The Prognostic Value of Ventilatory Efficiency with Beta-Blocker Therapy in Heart Failure

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ABSTRACT

ARENA, R. A., M. GUAZZI, J. MYERS, and J. ABELLA. The Prognostic Value of Ventilatory Efficiency with Beta-Blocker Therapy in Heart Failure. *Med. Sci. Sports Exerc*., Vol. 39, No. 2, pp. 213–219, 2007. **Purpose:** Beta-blockade (BB) has been shown to improve outcomes among patients with heart failure (HF). The impact this pharmacological approach has on the prognostic information gained from cardiopulmonary exercise testing (CPX) is, however, unclear. **Methods:** Four hundred seventeen subjects diagnosed with HF underwent CPX. The numbers of subjects prescribed and not prescribed a BB agent were 167 and 250, respectively. Subjects were tracked for cardiac-related mortality after CPX. **Results:** Values are reported for the no-BB versus the BB group throughout. Age (57.9 ± 13.3 vs 55.6 ± 12.5), peak $\dot{V}O_2$ (16.2 ± 5.7 vs 16.5 ± 5.5 $mL \cdot kg^{-1} \cdot min^{-1}$), $VE/\dot{V}CO_2$ slope (34.2 ± 9.0 vs 33.2 ± 7.4), and peak RER (1.07 ± 0.16 vs 1.05 ± 0.14) were similar between groups ($P > 0.05$). Multivariate Cox regression analysis revealed that the $VE/\dot{V}CO_2$ slope was the superior predictor of death in both groups (chi-square: 71.9, $P < 0.001$; and 18.4, $P < 0.001$). The optimal threshold values for $VE/\dot{V}CO_2$ slope in the no-BB and BB groups were 36.0 and 34.3, respectively. **Conclusions:** The results of the present study indicate that BB does not alter the prognostic value/characteristics of the $VE/\dot{V}CO_2$ slope. Findings from previous investigations examining the prognostic significance of CPX predominantly using HF groups not receiving a BB agent may, therefore, still be applicable in modern-day clinical practice. **Key Words:** EXERCISE TESTING, METABOLIC ANALYSIS, OXYGEN UPTAKE, MORTALITY

Cardiopulmonary exercise testing (CPX) is an established evaluation technique in patients diagnosed with heart failure (HF) (12,15). The acceptance of CPX by the treating HF physicians stems from its well-established prognostic value (5,8,19,21). In recent years, beta-blockade (BB) has become a primary pharmacologic intervention in patients with HF and systolic dysfunction. The addition of this intervention arises from an abundance of evidence demonstrating that BB improves survival and reduces hospitalization (17), although a parallel improvement in aerobic capacity has not been observed (1,30). The majority of existing literature establishing the prognostic value of CPX was performed before the BB era. The prognostic utility of CPX in patients with HF who are receiving BB therapy has, therefore, been questioned. Several recent investigations have attempted to address this issue (9,22,24,25). These studies have generally found that peak oxygen consumption ($\dot{V}O_2$), the most frequently assessed CPX variable, maintains prognostic value, although the optimal threshold value may require a downward adjustment in patients with HF receiving BB (22).

Other CPX variables have also demonstrated prognostic value in patients with HF. The relationship between minute ventilation (VE) and carbon dioxide production ($\dot{V}CO_2$), commonly expressed as a slope, has received considerable attention (5,8,11,18). Moreover, a number of investigations have found that the $VE/\dot{V}CO_2$ slope is prognostically superior to peak $\dot{V}O_2$ in patients with HF (5,8,11,18). However, research investigating the effect of BB on the prognostic value of the $VE/\dot{V}CO_2$ slope in HF is limited. The primary purpose of the present study is to examine the impact of BB on the prognostic value of CPX variables in a group of subjects diagnosed with HF. We hypothesized that CPX variables would maintain prognostic value in patients with HF, irrespective of BB use.

