Ventilatory Efficiency and the Selection of Patients for Heart Transplantation

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Background—Ventilatory efficiency, assessed by the slope of minute ventilation (V_E) versus carbon dioxide production (V_{CO_2}), is a powerful prognostic marker in patients with chronic heart failure. We hypothesized that V_E/V_{CO_2} slope would be more accurate than the current listing criteria for heart transplantation (HTx) in identifying patients likely to derive a survival benefit from this intervention.

Methods and Results—A total of 663 patients with chronic heart failure who underwent cardiopulmonary exercise testing were tracked for cardiac mortality and HTx. V_E/V_{CO_2} slope was the strongest independent predictor of mortality. Using a V_E/V_{CO_2} slope threshold instead of the current exercise criteria would classify 39 more subjects as being high risk (196 versus 157), correctly identifying 19 more patients who died during follow-up (57 versus 38) and 16 others who underwent transplantation (52 versus 36). Unlike the current listing criteria for HTx, V_E/V_{CO_2} slope provided significant discrimination between the 3-year survival of high- and low-risk patients and posttransplant patients selected from the International Society for Heart and Lung Transplantation registry. Reanalysis of survival data using death or HTx as the end point showed similar results.

Conclusions—V_E/V_{CO_2} slope is more accurate than the current listing criteria for HTx in identifying patients likely to derive a survival benefit from HTx. **(*Circ Heart Fail*. 2010;3:378-386.)**

Key Words: heart failure ■ exercise ■ transplantation ■ ventilation ■ prognosis

Cardiopulmonary exercise testing (CPX) is widely used to assess disease severity and prognosis in patients with chronic heart failure (CHF) due to left ventricular systolic dysfunction. Landmark studies have established peak oxygen consumption (V_{O_2}) as the cornerstone parameter of CPX particularly useful for prognostic stratification and for defining the optimal timing of heart transplantation (HTx).[1,2] Almost 2 decades after the seminal work of Mancini et al,[2] several reasons to reassess the role of peak V_{O_2} in guiding the listing for heart transplantation (HTx) have emerged. First, peak V_{O_2} has some intrinsic limitations, such as dependence on patient effort for optimal prognostic value[3] and its limited discriminatory power in patients with intermediate functional capacity,[4–6] where the survival benefit of HTx is less well demonstrated.[7] Second, important advances in the therapy of CHF have occurred in the past decade. β-blockers, implantable cardioverter defibrillators, and cardiac resynchronization therapy are now commonly prescribed to potential HTx candidates. These therapies improve the survival of patients with CHF, but with the exception of cardiac resynchronization therapy, they do not significantly change the exercise capacity.[8–10] Recent studies have shown that the prognostic yield of peak V_{O_2} is affected by β-blocker therapy,[11–15] and different peak V_{O_2} thresholds for listing patients for HTx according to β-blocker status have been proposed and accepted.[7,13]

These limitations of peak V_{O_2} have prompted the search for new and better CPX prognostic parameters among which the most prominent is ventilatory efficiency assessed by the slope of minute ventilation (V_E) versus carbon dioxide production (V_{CO_2}).[6,16–20] The rationale behind the use of ventilatory efficiency is that patients with CHF exhibit an excessive ventilatory response to exercise that is proportional to the degree of CHF severity, reflecting an increased ventilation-perfusion mismatch[21,22] and exaggerated chemosensitivity and ergoflex response.[23–25] The prognostic capabilities of V_E/V_{CO_2} slope were demonstrated in several studies where it outperformed peak V_{O_2},[6,16–19,23,26–31] but despite this apparent superiority, peak V_{O_2} continues to be the main CPX parameter used to guide listings for HTx.[7] A possible explanation is the absence of a widely accepted V_E/V_{CO_2} slope criterion to identify patients in whom a

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survival benefit from HTx is expected. We hypothesized that using V_E/V_{CO_2} slope would identify individuals likely to benefit from HTx more accurately than the current exercise criteria for this intervention.[7]

Methods

This study was a multicenter analysis of patients with heart failure from the CPX laboratories at Lariboisière Hospital (Paris, France), Santa Cruz Hospital (Carnaxide, Portugal), Heidelberg University Hospital (Heidelberg, Germany), and Brescia University (Brescia, Italy). The study cohort consisted of 663 consecutive patients identified retrospectively in the databases maintained by the 4 laboratories. All patients gave informed consent, and institutional review board approval for this retrospective analysis was obtained at each site. Clinical data were recorded prospectively on the day of CPX testing, performed between January 5, 1999, and December 22, 2006. Patients with left ventricular systolic dysfunction (ejection fraction ≤40% by echocardiography) in New York Heart Association class II to IV were included. Patients with primary valve disease, congenital heart disease, planned coronary revascularization, or cardiac surgery were excluded. Exclusion criteria also comprised age <18 years, known primary pulmonary disease, previous cardiac transplantation, and submaximal CPX (peak respiratory exchange ratio <1.05). In patients with >1 CPX test during the study period, only the first one was considered.

