili* bilirubin (mg/100 ml), *CI* cardiac index (l/min per m^2), *Cond* conduction disturbance (%), *Crea* creatinine (mg/100 ml), *FS* fractional shortening (%), *HR* heart rate (min^{-1}), *LBBB* left bundle branch block (%), *LVEDD* left ventricular end-diastolic diameter (cm), *LVEF* left ventricular ejection fraction (%), *LVESD* left ventricular end-systolic diameter (cm), *MAP* mean arterial pressure (mm Hg), *MPAP* mean pulmonary arterial pressure (mm Hg), *PCWP* pulmonary capillary wedge pressure (mm Hg), *PVR* pulmonary vascular resistance (dyn × s × cm^{-5}), *RAP* right atrial pressure (mm Hg), *RBBB* right bundle branch block (%), *Sod* sodium (mmol/l), *SVR* systemic vascular resistance (dyn × s × cm^{-5})]

	Total group referred	Stable	Contra indications	Total group listed	Transplanted	Waiting list	
						Alive	Dead
MAP	85 ± 15	94 ± 13	82 ± 15	82 ± 16	85 ± 16	88 ± 15	73 ± 14*
HR	91 ± 22	79 ± 20	94 ± 22	95 ± 23	90 ± 19	97 ± 23	101 ± 29
CI	2.4 ± 0.7	2.7 ± 0.7	2.1 ± 0.7	2.3 ± 0.7	2.3 ± 0.7	2.3 ± 0.7	2.1 ± 0.6
SVR	1548 ± 489	1518 ± 492	1442 ± 423	1574 ± 519	1586 ± 542	1427 ± 491	1783 ± 465
MPAP	30.6 ± 11.7	24.8 ± 12.4	33.3 ± 9.1	32.5 ± 10.3	31.3 ± 11.6	29.9 ± 7.2	38.0 ± 7.0*
PCWP	20.4 ± 9.0	15.9 ± 8.9	23.2 ± 8.3	21.9 ± 9.1	20.8 ± 9.3	19.7 ± 4.8	26.6 ± 6.9*
PVR	206 ± 129	156 ± 140	239 ± 149	215 ± 125	199 ± 119	195 ± 68	266 ± 155
RAP	6.5 ± 4.9	4.4 ± 2.9	7.0 ± 5.9	8.0 ± 5.3	7.3 ± 4.8	6.5 ± 3.9	10.5 ± 6.5
LVEF	25.7 ± 11.1	31.8 ± 12.3	24.0 ± 5.3	23.8 ± 10.4	23.1 ± 1.3	26.5 ± 7.0	23.3 ± 12
LVEDD	7.1 ± 1.2	7.0 ± 1.0	6.8 ± 1.4	7.2 ± 1.2	7.1 ± 1.1	7.0 ± 1.0	7.9 ± 1.0
LVESD	6.1 ± 1.2	5.9 ± 0.9	5.4 ± 1.5	6.2 ± 1.3	6.1 ± 1.3	6.0 ± 1.2	6.8 ± 1.1
FS	16 ± 6.9	18 ± 6.1	18 ± 7.6	15 ± 7.1	15 ± 8.0	17 ± 5.6	13 ± 5.8*
Sod	140 ± 4.9	142 ± 3.9	139 ± 5.0	139 ± 5.7	138 ± 6.9	141 ± 3.6	139 ± 7.9
Bili	1.2 ± 1.7	0.7 ± 0.4	1.6 ± 1.7	1.4 ± 1.8	1.1 ± 1.1	1.1 ± 1.4	2.2 ± 3.1
Crea	1.2 ± − 1.1	1.0 ± 0.3	1.6 ± 0.9	1.3 ± 0.9	1.2 ± 0.3	1.6 ± 1.7	1.4 ± 0.8
A-fib	16	14	8	21	19	22	24
LBBB	25	32	33	20	23	11	20
RBBB	1	0	0	2	4	0	0
Cond	10	16	0	9	4	6	20

* $p < 0.05$ waiting list dead vs waiting list alive

Results

Clinical data

Baseline data at the time of initial evaluation of all 140 patients referred for transplantation – the 37 patients considered stable, the 12 patients with contraindications, the 91 patients selected for transplantation, and the subgroups of those 48 patients transplanted (the 25 dying on the waiting list and those 18 alive on the waiting list) – are displayed in Table 1. The corresponding hemodynamic, echocardiographic, laboratory, and electrocardiographic profiles are summarized in Table 2. Within the total group selected, the mean age at the time of listing was 51 ± 15.7 years, the mean follow-up time was 8.5 ± 8.1 months, and the mean 1-year mortality was 35 %.