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METHODS

This was a multicenter retrospective analysis consisting of HF patients from the cardiopulmonary laboratories at San Paolo Hospital, Milan, Italy; Virginia Commonwealth University, Richmond, VA; and the VA Palo Alto Health Care System and Stanford University, Palo Alto, CA. A total of 417 consecutive patients with chronic HF who were tested between March 18, 1993 and October 25, 2004 were included. Two hundred fifty subjects were not receiving a BB agent at the time of CPX or during follow-up. The remaining 167 subjects were on a stable dose of a BB agent for at least 3 months before CPX. Within the BB group, 123, 30, and 14 subjects were receiving carvedilol (mean dose: 26.0 $mg \cdot d^{-1}$ (± 17.4)), metoprolol (mean dose: 74.2 $mg \cdot d^{-1}$ (± 34.4)), and atenolol (mean dose: 59.2 $mg \cdot d^{-1}$ (± 47.8)), respectively. A majority of the subjects (62%) in the no-BB group were tested before January 1, 2000. Conversely, 68% of the subjects in the BB group were tested after January 1, 2000. The difference in the percentage of subjects tested after the year 2000 between groups is indicative of the increased use of BB agents in the HF population. Subjects received follow-up care at the three institutions included in this study. History of prescribed medications was available for all subjects throughout their follow-up. None of the subjects in the no-BB or BB groups crossed over. All subjects completed a written informed consent, and institutional review board approval was obtained at each institution. Baseline subject characteristics are listed in Table 1.

Inclusion criteria consisted of a diagnosis of HF and evidence of left ventricular dysfunction (systolic or diastolic) by echocardiogram or cardiac catheterization obtained within 1 month of exercise testing. Subjects with both systolic and diastolic HF were included in the analysis because we have previously found CPX to be prognostically similar in both groups (13). Subjects with a left ventricular ejection fraction (LVEF) $\leq 45\%$ ($N = 363$) were considered to have systolic dysfunction, whereas those with an LVEF $> 45\%$ ($N = 53$; 38 (15%) in the no-BB group, 16 (9.6%) in the BB group) were considered to have preserved systolic function. Patients with significant obstructive lung disease or who were unable to perform a symptom-limited exercise test secondary to physical limitations (such as arthritis) were excluded from the study. The sample was a consecutive series of subjects during the specified period of time who met the inclusion criteria. Selection bias was, therefore, not a concern.

Equipment Calibration

Ventilatory expired gas analysis was performed using a metabolic cart at all three centers (Medgraphics CPX-D, Minneapolis, MN; or Sensormedics Vmax29, Yorba Linda, CA). The oxygen and carbon dioxide sensors were calibrated using gases with known oxygen, nitrogen, and carbon dioxide concentrations before each test. The flow sensors were also calibrated before each test using a 3-L syringe.

CPX Procedure and Data Collection

Symptom-limited CPX was performed on all patients using a treadmill (3) or cycle ergometry (14) ramping protocols. A treadmill was used for testing in American centers, whereas a lower-extremity ergometer was used in the European center. Previous work by our group has demonstrated optimal peak $\dot{V}O_2$ and $VE/\dot{V}CO_2$-slope prognostic threshold values were similar irrespective of mode of exercise in patients with HF (2). Therefore, we did not create subgroups based on mode of CPX. Standard 12-lead electrocardiograms were obtained at rest, each minute during exercise, and for at least 5 min during the recovery phase; blood pressure was measured using a standard cuff sphygmomanometer. Minute ventilation (VE, BTPS), oxygen uptake ($\dot{V}O_2$, STPD), carbon dioxide output ($\dot{V}CO_2$, STPD), and other cardiopulmonary variables were acquired breath-by-breath and were averaged for 10-s intervals. Peak $\dot{V}O_2$ and peak respiratory exchange ratio (RER) were expressed as the highest averaged samples obtained during the last 10 s of the exercise test, and VE and $\dot{V}CO_2$ responses, acquired from the initiation of exercise to peak, were input into spreadsheet software (Microsoft Excel, Microsoft Corporation, Bellevue, WA) to calculate the $VE/\dot{V}CO_2$ slope via least-squares linear regression ($y = mx + b$, m = slope). Previous work by our group and by others has shown this method of calculating the $VE/\dot{V}CO_2$ slope to be prognostically optimal (4,7).

End points

Subjects were observed for cardiac-related mortality after CPX via medical chart review. Any death with a

TABLE 1. Baseline characteristics.