CPX

Symptom-limited CPX testing was performed on all patients. In the Portuguese center, CPX was performed on a treadmill using Naughton or ramp protocols, whereas in the other centers, lower-extremity cycle ergometers were used, applying 10-W/min or 15-W/2 min workload increments. Respiratory gas analysis was carried out on an Oxycon-Delta metabolic cart in the German center and on MedGraphics metabolic carts in the other centers. The equipment was calibrated before each test session using reference gases. V_{O_2}, V_{CO_2}, and V_E were measured on a breath-by-breath basis. Peak V_{O_2} was defined as the highest 20- to 30-second average achieved during exercise and expressed in mL/kg/min. V_E/V_{CO_2} slope was calculated by least squares linear regression fitting performed by using breath-by-breath values obtained throughout the whole exercise, a method previously shown to maximize its prognostic value.[19,30,32,33] Ventilatory threshold was determined by standard graphical methods[34,35] (ventilatory equivalents in the French and Italian centers and V-slope in the German and Portuguese centers).

Follow-Up and End Points

Patients were evaluated for the occurrence of death or HTx. Dates of events and the most recent event-free follow-up were obtained by medical chart review, telephone interview, or both. Follow-up was right censored at 3 years. None of the patients underwent implantation of left ventricular assist devices during the follow-up.

Statistical Analysis

Categorical variables are presented as number and percentage, and continuous variables are presented as mean±SD. Unpaired *t* test and Fisher exact test were used to compare continuous and categorical data, respectively. To test our hypothesis, we performed 2 separate analyses: (1) using death as end point (treating HTx patients as censored observations) and (2) using the combined end point of death or HTx. Univariable proportional hazards Cox regression was used to assess the prognostic value of clinical variables (age, sex, body mass index, ischemic cause, New York Heart Association functional class, and β-blocker use at the time of testing), echocardiographic variables (left ventricular ejection fraction), and CPX testing variables (CPX center, type of ergometer, presence of detectable ventilatory threshold, ventilatory threshold value, peak V_{O_2}, and V_E/V_{CO_2} slope). Variables that showed a significant association with a fatal outcome ($P<0.10$) at univariable analysis were included in a multivariable Cox regression model. When the Pearson correlation coefficient between 2 continuous variables was ≥0.60, only the variable judged to be clinically more important was entered in the multivariable model in order to avoid multicollinearity.

The discriminative ability of V_E/V_{CO_2} slope was assessed by calculation of the censored c index for death at 1 year. For binary outcomes, the c index is identical to the area under the receiver operating characteristic curve.[36] The best cutoff value of V_E/V_{CO_2} slope for the prediction of death at 1 year was identified in receiver operating characteristic curve analysis as the best combination of sensitivity and specificity (assuming a cost-benefit relationship of 1), and subgroups of high- and low-risk patients were created according to this cutoff point. Thus, patients were dichotomously stratified according to 2 different criteria: (1) V_E/V_{CO_2} slope and (2) the current CPX criteria for listing for HTx (peak $V_{O_2} \leq 12.0$ mL·kg^{-1}·min^{-1} for patients taking beta blockers and peak $V_{O_2} \leq 14.0$ mL·kg^{-1}·min^{-1} for patients without beta blockers).[7] Kaplan–Meier analyses were used to assess the survival characteristics of each of these subgroups, and differences in event-free survival were evaluated by the log-rank test. The 1- and 3-year survival rates of low- and high-risk subgroups were then compared with those of post-HTx patients from the International Society for Heart and Lung Transplantation transplant registry (quarterly data report on survival rates for orthotopic heart transplants performed in Europe between January 1, 2003, and December 31, 2006),[37] a method previously used to identify patients in whom a survival benefit from HTx is expected.[13] For this purpose,

