

Additional predictive value of both left and right ventricular ejection fractions on long-term survival in idiopathic dilated cardiomyopathy

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Background In idiopathic dilated cardiomyopathy, long-term outcome is poor and left ventricular ejection fraction is a major powerful predictor of survival. However, right ventricular function might also play an important role in the long-term prognosis of this disease.

Aim The aim of this study was to determine the role of right ventricular parameters, mainly right ventricular ejection fraction, on survival in idiopathic cardiomyopathy.

Methods We prospectively assessed long-term follow-up and predictors of survival in 62 consecutive patients referred from 1990 to 1992 for evaluation of idiopathic dilated cardiomyopathy, including haemodynamic evaluation, thermodilution right ventricular ejection fraction and volume measurements.

Results At the time of catheterization, dyspnoea class III or IV was present in 60% of the patients, atrial fibrillation in 19% and complete left bundle branch block in 35%. Left ventricular ejection fraction was $30 \pm 10\%$ and right ventricular ejection fraction was $30 \pm 16\%$. During follow-up (2.2 ± 1.3 years), 15 patients (24%) had heart transplantation and nine (14%) died before cardiac transplantation. Cumulative survival rate without heart transplantation was 74% and 56% at 1 and 4 years, respectively. In univariate analysis, survival was related to: dyspnoea class I or II ($P < 0.04$), absence of complete left bundle branch block ($P < 0.05$), administration of lower doses of furosemide ($P < 0.01$), high left ventricular ejection fraction ($P < 0.0001$), low pulmonary artery pressure ($P < 0.002$), high right ventricular ejection fraction ($P < 0.0001$), high cardiac index ($P < 0.006$), and low right ventricular volumes ($P < 0.001$). Multivariate analysis showed only two independent predictors of survival: left ventricular ejection fraction ($P < 0.001$) and right ventricular ejection fraction ($P < 0.004$).

Conclusion In addition to left ventricular ejection fraction, right ventricular ejection fraction appears to be a complementary predictor of survival in idiopathic dilated cardiomyopathy, suggesting the importance of assessing right ventricular function in this disease.
(*Eur Heart J* 1997; 18: 276–280)

Key Words: Idiopathic dilated cardiomyopathy, long-term survival, left ventricular ejection fraction, right ventricular ejection fraction.

Introduction

Idiopathic dilated cardiomyopathy is defined as a disease of the cardiac muscle of unknown aetiology^[1] and is characterized by enlargement of the cardiac chambers^[2,3]. In this disease, long-term clinical outcome is poor^[4–7] and parameters reflecting abnormal left ventricular function are known to be the most powerful predictors of survival^[6–8]. However, right ventricular haemodynamics are important to consider in order to determine the proper timing of heart transplantation^[9].

Although right ventricular dysfunction in dilated cardiomyopathy is influenced by increased right ventricular afterload due to left ventricular dysfunction^[10,11], intrinsic right ventricular contractility may also be altered directly by primary right ventricular myocardial disease^[12]. Moreover, right ventricular ejection fraction is an indicator of increased mortality in patients with congestive heart failure associated with coronary artery disease^[13]. Therefore, right ventricular function might also play an important independent role in the long-term prognosis of idiopathic dilated cardiomyopathy.

The purpose of this prospective study was to assess long-term follow-up and predictors of survival in a consecutive series of patients with idiopathic dilated cardiomyopathy referred for a first thermodilution evaluation of right ventricular function.

Revision submitted 8 July 1996, and accepted 11 July 1996.

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Study population

From January 1990 to June 1992, 62 consecutive patients (51 men, 11 women) referred to our hospital for an evaluation of idiopathic dilated cardiomyopathy clinically stable for at least 2 weeks, were included. At the date of entry into the study, all patients underwent a haemodynamic evaluation of right ventricular parameters, including right ventricular ejection fraction measurement, and were followed up until April 1994.

Idiopathic dilated cardiomyopathy was defined as (1) dilatation of the left ventricular chamber so that the echocardiographic left ventricular end-diastolic diameter (measured from the parasternal short axis view) was 55 mm or more, (2) a diffuse hypokinesia of the left ventricle with an echocardiographic left ventricular ejection fraction (determined using the Teicholz's formula^[14]) of 55% or less, and (3) an absence of coronary artery disease defined on coronary angiography as a reduction of 50% or more in the intraluminal diameter of any of the major coronary arteries or their main side branches.