	Overall Group ($N = 417$)	No BB ($N = 250$)	BB ($N = 167$)
Age (yr)	56.9 ± 13.1	57.9 ± 13.3	55.6 ± 12.5
Sex (M/F)	338/79 (81.0%/19.0%)	199/51 (79.6%/20.4%)	139/28 (83.2%/16.8%)
CHF cause (ischemic/nonischemic)	227/190 (54.4%/45.6%)	131/119 (52.4%/47.6%)	96/71 (57.5%/42.5%)
NYHA class (I/II/III/IV and mean ± standard deviation)	146/154/100/17, 2.0 ± 0.87	95/85/57/13, 2.0 ± 0.90	51/69/43/4, 2.0 ± 0.81
Left ventricular ejection fraction (%)	33.1 ± 12.1	34.1 ± 12.0	31.4 ± 12.1*
Resting heart rate (bpm)	80.5 ± 16.1	81.5 ± 17.0	78.4 ± 15.7
ACE inhibitor†	301 (72.2%)	177 (70.8%)	124 (74.3%)
Diuretic†	228 (54.7%)	130 (52.0%)	98 (58.7%)
Digoxin†	206 (49.0%)	131 (52.4%)	75 (44.9%)

BB, beta-blockade; CHF, cardiac heart failure.
* Statistically significant ($P < 0.01$).
† Number of subjects on medication.

TABLE 2. Unpaired *t*-test results.

	Overall Group (*N* = 417)	No BB (*N* = 250)	BB (*N* = 167)	*P* Value
Peak $\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	16.3 ± 5.7	16.2 ± 5.7	16.5 ± 5.5	0.63
Peak RER	1.06 ± 0.16	1.07 ± 0.16	1.05 ± 0.14	0.34
$VE/\dot{V}CO_2$ slope	33.8 ± 8.4	34.2 ± 9.0	33.2 ± 7.4	0.23
Maximal heart rate (bpm)	132.0 ± 28.2	136.8 ± 30.1	125.0 ± 24.0	0.001

BB, beta-blockade; RER, respiratory exchange ratio.

cardiac-related discharge diagnosis, confirmed by diagnostic tests or autopsy, was considered an event. The most common causes of mortality, as per discharge diagnosis, were sudden cardiac death (45%) and HF (55%). Subjects in whom mortality was of a noncardiac origin were treated as censored cases. Clinicians conducting the CPX were not involved in decisions regarding cause of death.

Statistical Analysis

Unpaired *t*-tests were used to compare differences in age, LVEF, heart rate at rest and maximal exercise, peak RER, peak $\dot{V}O_2$, and the $VE/\dot{V}CO_2$ slope between the no-BB and BB groups. The Mann–Whitney U test was used to assess differences in NYHA class (ordinal level data) between the BB and no-BB groups.

Univariate and multivariate Cox regression analysis assessed the ability of variables to predict cardiac-related mortality after CPX. Variables found to be significant predictors in the univariate analysis were included in the multivariate analysis. The forward stepwise method was used for the multivariate analyses, with entry and removal *P* values set at 0.05 and 0.10, respectively.

Receiver operating characteristic (ROC) curves were constructed for peak $\dot{V}O_2$ and the $VE/\dot{V}CO_2$-slope prognostic classification schemes in the BB and no-BB groups. Optimal threshold values (highest combination of sensitivity/specificity) were identified via ROC curve analysis. Hazard ratios, with 95% confidence intervals, were determined for the peak $\dot{V}O_2$ and $VE/\dot{V}CO_2$-slope prognostic threshold values.

All data are reported as mean values ± standard deviation (SD). Statistical differences with a *P* value < 0.05 were considered significant.

RESULTS

Baseline characteristics listed in Table 1 indicate that the no-BB and BB groups were similar, with the exception of LVEF. The difference in LVEF between groups became nonsignificant (no-BB group, 31.0 ± 9.8%; BB group, 29.3 ± 10.2%; $P = 0.13$) when subjects with preserved systolic function were excluded from the analysis (LVEF > 45%). Results from CPX are listed in Table 2. None of the tests were stopped prematurely secondary to arrhythmias or evidence of ischemia. The primarily reason for test termination was subject request secondary to fatigue. Peak $\dot{V}O_2$, $VE/\dot{V}CO_2$ slope, and peak RER were similar between the no-BB and the BB groups. However, maximal heart rate was significantly higher in the no-BB group.