Table 1. Clinical Characteristics and CPX Data

	All Patients (N=663)	HTx Patients (n=101)	Nontransplanted	
			Survivors (n=471)	Nonsurvivors (n=91)
Clinical characteristics				
Age, y	55±11	52±10	55±11	58±9
Male	557 (84)	85 (84)	393 (83)	79 (87)
BMI, kg/m^2	26.1±4.1	25.5±4.3	26.5±4.1	25.2±3.6
Ischemic cause	227 (34)	31 (31)	166 (35)	30 (33)
NYHA class				
II	361 (54)	32 (32)	281 (60)	48 (53)
III	276 (42)	58 (57)	183 (39)	35 (39)
IV	26 (4)	11 (11)	7 (1)	8 (9)
LVEF	26±8	23±8	28±7	23±7
Taking β-blockers	429 (65)	57 (56)	320 (68)	52 (57)
Taking ACEi and/or ARB	623 (94)	94 (93)	444 (94)	85 (93)
CPX data				
Peak respiratory exchange ratio	1.14±0.09	1.13±0.08	1.14±0.09	1.18±0.11
Peak V_{O_2}, mL·kg^{-1}·min^{-1}	16.8±5.5	14.8±4.8	17.8±5.5	14.2±4.4
Detectable ventilatory threshold	578 (87)	85 (84)	419 (89)	74 (81)
Ventilatory threshold, mL·kg^{-1}·min^{-1}	11.3±3.6	9.8±2.9	11.8±3.6	9.9±3.3
V_E/V_{CO_2} slope	39.3±11.0	46.5±13.8	36.4±8.5	46.6±12.1

Values are presented as mean±SD or n (%). ACEi indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Table 2. Cox Regression Results: Predictors of Death

	Wald χ^2	β Coefficient	HR	95% CI	*P*
Univariable analysis					
Age, y	8.8	0.03	1.03	1.01–1.05	0.003
BMI, kg/m^2	6.9	−0.07	0.93	0.88–0.98	0.008
NYHA class	10.7	NA	NA	NA	0.005
III	0.4	0.14	1.14	0.74–1.77	0.545
IV	10.7	1.25	3.49	1.65–7.38	0.001
LVEF	28.3	−0.07	0.93	0.91–0.96	<0.001
CPX center	8.7	NA	NA	NA	0.013
Detectable ventilatory threshold	5.6	−0.64	0.53	0.31–0.90	0.018
Ventilatory threshold*	14.1	−0.14	0.87	0.81–0.94	<0.001
Peak Vo_2, mL · kg^{-1} · min^{-1}	29.7	−0.13	0.88	0.83–0.92	<0.001
V_E/Vco_2 slope	83.1	0.07	1.07	1.05–1.09	<0.001
Multivariable analysis					
V_E/Vco_2 slope	21.6	0.05	1.05	1.03–1.07	<0.001
Age, y	4.6	0.02	1.02	1.00–1.05	0.032
Peak Vo_2, mL · kg^{-1} · min^{-1}	3.8	−0.06	0.95	0.89–1.00	0.052
LVEF	3.6	−0.03	0.97	0.94–1.00	0.057

BMI indicates body mass index; HR, hazard ratio; LVEF, left ventricular ejection fraction; NA, not applicable; NYHA, New York Heart Association functional class.

*Excluded from multivariable analysis to avoid multicollinearity with peak Vo_2 (Pearson correlation coefficient=0.80).

we calculated the 95% CIs from the SEs of the mean event-free survival rates for each subgroup at 1 and 3 years. If there was no overlap between the 95% CIs of a particular subgroup and those of post-HTx patients, a significant difference was retained. This comparison between current and hypothetical listing criteria for HTx based on V_E/Vco_2 slope was repeated using the combined end point of death or HTx. The ability of the proposed ventilatory efficiency threshold to reclassify risk was further assessed by calculating the net reclassification improvement, which compares the proportions moving up or down in clinical risk categories in cases versus controls.[38]

Statistical analyses were performed using SPSS version 13.0 and MedCalc 6.0. Statistical significance was defined as $P<0.05$ (2-tailed). The authors had full access to and took full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

Results

The clinical characteristics and CPX data of the study population are summarized in Table 1. During a median follow-up period of 26 months for surviving patients (interquartile range, 15 to 36), 101 (15.2%) underwent HTx and 91 others (13.7%) died. Univariable Cox proportional hazards models yielded 9 variables predictive of mortality among patients not receiving HTx. Multivariable analysis revealed that V_E/Vco_2 slope and age were independent predictors, whereas peak Vo_2 and left ventricular ejection fraction had borderline significance (Table 2). The decreasing survival across ascending categories of V_E/Vco_2 slope is depicted in Figure 1. V_E/Vco_2 slope showed good discrimination ability