In addition, patients with severe systemic hypertension (higher than 180/100 mmHg or treatment with at least two drugs), viral myopericarditis in the previous months (infectious history and positive serology), cor pulmonale, organic valve disease, congenital heart disease or specific myocardial disease were excluded. Alcohol consumption was considered to be a risk factor for idiopathic dilated cardiomyopathy^[15,16], and patients were not excluded according to this criterion, whatever the importance of their alcohol intake.

Methods

Right heart catheterization

Right ventricular ejection fraction was measured according to a previously described thermodilution technique^[12,17,18], using a modified triple-lumen Swan-Ganz catheter with intracardiac electrodes and a fast-response thermistor. Data from the thermodilution curves were processed by a dedicated and well-validated^[18,19] fast-response computer (American Edwards Laboratory), together with an electrocardiographic signal, enabling determination of heart rate, cardiac output, right ventricular ejection fraction, and subsequent calculation of right ventricular end-systolic and end-diastolic volumes. The duration for a complete sequence of right ventricular ejection fraction/volumes measurements was approximately 25 s.

For each measurement, the thermodilution curve was displayed on the machine and systematically inspected. Moreover, the computer indicated abnormalities in the morphology of the curve by an alarm signal. Only measurements obtained from satisfactory curves were recorded for analysis. After two reference points were established on the curve from R-waves detected on the electrocardiogram, the slope of the curve was divided

by the R-R intervals to give the temperature range (ratio of change per heartbeat). This provided the residual fraction. Subtraction of residual fraction from 1 determined right ventricular ejection fraction.

In cases of permanent atrial fibrillation, only data from patients with satisfactory curves and a sufficiently regular ventricular rate were included in the analysis. Thermodilution right ventricular function was not assessed in cases of severe functional tricuspid regurgitation (grades III-IV) as shown on a baseline colour Doppler echocardiogram.

Baseline and follow-up data

The following baseline parameters were analysed: sex, age, height, weight, body surface, alcohol intake, smoking, date of the first episode of heart failure, New York Heart Association (NYHA) classification for dyspnoea, previous history of ventricular tachycardia, presence of permanent atrial fibrillation, presence of a complete left bundle branch block, echocardiographic left ventricular parameters (ejection fraction, end-diastolic and end-systolic diameters), angiographic left ventricular parameters (ejection fraction, end-diastolic volume), haemodynamic right ventricular parameters (mean pulmonary capillary wedge pressure, systolic and mean pulmonary artery pressures, mean right atrial pressure, cardiac index, ejection fraction, end-diastolic, end-systolic and stroke volumes), oral medications (angiotensin converting enzyme inhibitors, digoxin, and furosemide with evaluation of dosage regimen).

The follow-up period was defined as the interval from the date of entry into the study (date of right heart catheterization) to the date of death or heart transplantation, or, in the absence of these events, to April 1994.

Statistical analysis

All quantitative values are expressed as mean \pm standard deviation. Statistical analysis was performed with the BMDP Statistical Software P1L and P2L package^[20]. Cumulative survival rates without heart transplantation were estimated by the Kaplan-Meier method. Univariate and multivariate analyses were performed using the Cox's proportional hazards regression models^[21]. Correlations were obtained using a linear regression model. A probability value $P < 0.05$ was considered significant.

Results

Baseline data

The mean age of the 62 patients was 52 ± 12 years (19-72 years) at entry into the study. Thirty-seven patients (60%) were smokers (≥ 20 cigarettes per day) and 30 patients (48%) had an alcohol intake of more than 60 g of alcohol per day. Dyspnoea NYHA class III or IV was present in 37 patients (60%). Twelve patients

Table 1 Baseline haemodynamic parameters in the 62 included patients with idiopathic dilated cardiomyopathy

	Mean \pm SD	Range
Angiographic parameters		
LVEF (%)	32 \pm 12	5–58
Indexed LVEDV (ml . m ⁻²)	204 \pm 89	74–430
Haemodynamic parameters		
Mean PCWP (mmHg)	17 \pm 9	3–36
Systolic PAP (mmHg)	36 \pm 15	11–77
Mean PAP (mmHg)	26 \pm 12	8–51
Mean RAP (mmHg)	6 \pm 4	1–18
Cardiac index (l . min . m ⁻²)	2.6 \pm 0.8	1.0–4.6
RVEF (%)	30 \pm 16	4–57
Indexed RVEDV (ml . m ⁻²)	116 \pm 44	35–240
Indexed RVESV (ml . m ⁻²)	86 \pm 48	21–230
Indexed RVSV (ml . m ⁻²)	30 \pm 13	8–57
Body parameters		
Height (cm)	171 \pm 7	154–191
Weight (kg)	74 \pm 15	37–110
Body surface (m ²)	1.9 \pm 0.2	1.3–2.3

