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Right Ventricular Ejection Fraction Is an Independent Predictor of Survival in Patients With Moderate Heart Failure

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Objectives. **We sought to study the relationship between survival and right ventricular ejection fraction (RVEF) in a subgroup of patients with moderate congestive heart failure (CHF).**

Background. **It has been demonstrated that RVEF is an independent predictor of survival in patients with advanced CHF.**

Methods. **Cardiopulmonary exercise testing and radionuclide angiography (to determine right and left ventricular ejection fraction) were prospectively performed in 205 consecutive patients with moderate CHF (140 patients in New York Heart Association [NYHA] class II, 65 in class III).**

Results. **Left ventricular ejection fraction was 29.3% ± 10.1%, RVEF was 37.5% ± 14.6% and peak oxygen consumption (VO_2) was 16.2 ± 5.4 ml/min/kg (60.2% ± 19% of maximal predicted VO_2). After a median follow-up period of 755 days, there were 44 cardiac-related deaths, 3 deaths from noncardiac causes and 15 transplantations of whom 2 were urgent; 1 patient was lost to follow-up. Multivariate analysis showed that three variables—NYHA classification, percent of maximal predicted VO_2 and RVEF—were independent predictors of both survival and event-free cardiac survival. Left ventricular ejection fraction and peak VO_2 normalized to body weight had no predictive value. The event-free survival rates from cardiovascular mortality and urgent transplantation at 1 year were 80%, 90% and 95% in patients with an RVEF <25%, with a RVEF ≥25% and <35% and with a RVEF ≥35%, respectively. At 2 years, survival rates were 59%, 77% and 93% in the same subgroups, respectively.**

Conclusions. **In addition to the NYHA classification and to the percent of maximal predicted VO_2, RVEF is an independent predictor of survival in patients with moderate CHF.**

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Congestive heart failure (CHF) remains a leading cause of morbidity and mortality (1). While previous studies have investigated the relative value of different parameters in predicting survival, the majority were conducted in populations with severe cardiac failure, notably in patients awaiting heart transplantation (2–6). The majority of patients presenting with heart failure have moderate CHF. Nevertheless, the annual mortality rate in this less severely affected group remains high at around 10% per year. To improve the management of these patients, it is important to define parameters that could predict survival. Di Salvo et al. (7) recently demonstrated the independent prognostic value of the right ventricular ejection fraction (RVEF) in a subgroup of patients with advanced heart failure. The potential value of this parameter has not been reported in patients with moderate heart failure. To answer this question, we conducted a prospective study in this subgroup of patients. Our results demonstrate that RVEF is a powerful independent predictor of survival in patients with stable and moderate heart failure.

Methods

Study population. From November 1991 to June 1996, 205 consecutive stable patients with left ventricular systolic dysfunction were studied. Patients in sinus rhythm who had a left ventricular ejection fraction (LVEF) ≤45% (determined by radionuclide angiography) and who were stable and ambulatory for at least 3 months were included in the study. Patients were excluded if they had had unstable angina or recent (<6 months) myocardial infarction, percutaneous coronary angioplasty or coronary bypass grafting. Patients with significant pulmonary disease were also excluded as well as patients with intermittent claudication, ventricular tachycardia or angina during exercise that could lead to a nonmaximal exercise. Transplantation was not planned in any patients at the time of inclusion in the study. During the inclusion period, 45 patients were screened and excluded for the following reasons: atrial fibrillation, 33 patients; nonmaximal exercise test, 12 patients. Of these 45 patients, 8 died from a cardiovascular origin, 2 had a noncardiovascular death and 1 patient underwent a nonur-

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Abbreviations and Acronyms

CHF = congestive heart failure
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association
RVEF = right ventricular ejection fraction
SPAP = systolic pulmonary artery pressure
UNOS = United Network for Organ Sharing
VO_2 = oxygen consumption

gent transplantation. Of the 205 patients included in the study, 34 were women and the mean age was 54 ± 11 years. Most of the patients were in class II of the New York Heart Association (NYHA) functional classification (140; 68%) and 65 patients (32%) were in class III. The etiology of the left ventricular systolic dysfunction was ischemic cardiomyopathy in 80 patients (39%) and nonischemic cardiomyopathy in 121 patients (59%). The four other patients (2%) refused coronary angiography.

Exercise protocol. Exercise was performed in the morning after a light, standard meal (30 minutes to 2 hours before the test) and on an upright electromagnetically braked bicycle (Meditronic 35 Hellige [Freiburg, Germany] and from January 1995, Ergo-Metrics 900 Ergoline [Bitz, Germany]) using a continuous protocol (30 watts for the first 3 min, with subsequent increments of 10 watts/min). Medications were not withdrawn before the test. Patients cycled at a constant rate of 60 rpm throughout the test. They were allowed to continue until respiratory exchange ratio (defined as the ratio between oxygen consumption [VO_2] and carbon dioxide production) was >1. Exercise was terminated when the patient was unable to continue, which was the result of either dyspnea and/or leg/general fatigue. Heart rate was continuously recorded on a 12-lead electrocardiogram (Marquette Electronics Inc., Milwaukee, Wisconsin, Case 15). Blood pressure was measured every 2 min and at peak exercise with a mercury sphygmomanometer. The data for gas exchange were collected on a breath-by-breath basis using a computerized system (Medical Graphics Corporation, St. Paul, Minnesota, CPX system). The oxygen fraction was measured using a permanent zirconium oxide electrochemical cell and the carbon dioxide fraction was measured using a dual-beam infrared absorption chamber. A complete calibration (using standard gas mixtures) was performed prior to each exercise test. Anaerobic threshold was determined by the V slope method and by analyzing ratio of minute ventilation against VO_2 and ratio of minute ventilation against carbon dioxide production. Peak VO_2 and peak carbon dioxide production were defined as the highest average value during 10 s obtained during the last minute of exercise. Oxygen pulse was defined as the ratio of VO_2 against heart rate. Predicted value of maximal VO_2 was calculated using Wasserman's equation, normalizing maximal VO_2 for age, gender, weight and height (8).