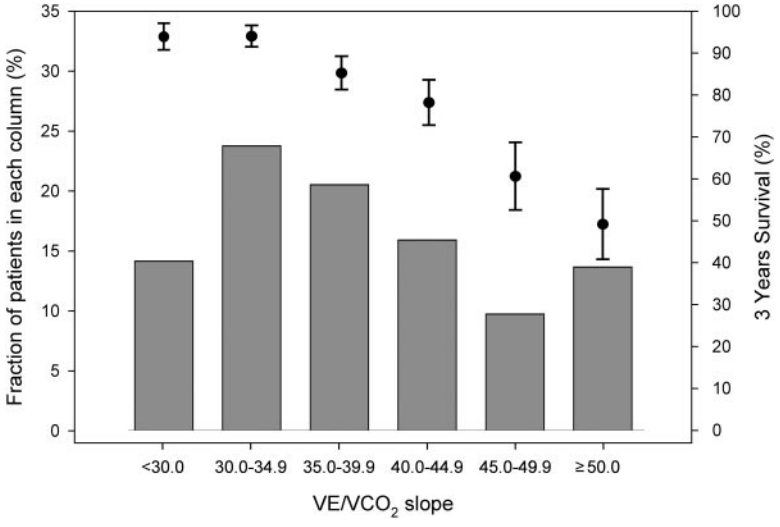

Figure 1. Histogram depicting the proportion of cases in ascending categories of V_E/Vco_2. The estimated 3-year mean survival and SE of the mean (error bars) are shown above each column.

Table 3. Comparison of Current and Hypothetical HTx Listing Criteria for Predicting Death

Listing Criteria for HTx	n	No. of Deaths	1-Year Survival, % (95% CI)	3-Year Survival, % (95% CI)	Log-Rank χ^2	Log-Rank *P*
Peak Vo_2 $\leq$12 mL · kg^{-1} · min^{-1} if taking BB or $\leq$14 mL · kg^{-1} · min^{-1} if not taking BB[7]						
No	506	53	94.9 (92.9–96.9)	84.4 (80.2–88.6)	28.4	<0.001
Yes	157	38	81.0 (74.2–87.8)	65.8 (55.9–75.7)		
V_E/Vco_2 slope $\geq$43.0						
No	467	34	97.0 (95.4–98.6)	89.4 (85.8–93.0)	79.2	<0.001
Yes	196	57	77.8 (71.3–84.3)	55.1 (45.2–65.0)		
ISHLT Transplant Registry Data[37]			82.2 (80.6–83.7)	77.6 (75.7–79.6)		

BB indicates β-blockers; ISHLT, International Society for Heart and Lung Transplantation.

in predicting death at 1 year, with a censored c index of 0.76 (95% CI, 0.73 to 0.79; $P<0.001$). Receiver operating characteristic curve analysis showed that a V_E/Vco_2 slope value of 43.0 produced an optimal balance of sensitivity and specificity (73% and 80%, respectively). The survival characteristics of the high- and low-risk subgroups created according to this cutoff point are shown in Table 3 along with survival data from the same patients stratified according to the current CPX criteria for listing for HTx. Although both these risk stratification schemes were significant, the use of a single cutoff point for V_E/Vco_2 slope resulted in the most unequal partitioning of events between high- and low-risk subgroups, as indicated by the highest log-rank score. The mortality hazard ratios for the current CPX criteria and V_E/Vco_2 slope criteria were 2.9 (95% CI, 1.9 to 4.4) and 5.6 (95% CI, 3.6 to 8.6), respectively. In absolute terms, using V_E/Vco_2 slope instead of the current CPX listing criteria for HTx would correspond to the classification of 39 more (196 versus 157) patients as high-risk, punctuated by the correct identification of 19 more (57 versus 38) who died during follow-up and 16 others (52 versus 36) who underwent HTx. The net reclassification improvement was 0.174 ($P=0.007$) for the prediction of death and 0.183 ($P<0.001$) for prediction of death or HTx, meaning that 17.4% and 18.3% more cases, respectively, appropriately saw their risk category increased rather than decreased compared with controls (Figure 2).