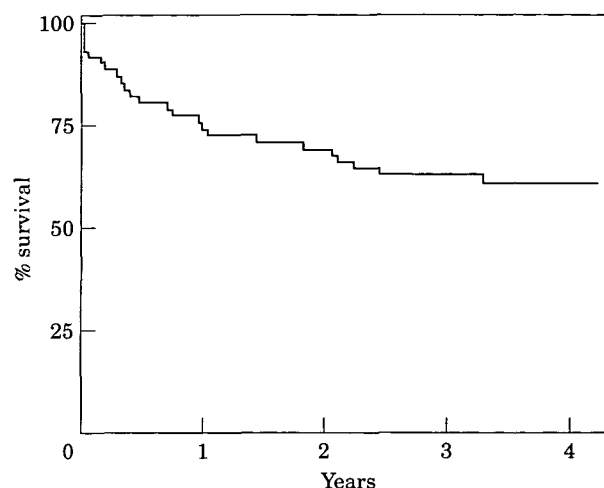
EDV=end-diastolic volume; EF=ejection fraction; ESV=end-systolic volume; LV=left ventricular; PAP=pulmonary artery pressure; PCWP=pulmonary capillary wedge pressure; RAP=right atrial pressure; RV=right ventricular; SV=stroke volume.

(19%) were in atrial fibrillation and 22 (35%) had a complete left bundle branch block. Only five patients (8%) had a previous history of ventricular tachycardia. The delay between the first episode of heart failure and right heart catheterization was 12 \pm 19 months (0.5–84 months).

The echocardiographic left ventricular ejection fraction was 30 \pm 10% (12–55%). Only four patients had an ejection fraction >40%, all of whom had a left ventricular end-diastolic diameter \geq 55 mm without valvular heart disease and were therefore considered to have dilated cardiomyopathy. The left ventricular end-diastolic diameter was 67 \pm 8 mm (55–91 mm) with all individual values \geq 55 mm; however, when the end-diastolic diameter was indexed to the body surface (mean: 37 \pm 6 mm . m⁻², range: 25–61 mm . m⁻²), two patients had a value <27 mm . m⁻² (25 and 26 mm . m⁻², respectively), which is the limit of definition proposed by the National Heart, Lung, and Blood Institute^[22]. Haemodynamic parameters are listed in Table 1. Among them, angiographic left ventricular ejection fraction was 32 \pm 12% and right ventricular ejection fraction was 30 \pm 16%. Eight patients had a mean right atrial pressure >10 mmHg; in these patients, functional tricuspid regurgitation may have been present. Among them, five had right ventricular ejection fraction \leq 15%.

Of the 62 patients, 47 (76%) took angiotensin converting enzyme inhibitors, 19 (31%) digoxin and 52 (84%) furosemide with a mean dosage regimen of 89 \pm 113 mg . day⁻¹ ranging from 40 mg to 500 mg per day.

Right ventricular ejection fraction was linearly correlated with echocardiographic left ventricular

**Figure 1** Cumulative survival curve without heart transplantation in 62 patients with idiopathic dilated cardiomyopathy.

ejection fraction ($r=0.49$, $P<0.001$) and mean pulmonary artery pressure ($r=-0.50$, $P<0.001$); however, no correlation was found with mean right atrial pressure ($r=-0.06$). Mean pulmonary artery pressure was correlated with right ventricular volumes (end-diastolic volume: $r=0.39$, $P<0.002$; end-systolic volume: $r=0.44$, $P<0.001$; stroke volume: $r=-0.36$, $P<0.005$).

Follow-up data

The mean follow-up period was 2.2 \pm 1.3 years (0–4.2 years). No patient was lost to follow-up. Fifteen patients (24%) underwent heart transplantation (among whom five died after the event), and nine (14%) died before. Cumulative survival rates without heart transplantation were 74% and 56% at 1 and 4 years, respectively (Fig. 1).

On univariate analysis, parameters predictive of survival without heart transplantation were: dyspnoea NYHA class I or II ($P<0.04$), absence of a complete left bundle branch block ($P<0.05$), high left ventricular ejection fraction (echocardiographic: $P<0.0001$ and angiographic: $P<0.006$), low pulmonary artery pressure (systolic: $P<0.02$ and mean: $P<0.002$), high cardiac index ($P<0.006$), high right ventricular ejection fraction ($P<0.0001$), low right ventricular end-diastolic ($P<0.001$) and end-systolic ($P<0.0001$) volumes, high right ventricular stroke volume ($P<0.004$), and administration of lower doses of furosemide ($P<0.01$).