Radionuclide determination. Radionuclide angiography was performed at rest in the supine position with use of an in vivo red blood cell labeling method. An equilibrium multigated acquisition was initiated after the injection of 20 mCi of technetium-99m. Imaging was performed in two views on a DST camera (Sopha Medical, Twinsburg, Ohio): the left anterior oblique projection that best visualized the interventricular septum and a 70° left anterior oblique projection. Studies were acquired on a 64 × 64 matrix with 16 frames per cardiac cycle for a preset count of 400,000 cps. Right ventricular ejection fraction and LVEF were calculated by automated detection of end diastolic and end systolic contours with manual correction if necessary. All the studies were performed by the same investigator (C.F.-H.) who was not aware of the results of the cardiopulmonary exercise test.

End points and follow-up. Follow-up was performed by direct examination or by contact with the general practitioner or the cardiologist. All the patients were followed up for at least 1 year except if a major end point terminated the follow-up. Major end points were total events (mortality and transplantation), total mortality, cardiovascular events (cardiovascular death and transplantation) and cardiovascular mortality (that included cardiovascular death and urgent transplantation [United Network for Organ Sharing status 1 {UNOS1}]) (9).

Statistics. Results are presented as mean ± SD. Differences between groups were assessed by analysis of variance and by unpaired Student's *t* tests followed by the Student–Newman–Keuls test. Discrete variables were compared using a chi-square analysis. Relationships between variables were studied by a linear regression analysis.

A Kaplan–Meier method was performed to estimate the cumulative survival. We stratified the population study into two subgroups on the basis of the median value of the variable tested for quantitative variable and in the different subgroups for qualitative variables. A comparative log rank test was used to compare the survival rates of the different subgroups. A stepwise multivariate Cox proportional hazards analysis was performed to determine the independent predictors of cardiac survival (freedom from cardiovascular mortality and urgent transplantation). We included in the model variables that were significant at a level of 0.1 in the univariate analysis. Quantitative variables were entered as continuous variables. Systolic pulmonary arterial pressure (SPAP), estimated by the maximal velocity of the tricuspid regurgitation on a echoDoppler study (VingMed, Horten, Norway, CFM 750), was included in the model as a qualitative variable, coded 0 if SPAP ≤35 mm Hg, coded 1 if SPAP was between 35 and 45 mm Hg and coded 2 if SPAP ≥45 mm Hg. In 35 patients there was no significant tricuspid regurgitation (pulsed Doppler mode guided by color Doppler mode) and these patients were coded 0. Previous studies have demonstrated that patients without tricuspid regurgitation had normal pulmonary pressure (10). In another model we included the SPAP as a quantitative variable, excluding the 35 patients with no tricuspid regurgitation. Etiology was entered as a qualitative variable, coded 0 for nonischemic cardiomyopathy, coded 1 for ischemic cardiomyopathy and coded 2 for the four women who refused the

Table 1. Characteristics in the Whole Population, in Survivors and in Nonsurvivors (Cardiovascular Mortality and Urgent Transplantation)

	Whole Population	Survivors	Nonsurvivors	p Value
n	205	159	46	
Gender (M/F)	171/34	131/28	40/6	0.61
Age (yr)	54 ± 11	54.2 ± 10.6	53.2 ± 12.5	0.58
Ischemic/nonischemic*	80/121	61/94	19/27	0.85
NYHA II/III	140/65	121/38	19/27	<0.0001
LVEF (%)	29.3 ± 10.1	30.4 ± 9.9	25.4 ± 10	0.003
RVEF (%)	37.5 ± 14.6	40 ± 13.8	28.9 ± 14	<0.0001
LVEDD (mm)	65.9 ± 8.55	65.6 ± 8.2	66.8 ± 9.8	0.41
SPAP (mm Hg)†	39.3 ± 14.9	38 ± 15	43 ± 14	0.052
Duration of exercise (s)	587 ± 224	616 ± 228	496 ± 200	0.0016
Rest HR (beats/min)	88.7 ± 18.7	87.3 ± 18.3	92 ± 19.3	0.14
Peak HR (beats/min)	142 ± 28	143 ± 27	140 ± 23	0.49
Rest SBP (mm Hg)	122 ± 21	123 ± 20	119 ± 23	0.25
Peak SBP (mm Hg)	157 ± 33	161 ± 32	144 ± 31	0.002
VO_2 at AT (ml/min)	771 ± 309	810 ± 304	609 ± 287	0.0001
Peak VO_2 (ml/min)	1,226 ± 477	1,285 ± 459	1,036 ± 472	0.0015
Peak VO_2 (ml/min/kg)	16.2 ± 5.4	17 ± 5.13	13.7 ± 5.5	0.0002
%Peak VO_2	60.2 ± 19	63 ± 18	50.2 ± 19.5	<0.0001
Peak RER	1.18 ± 0.12	1.18 ± 0.12	1.2 ± 0.14	0.34
Peak O_2 pulse (ml/min/beats)	9.55 ± 13.5	9.1 ± 15.2	7.34 ± 2.68	0.0006
%Peak O_2 pulse	71.9 ± 24.3	75 ± 24	60.7 ± 20.6	0.0003