Kaplan–Meier analysis showed that at 3 years, the survival rate of patients with V_E/Vco_2 slope <43.0 was superior to that of patients who had undergone HTx (no overlap between the 95% CIs). Conversely, the 3-year survival rate of patients with V_E/Vco_2 slope $\geq$43.0 was inferior to that of HTx patients. Risk stratification based on the current exercise criteria for HTx resulted in an overlap between the 95% CIs for the 3-year survival between patients with HTx criteria and post-HTx patients (Figure 3 and Table 3). Table 4 shows the survival characteristics of patients in subgroups of β-blocker status, peak Vo_2, ischemic versus nonischemic cause, sex, and type of ergometer stratified according to V_E/Vco_2 slope. The prognostic ability of the V_E/Vco_2 slope criterion was consistent across subgroups, except in patients with peak Vo_2 $\leq$10.0 mL · kg^{-1} · min^{-1} (n=64) where it did not reach statistical significance ($P=0.266$). No significant interaction was found between each factor and the prognostic yield of a V_E/Vco_2 slope $\geq$43.0 (all *P* values for interaction were >0.05).

The reanalysis of survival data using the combined end point of death or HTx showed similar results. Although both risk stratification schemes were significant, the V_E/Vco_2 slope criterion remained prognostically superior, as indicated by the highest log-rank score (Table 5). The hazard ratios for the current exercise criteria and V_E/Vco_2 slope criteria were 2.7 (95% CI, 2.0 to 3.6) and 4.7 (95% CI, 3.5 to 6.3), respectively.

Discussion

The selection of patients with CHF for HTx is a challenging and important task given the shortage of donor hearts and the nonnegligible morbidity and mortality associated with this intervention.[39] An adequate selection assures that scarce resources are allocated to the patients who really need them and that HTx recipients (>5000 annually worldwide[39]) see their life expectancy improved by transplantation. CPX testing still plays an important role in assessing candidacy for HTx, although there is a growing tendency to perform fewer

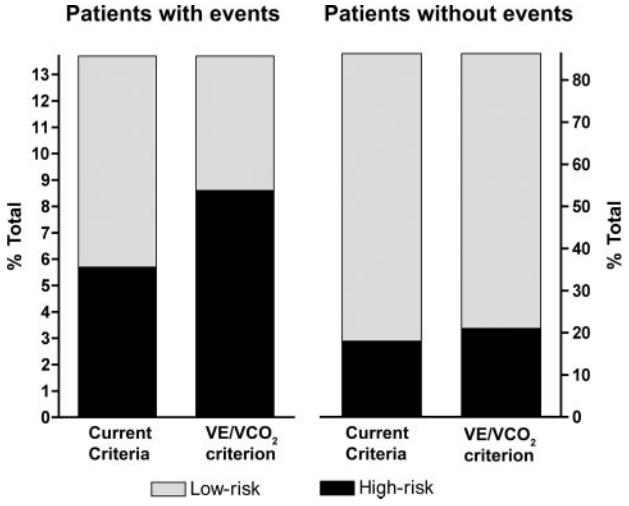

Figure 2. Differences in risk classification between current and V_E/Vco_2 slope criteria for HTx in patients who did and did not die during follow-up. Percentages refer to the total number of patients.