After multivariate analysis, only two parameters were independent predictors of survival without heart transplantation: echocardiographic left ventricular ejection fraction ($P<0.001$) and right ventricular ejection fraction ($P<0.004$). Initially, only 10 patients had a normal right ventricular ejection fraction ($\geq 50\%$), of whom one underwent heart transplantation. Among the 24 patients who died or had heart transplantation during follow-up, only eight (33%) had a baseline right

ventricular ejection fraction >20%. In contrast, of the 38 survivors without a heart transplant, 34 (89%) had a baseline right ventricular ejection fraction >20%.

Discussion

Left ventricular parameters are of major importance in determining the prognosis of idiopathic dilated cardiomyopathy^[6-8]. Impairment of left ventricular function negatively influences right ventricular function in this disease^[10,11]. However, intrinsic right ventricular contractility may also be directly altered by primary right myocardial disease^[12]. Until recently, right ventricular parameters were considered to be of secondary importance in dilated cardiomyopathy. However, the role of the right ventricle as a determinant of timing for heart transplantation has been emphasized^[9].

Because of the peculiar shape of the right ventricle, right ventricular ejection fraction is difficult to measure. Contrast right ventriculography gives reproducible results^[23], but simultaneous measurements of haemodynamic parameters may be modified by injection of contrast material. Radionuclide techniques do not need geometric assumptions of the right ventricular chamber^[24], but these techniques cannot be applied easily in a catheterization laboratory^[25] and therefore do not allow simultaneous assessment of pulmonary artery pressure. Thermodilution measurement of right ventricular ejection fraction has none of these drawbacks. The results of measuring right ventricular ejection fraction by the thermodilution technique and by contrast angiography are closely correlated^[26] and the reproducibility of thermodilution measurements of right ventricular ejection fraction has been well documented^[19] with a satisfactory coefficient of variation (8%)^[18]. In our catheterization laboratory, this technique began to be used in 1988, and has been used in routine clinical practice since 1990. In our study, functional tricuspid regurgitation might have been present in some patients during determination of right ventricular ejection fraction. However, although Doppler echocardiography was not performed during catheterization, no patient had severe tricuspid regurgitation on baseline echocardiography; in addition, right ventricular preload was high in only eight patients. Furthermore, the role of tricuspid regurgitation in the assessment of right ventricular ejection fraction remains controversial^[27-29].

Our population is similar to that described in several studies, having a predominance for male patients and a mean age of 52 years^[5,6,9]. Patients with either permanent atrial fibrillation or mild to moderate tricuspid regurgitation were included when thermodilution curves were satisfactory and reproducible, in order to assess a study population as close as possible to the population seen in routine clinical practice. The cumulative survival rates are concordant with previous reports^[4-6]. Because heart transplantation obviously alters the natural history of end-stage dilated cardiomyopathy, we deliberately chose to consider this

event as a primary end-point like death, for studying prognostic factors in this setting.

Many parameters are related to patient outcome. The presence of severe dyspnoea or of a complete left bundle branch block are predictive of mortality as reported^[4-6]. Among the different medications, high doses of furosemide are associated with an adverse prognosis. Parameters of both left and right ventricular function clearly influence survival and left ventricular parameters are well established^[6-8]. Our study demonstrates that right ventricular dysfunction is also an important predictive factor. Using multivariate analysis, only two haemodynamic parameters are independent predictors of survival. Left ventricular ejection fraction is the most important predictor, as already found by our group^[6] and others^[7,8]. In addition, right ventricular ejection fraction is an important, complementary, independent prognostic factor, though significant correlations exist between both left and right parameters of ventricular function. A previous recent study^[30] has already shown that preserved rest or exercise right ventricular ejection fraction was a better predictor of survival in patients with advanced heart failure than exercise peak oxygen consumption. In our population, and as previously shown^[10,11], right ventricular dysfunction appeared to be related to increased afterload consecutive to disturbed pulmonary haemodynamics. In contrast, no relationship existed between preload and right ventricular ejection fraction. Moreover, the independent prognostic role of right ventricular ejection fraction showed the importance of independent right ventricular contractile dysfunction in dilated cardiomyopathy. These data might explain why in some cases, and despite a severely depressed left ventricular ejection fraction, idiopathic dilated cardiomyopathy can paradoxically, be well tolerated.

Conclusion

In addition to left ventricular ejection fraction, right ventricular ejection fraction appears to be an important complementary predictor of survival in idiopathic dilated cardiomyopathy, thereby suggesting the clinical importance of assessing right ventricular function in this disease.

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