*The four patients who refused angiography were excluded; †the 35 patients with nonsignificant tricuspid regurgitation were excluded. AT = anaerobic threshold; F = females; HR = heart rate; LVEDD = left ventricular end diastolic diameter; LVEF = left ventricular ejection fraction; M = males; NYHA = New York Heart Association; O_2 = oxygen; RER = respiratory exchange ratio; RVEF = right ventricular ejection fraction; SBP = systolic blood pressure; SPAP = systolic pulmonary artery pressure; VO_2 = oxygen consumption.

Table 2. Coefficients of Correlation and Respective p Values Between RVEF and Other Variables in the Whole Population, in Patients With Ischemic Cardiomyopathy and in Patients With Nonischemic Cardiomyopathy

Variables	Whole Population	Ischemic*	Nonischemic*
Peak VO_2	r = 0.21	r = 0.22	r = 0.27
	p = 0.0029	p = 0.05	p = 0.0024
Peak VO_2/kg	r = 0.17	r = 0.18	r = 0.26
	p = 0.014	p = 0.1	p = 0.004
%Peak VO_2	r = 0.29	r = 0.36	r = 0.32
	p < 0.0001	p = 0.0009	p = 0.0003
Peak O_2 pulse	r = 0.28	r = 0.30	r = 0.27
	p < 0.0001	p = 0.0071	p = 0.0031
% Peak O_2 pulse	r = 0.26	r = 0.29	r = 0.24
	p = 0.0001	p = 0.0098	p = 0.0085
SPAP†	r = −0.31	r = −0.29	r = −0.36
	p < 0.0001	p = 0.03	p = 0.0001
LVEF	r = 0.39	r = 0.395	r = 0.40
	p < 0.0001	p = 0.0003	p < 0.0001

*The four patients who refused angiography were excluded; †the 35 patients with nonsignificant tricuspid regurgitation were excluded. Abbreviations as in Table 1.

coronary angiography. These four patients were still alive at the end of the follow-up period. Statistics were performed with the SAS software version 6.08 (SAS Institute Inc., Cary, North Carolina). A value of $p < 0.05$ was considered statistically significant.

Results

Patients. Clinical characteristics of the study population are summarized in Table 1. Most of the patients were taking angiotensin-converting enzyme inhibitors (194, 94.6%), diuretics (165, 80.5%) and digoxin (129, 62.9%). Other medications were nitrates (94, 45.8%), amiodarone (67, 32.7%), aspirin (83, 40.5%), anticoagulants (80, 39%), beta blocking agents (34, 16.6%) and calcium inhibitors (9, 4.4%). The mean LVEF was 29.3% ± 10.1% (median: 29%), the mean RVEF was 37.5% ± 14.6% (median: 39%), the mean peak VO_2 normalized to body weight was 16.2 ± 5.4 ml/min/kg (median: 15.8 ml/min/kg) and the mean percent of maximal predicted value was 60.2% ± 19% (median: 60%).

Relationship between RVEF and other parameters. Coefficients of correlation between peak VO_2 and RVEF were determined in the whole population and in subgroups divided according to etiology (Table 2). All the coefficients of correlation were similar, suggesting that etiology did not modify the relationship between exercise capacity and RVEF. We also studied the relationship between RVEF and SPAP (excluding the 35 patients with no significant tricuspid regurgitation). Figure 1 shows the scatterplot between RVEF and %peak VO_2 (top) and between RVEF and SPAP (bottom). Although the p values were statistically significant, coefficients of correlation were always <0.4 with wide 95% prediction intervals.

Survival analysis. During a median follow-up period of 722 days (49 to 1,940 days), there were 44 cardiac-related deaths, 15 transplantations of whom 2 were urgent (UNOS1), 3 deaths from noncardiac causes (malignant diseases) and 1 patient was lost to follow-up. The cardiovascular event rates (cardiovascular mortality and transplantation) at 1 and 2 years were 10% and 21%, respectively. The cardiovascular mortality rates (cardiovascular mortality and UNOS1) at 1 and 2 years were 10% and 19%, respectively. Figure 2 shows the event-free survival curve from cardiovascular mortality and urgent transplantation for the whole study population. Table 1 summarizes the differences between patients without events and patients with either a cardiovascular death or an urgent transplantation. Table 3 summarizes the differences in the two subgroups of patients divided according to the median value of the RVEF (median value: 39%). Figure 3 shows the event-free survival curves from cardiovascular mortality and urgent transplantation in the two subgroups of patients divided according to the median values of the RVEF (top), the LVEF (middle) and the percent of maximal predicted VO_2 (bottom).