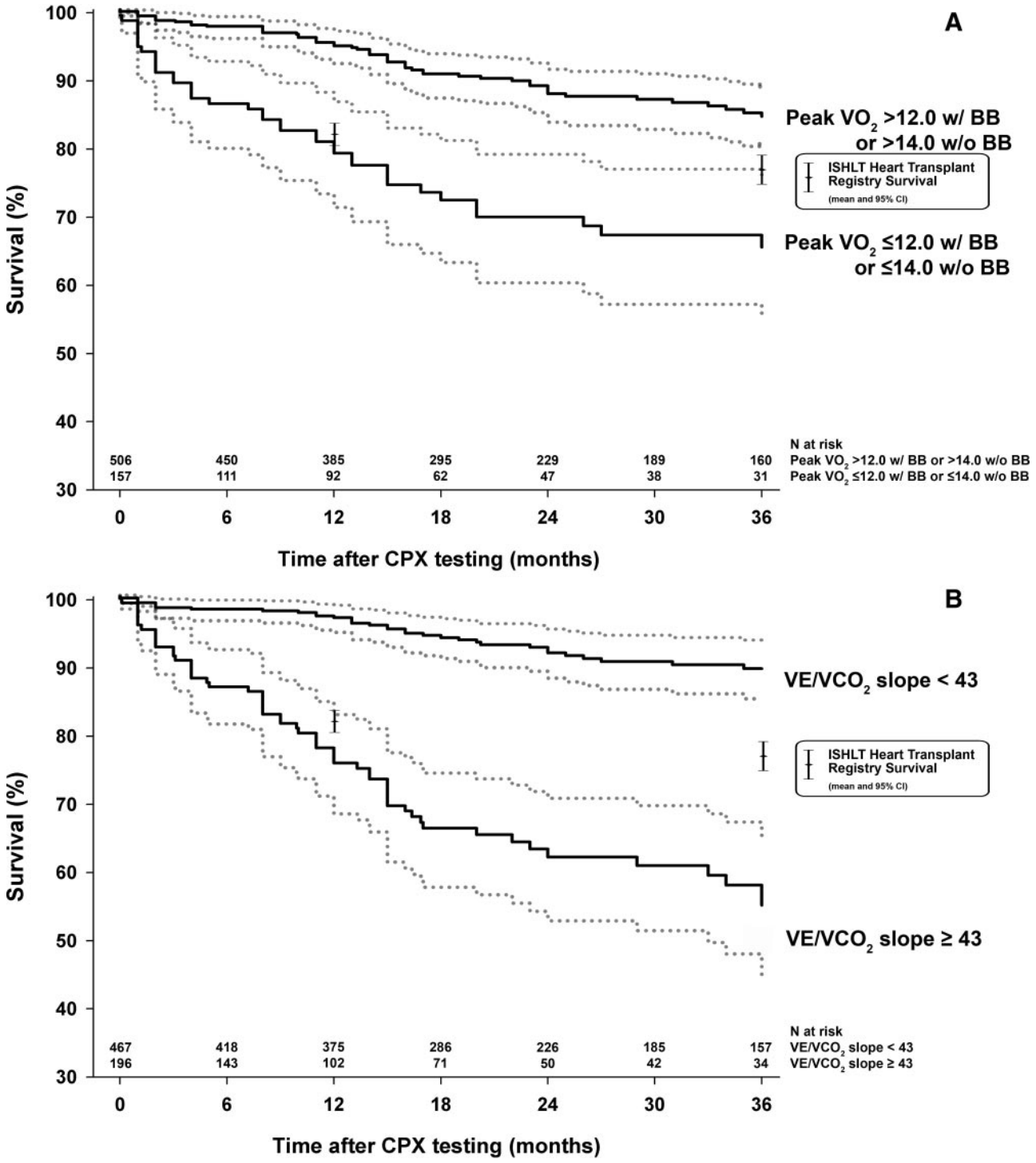

Figure 3. Kaplan–Meier survival curves according to the current listing criteria for HTx (A) and the best cutoff value of V_E/V_{CO_2} slope (B). Dotted lines represent the 95% CI. The 1- and 3-year post-HTx survival rates from the International Society of Heart and Lung Transplantation Heart Transplant Registry are represented with their respective 95% CIs (vertical bars).

elective procedures. Early studies in this area focused on peak V_{O_2} for risk stratification.[1,2] Although the value of peak V_{O_2} has been confirmed by several subsequent studies,[14,40] indices of ventilatory efficiency were not assessed until the late 1990s. Since, ventilatory efficiency has been repeatedly reported to be a more accurate prognostic index than peak V_{O_2}.[6,16–19,23,26–31] A recent comprehensive review on this topic showed that the V_E/V_{CO_2} relationship was superior to peak V_{O_2} as a CHF prognostic marker in 24 of the 26 peer-reviewed publications that included both aerobic capacity and ventilatory efficiency.[41]

The findings of our study expand the body of evidence supporting the prognostic superiority of ventilatory efficiency. Our results suggest that a dichotomous risk stratification based on V_E/V_{CO_2} slope is more discriminative and more accurate than the current exercise criteria in identifying

Table 4. Prognostic Performance of a Single V_E/V_{CO_2} Slope Cutoff Point: Subgroup Analysis