The mean tracking periods after CPX in the no-BB and BB groups were 36.9 (± 28.1 months, range 1–111) and 24.3 (± 20.1 months, range 1–108), respectively. During the tracking period, there were 55 (22%) cardiac-related deaths in the no-BB group and 29 (17%) cardiac-related deaths in the BB group. There were four deaths (three in the no-BB group and one in the BB group) attributed to noncardiac causes, four heart transplantations, and three left ventricular assist device implantations that were classified as censored cases. Univariate and multivariate Cox regression analysis results are listed in Tables 3 and 4, respectively. LVEF, peak $\dot{V}O_2$, and the $VE/\dot{V}CO_2$ slope were significant univariate predictors overall and in both subgroups. Age was a significant predictor of cardiac mortality in the overall group. In the multivariate analysis, the $VE/\dot{V}CO_2$ slope was the strongest prognostic variable in the overall group and in both the no-BB and BB groups. LVEF added significant predictive value to the $VE/\dot{V}CO_2$ slope in the overall group and both subgroups and was retained in the multivariate regression. Age also added significant predictive value in the overall group. Peak $\dot{V}O_2$ did not add significant predictive value and was removed from the multivariate regression analysis in the overall groups as well as the no-BB and BB groups.

When limiting the follow-up period to 1 yr after CPX, the prognostic trends were consistent with that of the overall follow-up period. There were 38 deaths within 1 yr after CPX in the overall group (26 in the no-BB group

TABLE 3. Univariate Cox regression analysis.

	Overall Group		No-BB Group		BB Group	
	Chi Square	*P* Value	Chi Square	*P* Value	Chi Square	*P* Value
Age	4.5	0.04*	1.1	0.29	3.9	0.05
Sex	2.5	0.11	3.7	0.05	0.01	0.34
HF cause	0.30	0.60	0.24	0.63	0.17	0.68
Resting HR	3.0	0.08	3.3	0.07	0.30	0.60
LVEF	39.7	<0.001*	24.4	<0.001*	17.9	<0.001*
$VE/\dot{V}CO_2$ slope	88.9	<0.001*	71.9	<0.001*	18.4	<0.001*
Peak $\dot{V}O_2$	21.6	<0.001*	13.7	<0.001*	9.5	0.002*

BB, beta-blockade; HF, heart failure; LVEF, left ventricular ejection fraction.
* Statistically significant.

TABLE 4. Multivariate Cox regression analysis.

	Overall Group	
	Chi Square	***P* Value**
$VE/\dot{V}CO_2$ slope	88.9	<0.001
	Residual Chi Square	
LVEF	17.2	<0.001
Age	4.9	0.03
Peak $\dot{V}O_2$	0.60	0.46
	No-BB Group	
$VE/\dot{V}CO_2$ slope	71.9	<0.001
	Residual Chi Square	
LVEF	9.7	0.002
Peak $\dot{V}O_2$	0.32	0.57
	BB Group	
$VE/\dot{V}CO_2$ slope	18.4	<0.001
	Residual Chi Square	
LVEF	15.3	<0.001
Peak $\dot{V}O_2$	1.4	0.23

LVEF, left ventricular ejection fraction; BB, beta-blockade.

(10.4%) and 12 in the BB group (7.2%)) The $VE/\dot{V}CO_2$ slope was still the strongest prognostic marker in the overall (chi-square: 72.5, $P < 0.001$), no-BB (chi-square: 55.3, $P < 0.001$) and BB (chi-square: 14.7, $P < 0.001$) groups. LVEF added prognostic value to the $VE/\dot{V}CO_2$ slope in the overall group only (residual chi-square: 5.3, $P = 0.02$). No other variables added prognostic value in the multiple regression analyses.