Multivariate Cox analysis. The stepwise multivariate Cox analysis selected three independent predictors of cardiac survival: the NYHA classification, the percent of maximal pre-

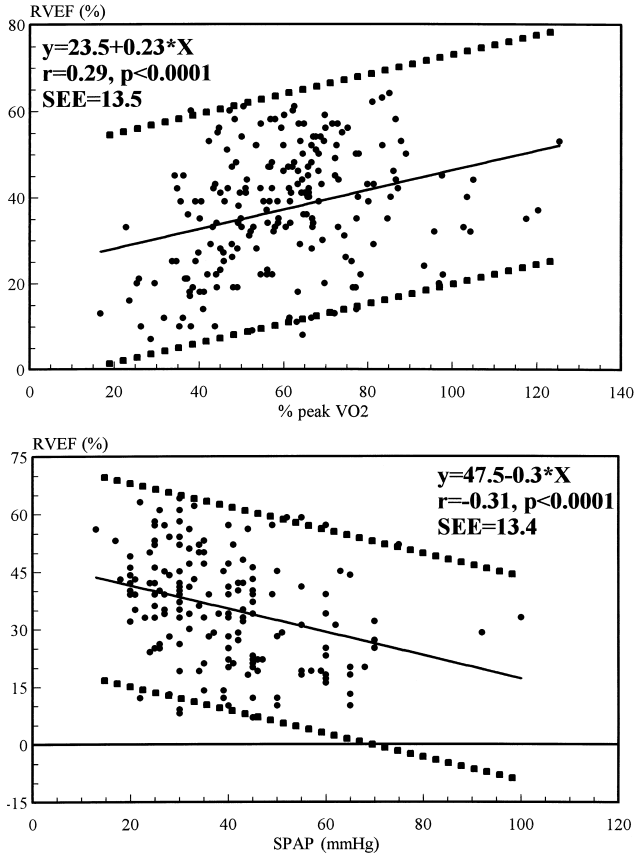


Figure 1. Relationship between RVEF and percent of maximal predicted VO_2 (**top**) and between RVEF and SPAP (**bottom**). The 35 patients with nonsignificant tricuspid regurgitation were excluded. Figure shows individual values, regression line and 95% prediction intervals.

dicted VO_2 and the RVEF (Table 4). Neither LVEF nor peak VO_2 normalized to body weight were predictors of survival.

The result of the stepwise multivariate Cox analysis was similar if we included in the model the following parameters in this order: NYHA classification, LVEF, peak VO_2 normalized to body weight, %peak VO_2 and RVEF. Right ventricular ejection fraction remained the only significant independent predictor of event-free survival from cardiovascular mortality and urgent transplantation (chi-square = 3.93, p = 0.0475), followed by NYHA classification (chi-square = 2.84, p = 0.09). Left ventricular ejection fraction, %peak VO_2 and peak VO_2/kg were not predictors of survival.

The result was similar if we entered in the model the SPAP as a continuous variable (excluding the 35 patients with nonsignificant tricuspid regurgitation) or as a qualitative variable. If we performed another multivariate Cox analysis with a stratification according to etiology, the best predictor of event-free survival from cardiovascular mortality and urgent transplantation was the RVEF (chi-square = 19.9, p = 0.0001), followed by the NYHA classification (chi-square = 11, p = 0.0009). If the study population was stratified according to the NYHA classification, independent predictors of major cardiac events were the RVEF (chi-square = 11.5, p = 0.0007) and the peak VO_2/kg (chi-square = 4.7, p = 0.03). In the 140 class II patients, event-free survival from cardiovascular mortality and urgent transplantation were 93% and 99% at 1 year and 81% and 98.5% at 2 years in the two subgroups divided according to the median value of the RVEF, respectively. In the 65 class III patients, the corresponding values were 72% and 87% at 1 year and 56% and 75% at 2 years.

New York Heart Association classification, RVEF and %peak VO_2 were also independent predictors of cardiovascular mortality and transplantation (urgent and nonurgent) whether we considered the date of transplantation or the date the patient was put on the waiting list for transplantation.

Figure 2. Event-free survival curve from cardiovascular mortality and urgent transplantation (UNOS1) for the whole population.

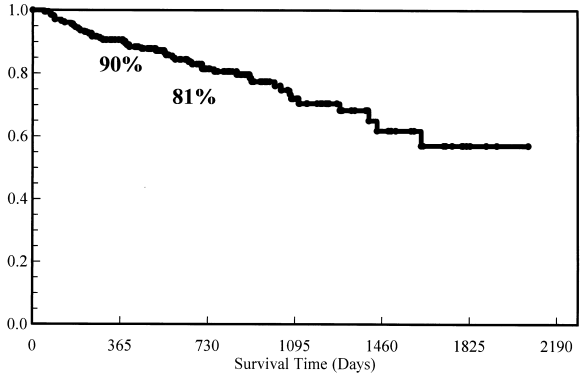


Table 3. Differences Between Patients Divided According to the Median Value of the RVEF (Median Value: 39%)