Variable and Subgroup	n	No. of Deaths	1-Year Survival % (95% CI)	3-Years Survival % (95% CI)	Log-Rank χ^2	Log-Rank *P*
β-blocker status						
With β-blocker (n=429)						
V_E/V_{CO_2} slope <43	303	21	96.8 (94.7–98.9)	89.9 (85.6–94.2)	33.2	<0.001
V_E/V_{CO_2} slope ≥43	126	31	81.1 (73.5–88.7)	63.5 (52.0–75.0)		
Without β-blocker (n=234)						
V_E/V_{CO_2} slope <43	164	13	97.4 (94.9–99.9)	89.0 (83.3–94.7)	52.4	<0.001
V_E/V_{CO_2} slope ≥43	70	26	71.7 (59.6–83.8)	40.0 (23.0–57.0)		
Peak V_{O_2}, $mL \cdot kg^{-1} \cdot min^{-1}$						
Peak V_{O_2} ≥10.0 (n=64)						
V_E/V_{CO_2} slope <43	17	3	79.4 (58.1–100)	69.4 (47.6–91.2)	1.2	0.266
V_E/V_{CO_2} slope ≥43	47	14	72.2 (58.0–86.4)	53.7 (31.7–75.7)		
Peak V_{O_2} 10.1–14.0 (n=178)						
V_E/V_{CO_2} slope <43	99	11	97.8 (94.7–100)	82.3 (72.6–92.1)	12.2	<0.001
V_E/V_{CO_2} slope ≥43	79	23	76.4 (66.1–86.7)	60.2 (46.4–74.0)		
Peak V_{O_2} >14.0 (n=421)						
V_E/V_{CO_2} slope <43	351	20	97.6 (95.8–99.4)	91.7 (88.0–95.4)	53.0	<0.001
V_E/V_{CO_2} slope ≥43	70	20	83.1 (73.0–93.2)	49.5 (32.1–66.9)		
Cause						
Ischemic (n=227)						
V_E/V_{CO_2} slope <43	158	12	96.0 (92.9–99.1)	88.8 (82.4–95.2)	17.9	<0.001
V_E/V_{CO_2} slope ≥43	69	18	79.6 (69.3–89.9)	56.6 (38.9–74.3)		
Nonischemic (n=436)						
V_E/V_{CO_2} slope <43	309	22	97.5 (95.7–99.3)	89.6 (85.3–93.9)	63.0	<0.001
V_E/V_{CO_2} slope ≥43	127	39	76.8 (68.4–85.2)	54.1 (42.4–65.8)		
Sex						
Male (n=557)						
V_E/V_{CO_2} slope <43	392	30	97.0 (95.2–98.8)	89.6 (85.5–93.7)	62.7	<0.001
V_E/V_{CO_2} slope ≥43	165	49	81.1 (74.7–87.5)	55.6 (45.3–65.9)		
Female (n=106)						
V_E/V_{CO_2} slope <43	75	4	97.1 (93.2–100)	93.4 (87.0–99.8)	15.4	<0.001
V_E/V_{CO_2} slope ≥43	31	8	74.4 (55.9–92.9)	56.7 (31.0–82.4)		
Ergometer						
Bicycle (n=504)						
V_E/V_{CO_2} slope <43	349	33	96.0 (93.9–98.1)	86.9 (82.6–91.2)	56.9	<0.001
V_E/V_{CO_2} slope ≥43	155	49	75.6 (68.0–83.2)	52.6 (42.1–63.1)		
Treadmill (n=159)						
V_E/V_{CO_2} slope <43	118	1	100*	98.4 (95.3–100)	24.4	<0.001
V_E/V_{CO_2} slope ≥43	41	8	86.3 (75.0–97.6)	73.7 (57.3–90.1)		

*CI could not be determined.

patients who will get a survival benefit from HTx. Moreover, the prognostic power of V_E/V_{CO_2} slope seems to be independent of sex, cause, mode of exercise, β-blocker therapy, and peak V_{O_2}, with the possible exception of patients with peak $V_{O_2} \leq 10.0$ $mL \cdot kg^{-1} \cdot min^{-1}$, where this study was limited by small sample size. The fact that the prognostic performance of the V_E/V_{CO_2} slope was unaltered using different end points further supports the robustness of this CPX variable.

The reasons for the prognostic superiority of ventilatory efficiency over peak V_{O_2} are yet to be fully ascertained, but they probably include the relative independence of V_E/V_{CO_2} slope from patient effort[3] and its capacity to reflect the improvement in prognosis associated with

Table 5. Comparison of Current and Hypothetical HTx Listing Criteria for Predicting the Combined End Point of Death or HTx

Listing Criteria for HTx	n	No. of Events	1-Year Event-Free Survival, % (95% CI)	3-Years Event-Free Survival, % (95% CI)	Log-Rank χ^2	Log-Rank *P*
Peak Vo_2 $\leq$12 mL · kg^{-1} · min^{-1} if taking BB or $\leq$14 mL · kg^{-1} · min^{-1} if not taking BB[7]						
No	506	109	86.6 (83.5–89.7)	72.8 (68.1–77.5)	48.2	<0.001
Yes	157	74	65.4 (57.8–73.0)	43.8 (34.6–53.0)		
V_E/Vco_2 slope $\geq$43.0						
No	467	74	91.5 (89.0–94.9)	79.4 (75.1–83.7)	127.8	<0.001
Yes	196	109	58.2 (51.2–65.2)	34.9 (26.9–42.9)		

BB indicates β-blockers.