Table 3 Predicting factors (listed nonsurvivors vs listed survivors) at the time of initial evaluation (*MAP* mean arterial pressure, *PCWP* pulmonary capillary wedge pressure, *MPAP* mean pulmonary arterial pressure)

	Nonsurvivors ($n = 25$)	Survivors ($n = 18$)	P multivariable
MAP (mm Hg)	73 ± 14	88 ± 15	0.03
PCWP (mm Hg)	27 ± 7	20 ± 5	0.002
MPAP (mm Hg)	38 ± 7	30 ± 7	0.001
Fractional shortening (%)	13 ± 6	17 ± 6	0.007

Functional class

At the time of initial evaluation, patients selected and transplanted during follow-up were more often in NYHA class IV than patients selected and not transplanted (77 % vs 42 %; $P = 0.0006$) and patients who subsequently died while on the waiting list (77 % vs 44 %; $P = 0.005$).

Survival

The total group of 91 patients selected for transplantation had a 65 % 1-year survival rate after listing. The subgroup of patients transplanted had a 1-year survival rate of 83 % after listing, while patients not receiving an organ had a 1-year survival rate of 45 % after listing ($P < 0.00005$).

Predictors at the time of initial evaluation

At initial evaluation, the 25 patients who eventually would die while on the waiting list had a lower mean arterial pressure than the 18 survivors awaiting transplantation (73 ± 14 vs 88 ± 15 mmHg, $P = 0.03$), a higher pulmonary capillary wedge pressure (27 ± 7 vs 20 ± 5 mmHg, $P = 0.002$), higher pulmonary arterial pressure (38 ± 7 vs 30 ± 7 mmHg, $P = 0.001$), and lower fractional shortening (13 ± 6 vs 17 ± 6, $P = 0.007$; Table 3) by multivariate analysis. The only univariate parameter that did not reach significance by multivariate analysis was bilirubin. Between patients transplanted and those listed but not transplanted there were no differences at initial evaluation except for functional class.

Correlation between mean arterial pressure and heart rate

There was an inverse correlation between mean arterial pressure and heart rate in the total group evaluated ($r = -0.33$, $P = 0.0001$). The mean heart rate was 91 ± 22 min^{-1} and the mean arterial pressure was 85 ± 15 mmHg. This correlation was more pronounced when analysing only those patients who were considered stable and those who died while awaiting transplantation ($r = -0.55$, $P = 0.00001$). Those patients considered stable appear in the left upper quadrant, while those patients who died while on the waiting list appear in the right lower quadrant of Fig. 1.

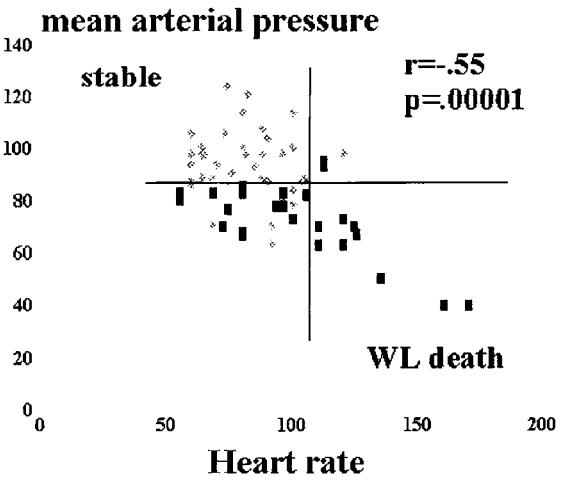

Fig. 1 Relationship between heart rate and mean arterial pressure in the subgroup of patients who were stable at initial evaluation ($n = 37$, grey boxes) and the subgroup of patients who died while on the waiting list ($n = 25$, dark boxes)

Causes of death

Of the 25 patients who died while on the waiting list, 18 (72 %) were classified as having died from nonsudden cardiac death, i.e., progressive pump failure, while 7 (28 %) were classified as having died from sudden cardiac death. There was no different distribution of prognostic markers at initial evaluation in the two groups that could predict the mode of death.

Discussion

Four independent parameters at the time of initial evaluation for transplantation were identified that may allow a distinction to be made between those patients who have to be transplanted urgently and those for whom transplantation may be safely deferred. These included mean arterial pressure, fractional shortening, pulmonary capillary wedge pressure, and pulmonary artery pressure.