	RVEF ≤39%	RVEF >39%	p Value
n	107	98	
Gender (M/F)	87/20	84/14	0.51
Age (yr)	52 ± 11.2	56.2 ± 10.6	0.0063
NYHA II/III	63/44	77/21	0.004
Ischemic/nonischemic*	33/72	47/49	0.017
LVEF (%)	25.7 ± 9.92	33.2 ± 8.9	<0.0001
LVEDD (mm)	68 ± 8.8	63.7 ± 7.7	0.0003
SPAP (mm Hg)†	42.6 ± 15.3	34.4 ± 12.8	0.0003
Duration of exercise (s)	558 ± 219	623 ± 232	0.04
Rest HR (beats/min)	91.3 ± 19.2	85.2 ± 17.3	<0.019
Peak HR (beats/min)	145 ± 26.5	140 ± 26.6	0.2
Rest SBP (mm Hg)	117 ± 21	127 ± 19	<0.0001
Peak SBP (mm Hg)	148 ± 32	166 ± 31	<0.0001
VO_2 at AT (ml/min)	705 ± 333	831 ± 274	0.0043
Peak VO_2 (ml/min)	1,151 ± 494	1,315 ± 434	0.013
Peak VO_2 (ml/min/kg)	15.5 ± 5.94	17 ± 4.6	0.042
%Peak VO_2	55.7 ± 20.3	64.95 ± 15.8	0.0004
Peak RER	1.21 ± 0.13	1.15 ± 0.1	<0.0001
Peak O_2 pulse (ml/min/beats)	7.92 ± 2.86	9.57 ± 3.16	0.0001
%Peak O_2 pulse	65.8 ± 23	78.5 ± 24.1	0.0002

*The four patients who refused angiography were excluded; †the 35 patients with nonsignificant tricuspid regurgitation were excluded. Abbreviations as in Table 1.

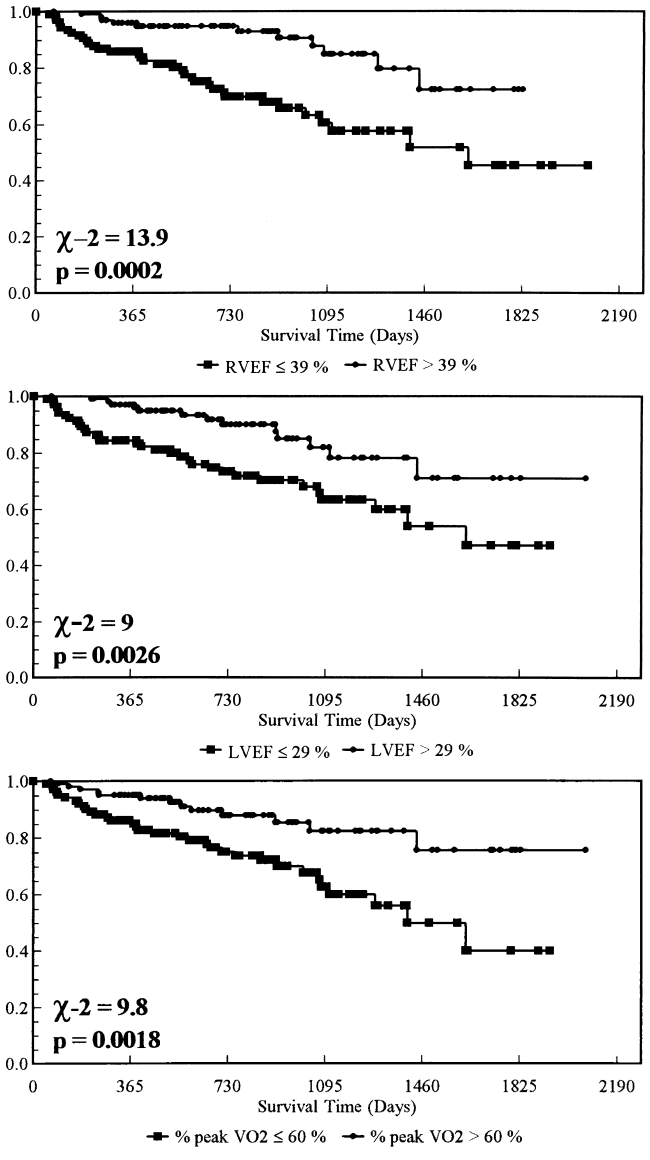


Figure 3. Event-free survival curves from cardiac mortality and urgent transplantation (UNOS1) in the two subgroups of patients divided according to the median value of the RVEF **(top)**, of the LVEF **(middle)** and of the percent of maximal predicted VO_2 **(bottom)**.

Figure 4 shows the receiver operating characteristic curve of RVEF in determining cardiovascular mortality and urgent transplantation at 1 year. The value of 35% has the highest sensitivity and specificity (70% and 58%, respectively). Figure 5 shows the event-free survival curves from cardiovascular mortality and urgent transplantation in three subgroups of patients divided according to the value of the RVEF (<25%, between 25% and 35% and ≥35%). The survival rates at 1 year were 80%, 90% and 95% in patients with an RVEF <25%, with an RVEF between 25% and 35% and with an RVEF ≥35%, respectively. At two years, the survival rates in these three subgroups were 59%, 77% and 93%, respectively.