β-blocker therapy,[15,42,43] ultimately resulting in a more accurate assessment of CHF severity.[41] On a pathophysiological level, an increased V_E/Vco_2 slope has been associated with a number of abnormalities that underlie CHF, such as increased ventilation-perfusion mismatching[21,22] and an abnormally heightened chemosensitivity and ergoreflex response.[23–25]

Previous studies have shown that the risk of events is continuous across a wide range of V_E/Vco_2 slope values.[6,18,19] Even though this favors a continuous or multilevel classification, the use of thresholds is justified in clinical practice by the need to translate risk assessment into a dichotomous decision of whether or not to list for HTx. Although the most commonly cited threshold for the V_E/Vco_2 slope is $\approx$34,[16,17,23,27,31,44] our findings suggest that a significantly higher value of 43.0 yields the best discriminative power to predict mortality among patients with CHF. Several reasons may account for this discrepancy. First, some of these studies report a V_E/Vco_2 slope value of 34 not as the optimal prognostic threshold, but as the median value or the upper limit of normality (mean+2SD).[16,23,44] Second, the expression of ventilatory efficiency was not standardized until recently. We assessed ventilatory efficiency as the slope of the V_E-Vco_2 relationship in the whole exercise period, including data past the respiratory compensation point that not only increase the steepness of the slope and create a degree of nonlinearity, but also maximize its prognostic value.[19,30,32,33] Therefore, our V_E/Vco_2 slope values may not be comparable with those from studies that expressed ventilatory efficiency as a V_E/Vco_2 ratio (at peak exercise or at the ventilatory threshold) or as a V_E/Vco_2 slope that excludes data after the respiratory compensation point. Finally, differences in end points used for prognostic evaluation and different characteristics of the populations studied (eg, the inclusion of patients with diastolic CHF) may affect the optimal threshold of this and other prognostic variables. Notably, all 4 studies that used V_E/Vco_2 thresholds >40 used mortality as an end point.[45–48]

Some limitations of this observational study should be acknowledged. Being nonrandomized, differences in outcomes may reflect selection bias or the effect of confounding variables that were not consistently recorded in this study.

Because the comparison between common criteria for HTx and an internally defined V_E/Vco_2 slope threshold may inherently favor the latter, our ventilatory efficiency cutoff point cannot be recommended without prior external validation. Clinicians also should be aware that the ability of V_E/Vco_2 slope to estimate improvement after transplantation and its relationship to exercise capacity and quality of life are much less well studied than for peak Vo_2.

Comparison with International Society for Heart and Lung Transplantation registry data should be interpreted with caution because of possible differences in patient characteristics. (Peak Vo_2, β-blocker status, and V_E/Vco_2 slope are not available in the database for comparison.) The participating centers used different ergometers and different methods for estimating the ventilatory threshold. Although the use of different types of ergometers and exercise protocols can be viewed as a limitation, our findings corroborate previous studies that suggested that the prognostic power of ventilatory efficiency and peak Vo_2 is not significantly affected by the mode of exercise.[49] Finally, medication use was not tracked, and other prognostic variables, such as periodic breathing, neurohormonal markers, cardiac resynchronization therapy, or cardioverter defibrillator implantation, and established CHF survival scores were not systematically collected. Quality-of-life issues, which may influence the decision to transplant, also were beyond the scope of this study. Despite these limitations, our findings should stimulate the systematic measurement of V_E/Vco_2 slope in patients with CHF being evaluated for HTx and encourage the reevaluation of the current listing criteria to reflect the prognostic superiority of V_E/Vco_2 slope over the currently used parameters.

Conclusions

A dichotomous risk stratification based on V_E/Vco_2 slope is more accurate than the current exercise criteria for HTx in identifying patients who will likely get a survival benefit from this intervention. The reevaluation of current HTx listing criteria to reflect the prognostic superiority of ventilatory efficiency over currently used parameters should be considered.

Disclosures

None.

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