Mean arterial pressure

A lower mean arterial pressure at initial evaluation in the subgroup that eventually died while awaiting transplantation despite identical doses of angiotensin converting enzyme inhibition suggests that the inability to generate a higher arterial perfusion pressure as a consequence of impairment of left ventricular function is, independent of the beneficial influence of vasodilators on systemic vascular resistance, left ventricular afterload, and survival, an important predictor of outcome. Mean arterial pressure has been described as a predictor of mortality in dilated cardiomyopathy before [4, 6, 28]. In our study, mean arterial pressure at initial evaluation was a significant predictor. The location of the mean arterial pressure/heart rate value along the regression line of the heart rate/mean arterial blood pressure diagram may constitute a practical tool for estimating risk at initial referral. Heart rate has been described as a prognostic parameter [9].

Fractional shortening

A left ventricular ejection fraction below 20 % and fractional shortening below 15 % are classical indicators of left ventricular dysfunction [8, 12, 14, 16, 19, 22, 27, 31, 32, 36, 40, 46, 48, 55, 57, 60, 61, 64, 65, 67] that are quite controversial with regard to their ability to differentiate between the different subgroups selected and listed for transplantation.

Pulmonary capillary wedge pressure

Patients who died while waiting for a heart transplant had a significantly higher mean pulmonary capillary wedge pressure despite identical doses of furosemide, indicative of more severe left ventricular pump dysfunction. According to the law of Frank-Starling, refractory elevation of pulmonary capillary wedge pressure associated with low cardiac index predicts the most advanced hemodynamic impairment and the highest likelihood of deteriorating pump function. A cardiac index below 2.0 l/min per m^2 and left ventricular filling pressures above 20 mmHg have been described as prognostic markers [28]. A low cardiac output and a high pulmonary capillary wedge pressure were described as relevant factors of mortality [4, 31].

Pulmonary arterial pressure

Elevated pulmonary arterial pressure indicates advanced left ventricular dysfunction with consecutive impairment of pulmonary hemodynamics [36]. Signs of right ventricular dysfunction and hepatic congestion have been described as prognostic markers [65]. In our study, pulmonary arterial pressure was of prognostic importance while bilirubin was only a univariate predictor.

Further prognostic markers

Functional prognostic markers recently proposed include the response to tailored therapy [58, 60, 62]. Dilatation of the left ventricle, left ventricular volume, left ventricular filling pressures, and atrioventricular regurgitation are reduced by individually tailored therapy. Moreover, the risk of ventricular tachyarrhythmias and sudden cardiac death [11, 44, 49, 53] caused by the high level of neurohormonal stimulation [52, 63] and abnormal baroreceptor function [25] can be reduced, as well as abnormal vagal reflexes causing bradycardia, vasodilatation, and hypotension [43], which are registered in up to 50 % of patients with sudden cardiac death [41]. Electrocardiographic markers that have been described [15, 20, 23, 26, 33, 34, 37, 39, 66] were not predictive in our cohort. Other functional prognostic parameters not assessed in our cohort include a maximum oxygen uptake below 10–12 ml/kg per minute [42], mitral regurgitation as assessed by Doppler echocardiography [10, 29, 55], and exercise time in the modified Bruce protocol [6]. Biochemical markers proposed recently include signs of neurohormonal activation, such as elevated plasma norepinephrine, vasopressin, and plasma renin [7, 9, 47, 50, 51], elevated plasma levels of tumor necrosis factor α [38], and an elevated plasma atrial natriuretic peptide level [21]. These parameters have not been addressed in this retrospective study.

Limitations

The retrospective nature of this study may have allowed for bias in hypothesis testing, and the small sample size limits the strength of the results. Yet, these methodological shortcomings hold for most studies published on prognostic markers in severe, chronic heart failure [3]. During the study period, extended functional testing, such as peak oxygen uptake and neurohormonal monitoring, were not yet applied on a routine basis.

Implications

The existence of prognostic markers at initial evaluation within a group listed for transplantation that indicate more advanced hemodynamic impairment may allow for the identification of patients who may derive clear survival benefit from cardiac transplantation and, potentially, mechanical bridging. These markers might

eventually, along with other pertinent parameters such as peak oxygen consumption, be incorporated into a scoring system that could support the clinical decision-making process at the time of the listing decision. Identification of heart transplant candidates with the highest risk of dying will help to increase the long-term, rather than short-term, benefit from transplantation as compared to conventional therapy. This will hopefully contribute to optimal use of the scarce donor organs for the benefit of patients with terminal heart failure.

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