Table 4. Results of the Multivariate Stepwise Cox Analysis

	Parameters	Chi-square	p Value
Total events	%peak VO_2	32.9	0.0001
	NYHA	7.82	0.0052
	RVEF	4.27	0.039
Total mortality	%peak VO_2	17	0.0001
	RVEF	7.75	0.0059
Cardiovascular events	NYHA	31.67	0.0001
	%peak VO_2	15.2	0.0001
	RVEF	6.19	0.013
Cardiovascular mortality and UNOS1	NYHA	23	0.0001
	RVEF	10.96	0.0009
	%peak VO_2	4.25	0.039

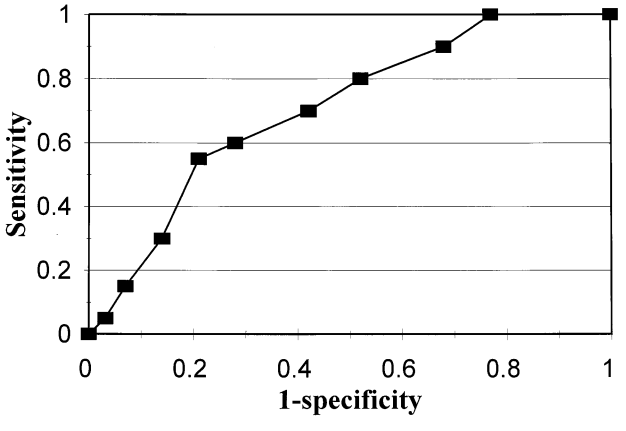
UNOS1 = United Network for Organ Sharing status 1. Other abbreviations as in Table 1.

Discussion

The major and novel finding of the present study was that RVEF is an independent predictor of survival in a large group of patients with stable and moderate CHF. In addition, given the large number of patients studied, we were able to analyze the relationship between RVEF, exercise capacity and SPAP.

Relationship between RVEF and other variables. The right ventricle is very sensitive to load, and SPAP is an important determinant of right ventricular function. We demonstrated that there was a significant but weak correlation between RVEF and SPAP in patients with moderate heart failure. The coefficient of correlation was 0.3 with wide 95% confidence intervals (Fig. 1). This is not surprising since our patients were stable and is not inconsistent with previous studies that failed to demonstrate a correlation between SPAP and right ventricular function in patients with heart failure. Schulman et al. (11) did not find a relationship between RVEF and SPAP in patients awaiting heart transplantation. Lewis et al. (12) demonstrated that SPAP was not correlated with right ventricular dilation in patients with dilated cardiomyopathy. Right ventricular ischemia in ischemic cardiomyopathy (13) or right ven-

Figure 4. Receiver operating characteristic curve of the RVEF in determining event-free survival from cardiovascular mortality and urgent transplantation at 1 year.



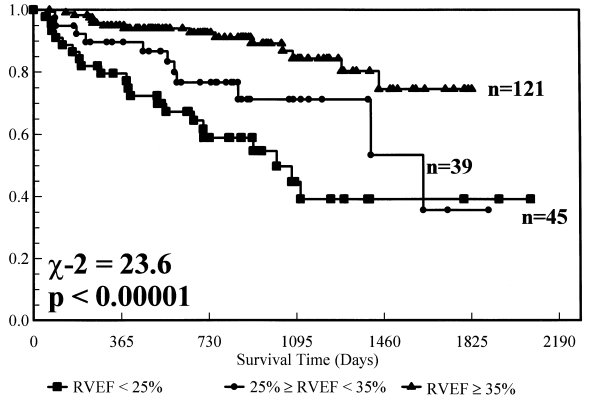


Figure 5. Event-free survival curves from cardiovascular mortality and urgent transplantation in the three subgroups of patients divided according to the RVEF <25%, RVEF between 25 and 35% and RVEF ≥35%.

tricular involvement in patients with idiopathic cardiomyopathy could explain the absence of a relationship between RVEF and SPAP. Our multivariate analysis did not select SPAP as an independent predictor of survival, whether we included this parameter as a continuous variable or as a qualitative variable. The SPAP was estimated noninvasively during an echoDoppler evaluation. It is possible that the results might be different if SPAP were measured invasively. However, previous studies have demonstrated a good correlation between values of SPAP determined by right heart catheterization and those estimated by echoDoppler (10,14). We also analyzed the relationship between RVEF and exercise capacity, assessed by the estimation of the peak VO_2. In our study, which represents the largest series of patients published to date, the relationship between peak VO_2 and RVEF is statistically significant. However, this relationship is weak, with a coefficient of correlation less than 0.3 and wide 95% confidence intervals (Fig. 1). While it has been suggested that this relationship is more marked in patients with ischemic cardiomyopathy, our results do not support this hypothesis (15). All the coefficients of correlation were similar whatever the etiology of heart failure (Table 2). Our results are thus in agreement with those of Clark et al. (16) who demonstrated that there was no relationship between RVEF and either peak VO_2 or the VE/VCO_2 slope. Di Salvo et al. (7) concluded that RVEF was correlated with peak VO_2 with an $r = 0.37$. Although confidence intervals were not given in the report by Di Salvo et al., the accompanying figure suggests that they were wide, as in the present study and that of Clark et al. (16). The mechanism of exercise intolerance in patients with heart failure is very complex and is related to several parameters (cardiac, vascular, lung function and muscle metabolism). It is difficult to conclude that RVEF plays the most important role in determining exercise capacity in patients with heart failure.

Survival analysis. The most important result of our study is the independent prognostic information derived from the determination of the RVEF in a subgroup of patients with stable heart failure. Previous studies have demonstrated a similar result but in patients with advanced heart failure, most of whom were awaiting heart transplantation (7,17–19). The mortality rate of our population was around 10% per year compared to almost 40% at 1 year in the study by Di Salvo et al. (7). Most of our patients were in class II of the NYHA classification (68%); the vast majority (94.6%) were taking angiotensin-converting enzyme inhibitors and all the patients were ambulatory. In the study by Di Salvo et al. (7), 24% of the 67 patients were in NYHA class II, the mean LVEF was 22% ± 7%, the mean RVEF was 29% ± 11%, the mean peak VO_2 and %peak VO_2 were 11.8 ± 4.2 ml/min/kg and 38% ± 12%, respectively. All these values were different in our study, supporting the fact that our patients had moderate heart failure. If the analysis was restricted to NYHA class II patients, or to NYHA class III patients, RVEF remains the best predictor of event-free survival from cardiovascular death and urgent transplantation. This demonstrates the usefulness of the RVEF in the selection of patients at higher risk of events, whatever the degree of CHF. Right ventricular ejection fraction was the more powerful predictor of survival when we stratified the population according to etiology or when we included it in the multivariate model after the previously documented prognostic parameters, namely, NYHA classification, LVEF, peak VO_2 normalized to body weight and % of maximal predicted VO_2 (2,4,6). Therefore, RVEF gives additional independent prognostic information in this subgroup of patients. The reason why LVEF was not an independent predictor of cardiac survival is probably because impaired left ventricular function was an inclusion criterion (LVEF ≤45%), whereas RVEF could be normal or abnormal (Fig. 5).

The large number of patients studied and the extremely high follow-up rate at 1 year allowed us to determine the sensitivities and specificities for the different values of RVEF in determining survival at 1 year. Figure 4 shows that a value of 35% gives the highest sensitivity and specificity. Figure 5 shows the different survival curves as a function of RVEF. There is a clear relationship between survival and the degree of right ventricular dysfunction. Patients with an RVEF <35% are at higher risk of major cardiac events.

We demonstrated, as did Stelken et al. (4) and DiSalvo et al. (7), that percent of maximal predicted VO_2 is more powerful than peak VO_2 normalized to body weight in predicting survival in patients with advanced heart failure or moderate heart failure. This result confirms our previous work in which we demonstrated the independent prediction of survival given by %peak VO_2 (20). However, the advantage of %peak VO_2 on peak VO_2 normalized to body weight is obtained in some subgroups of patients (young or old patients, women and overweight patients). In most of the patients there is an agreement between %peak VO_2 and peak VO_2/kg. We have to keep in mind a value of 50% of maximal predicted VO_2 and a peak VO_2 of 10 ml/min/kg as crucial values for the selection of patients with a high risk of major events at 1 year.

Study limitations. The determination of the RVEF by radionuclide angiography required a regular ventricular rhythm, so patients with atrial fibrillation were excluded. Serial

RVEF determinations will probably increase the power to predict survival, as it has been demonstrated for LVEF (21). Systolic pulmonary artery pressure was estimated by the peak velocity of the tricuspid regurgitation and not by an invasive method. Because all our patients were ambulatory patients with stable heart failure, it was not ethical to perform catheterization just to determine cardiac pressures. Our results cannot be extended to asymptomatic patients with left ventricular systolic dysfunction. Few patients were treated with beta-blockers, a therapy that is currently extensively investigated (22–24). It is possible that beta-blockers could change the relationship between RVEF and survival (as the one between peak VO_2 and survival). We did not include new noninvasive parameters of prognosis (mitral deceleration time, QT variability, recovery parameters after a maximal exercise test) (20,25–27). In the future, it will be important to combine these parameters in the same population to define the most powerful prognostic variables. Finally, the evaluation of the systolic and the diastolic function of the right ventricle by other methods is currently under investigation. Some new echocardiographic techniques (automated border detection, tissue Doppler imaging) are promising methods. Probably, in the coming years, accurate evaluation of right ventricular function will be easily possible using echocardiography. This would reduce the cost and simplify the management of patients with CHF. Further echocardiographic studies are required to evaluate the most useful parameters to define right ventricular systolic and diastolic functions.

Conclusion. We demonstrated that in patients with moderate heart failure, RVEF in addition to the NYHA functional classification and the percent of maximal predicted VO_2 was an independent predictor of survival and of major cardiac events. The determination of the RVEF in patients with moderate heart failure, particularly in NYHA class II patients, seems to be useful to improve their management.

References

1. Massie BM, Shah NB. Evolving trends in the epidemiologic factors of heart failure: rationale for preventive strategies and comprehensive disease management. Am Heart J 1997;133:703–12.
2. Mancini DM, Eisen H, Kussmaul W, et al. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation 1991;83:778–86.
3. Stevenson LW, Sietsema K, Tillisch JH, et al. Exercise capacity for survivors of cardiac transplantation or sustained medical therapy for stable heart failure. Circulation 1990;81:78–85.
4. Stelken AM, Younis LT, Jennison SH, et al. Prognostic value of cardiopulmonary exercise testing using percent achieved of predicted peak oxygen uptake for patients with ischemic and dilated cardiomyopathy. J Am Coll Cardiol 1996;27:345–52.
5. Pacher R, Stanek B, Hulsmann M, et al. Prognostic impact of big endothelin-1 plasma concentrations compared with invasive hemodynamic evaluation in severe heart failure. J Am Coll Cardiol 1996;27:633–41.
6. Cohn JN, Johnson GR, Shabetai R, et al. Ejection fraction, peak exercise oxygen consumption, cardiothoracic ratio, ventricular arrhythmias, and plasma norepinephrine as determinants of prognosis in heart failure. The V-HeFT VA Cooperative Studies Group. Circulation 1993;87:V15–16.
7. Di Salvo TG, Mathier M, Semigran MJ, Dec GW. Preserved right ventricular ejection fraction predicts exercise capacity and survival in advanced heart failure. J Am Coll Cardiol 1995;25:1143–53.
8. Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. Am Rev Respir Dis 1984;129:S49–S55.
9. Mudge GH, Goldstein S, Addonizio LJ, et al. 24th Bethesda conference: cardiac transplantation. Task Force 3: recipient guidelines/prioritization. J Am Coll Cardiol 1993;22:21–31.
10. Berger M, Haimowitz A, Van Tosh A, Berdoff RL, Goldberg E. Quantitative assessment of pulmonary hypertension in patients with tricuspid regurgitation using continuous wave Doppler ultrasound. J Am Coll Cardiol 1985;6:359–65.
11. Schulman DS, Grandis DJ, Deloplaine KA, Orie JE, Flores AR. Relationship between hemodynamics and right ventricular function in patients with cardiomyopathy. Important role of tricuspid regurgitation. Chest 1995;107:14–9.
12. Lewis JF, Webber JD, Sutton LL, Chesoni S, Curry CL. Discordance in degree of right and left ventricular dilation in patients with dilated cardiomyopathy: recognition and clinical implications. J Am Coll Cardiol 1993;21:649–54.
13. Shah PK, Maddahi J, Staniloff HM, et al. Variable spectrum and prognostic implications of left and right ventricular ejection fractions in patients with and without clinical heart failure after acute myocardial infarction. Am J Cardiol 1986;58:387–93.
14. Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. Circulation 1984;70:657–62.
15. Baker BJ, Wilen MM, Boyd CM, Dinh H, Franciosa JA. Relation of right ventricular ejection fraction to exercise capacity in chronic left ventricular failure. Am J Cardiol 1984;54:596–9.
16. Clarck AL, Swan JW, Laney R, et al. The role of right and left ventricular function in the ventilatory response to exercise in chronic heart failure. Circulation 1994;89:2062–9.
17. Polak JF, Holman L, Wynne J, Colucci WS. Right ventricular ejection fraction: an indicator of increased mortality in patients with congestive heart failure associated with coronary artery disease. J Am Coll Cardiol 1983;2:217–24.
18. Szlachcic J, Massie BM, Kramer BL, Topic N, Tubau J. Correlates and prognostic implication of exercise capacity in chronic congestive heart failure. Am J Cardiol 1985;55:1037–42.
19. Juilliere Y, Barbier G, Feldmann L, et al. Additional predictive value of both left and right ventricular ejection fractions on long-term survival in idiopathic dilated cardiomyopathy. Eur Heart J 1997;18:276–80.
20. de Groote P, Millaire A, Decoulx E, et al. Kinetics of oxygen consumption during and after exercise in patients with dilated cardiomyopathy. New markers of exercise intolerance with clinical implications. J Am Coll Cardiol 1996;28:168–75.
21. Cintron G, Johnson G, Francis G, Cobb F, Cohn JN. Prognostic significance of serial changes in left ventricular ejection fraction in patients with congestive heart failure. The V-HeFT VA Cooperative Studies Group. Circulation 1993;87:VI17–23.
22. Waagstein F, Bristow MR, Swedberg K, et al. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group. Lancet 1993;342:1441–6.
23. CIBIS Investigators and Committees. A randomized trial of beta-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). Circulation 1994;90:1765–73.
24. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. N Engl J Med 1996;334:1349–55.
25. Shen WF, Tribouilloy C, Rey JL, et al. Prognostic significance of Doppler-derived left ventricular diastolic filling variables in dilated cardiomyopathy. Am Heart J 1992;124:1524–33.
26. Xie GY, Berk MR, Smith MD, Gurley JC, De Maria AN. Prognostic value of Doppler transmitral flow patterns in patients with congestive heart failure. J Am Coll Cardiol 1994;24:132–9.
27. Barr CS, Naas A, Freeman M, Lang CC, Struthers AD. QT dispersion and sudden unexpected death in chronic heart failure. Lancet 1994;343:327–9.