When removing the 53 subjects with preserved systolic function from the analysis, the prognostic trends were again consistent with the larger group. There were 80 deaths in the overall group (51 of 212 in the no-BB group, 29 of 151 in the BB group). The $VE/\dot{V}CO_2$ slope was still the strongest prognostic marker in the overall (chi-square: 64.3, $P < 0.001$), no-BB (chi-square: 51.1, $P < 0.001$), and BB (chi-square: 13.1, $P = 0.001$) groups. LVEF added prognostic value to the $VE/\dot{V}CO_2$ slope in the overall (residual chi-square: 14.7, $P = 0.001$), no-BB (residual chi-square: 8.9, $P = 0.003$), and BB groups (residual chi-square: 5.4, $P = 0.02$). No other variables added prognostic value in the multiple-regression analyses.

ROC curve analysis results are listed in Table 5 and Figure 1. The prognostic classification schemes for peak $\dot{V}O_2$ and the $VE/\dot{V}CO_2$ slope were statistically significant in both the no-BB and BB groups. Using the threshold values listed in Table 5, hazard ratios for peak $\dot{V}O_2$ and the $VE/\dot{V}CO_2$ slope in the no-BB group were 2.6 (95% confidence interval: 1.5–4.5, $P = 0.001$) and 6.0 (95% confidence interval: 3.3–10.9, $P < 0.001$), respectively.

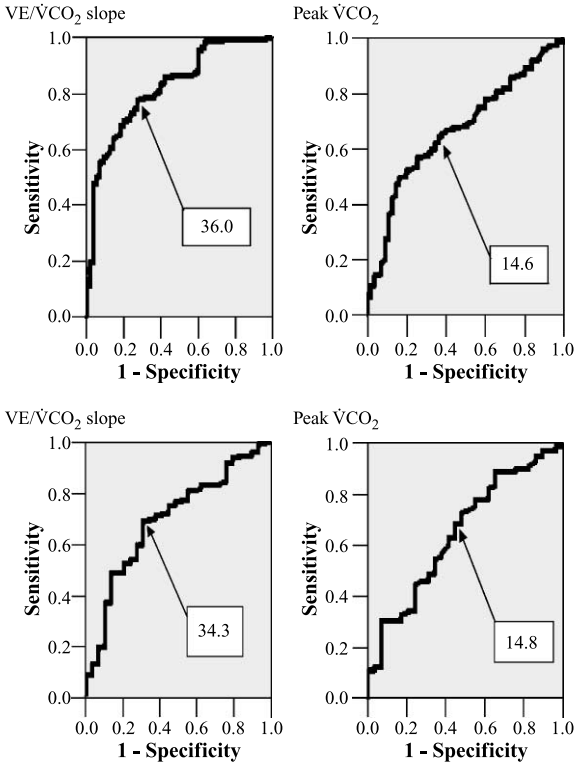

FIGURE 1—ROC curve analysis for BB group: optimal cut points.

In the BB group, hazard ratios for peak $\dot{V}O_2$ and the $VE/\dot{V}CO_2$ slope were 2.8 (95% confidence interval: 1.3–6.2, $P = 0.01$) and 5.4 (95% confidence interval: 2.4–11.9, $P < 0.001$), respectively.

When limiting follow-up to 1 yr after CPX, the prognostic classification schemes for peak $\dot{V}O_2$ and the $VE/\dot{V}CO_2$ slope improved in both the no-BB and BB groups. The area under the ROC curve for peak $\dot{V}O_2$ improved to 0.75 (95% CI: 0.67–0.85, optimal threshold: ≤/> 14.0 $mL \cdot kg^{-1} \cdot min^{-1}$ (67% sensitivity/77% specificity), $P < 0.001$) in the no-BB group and 0.70 (95% CI: 0.51–0.85, optimal threshold: ≤/> 13.3 $mL \cdot kg^{-1} \cdot min^{-1}$ (71% sensitivity/67% specificity), $P = 0.04$) in the BB group. Using the 1-yr threshold values, the hazard ratio for peak $\dot{V}O_2$ increased to 5.9 (95% CI: 2.4–14.7. $P = 0.005$) in the no-BB group and 4.3 (95% CI: 1.4–14.4, $P = 0.02$) in the BB group. Likewise, the area under the ROC curve for the $VE/\dot{V}CO_2$ slope improved to 0.86 (95% CI: 0.80–0.93, optimal threshold: ≤/> 38.5 (80% sensitivity/81% specificity), $P < 0.001$) in the no-BB group and 0.82 (95% CI: 0.74–0.91, optimal threshold: ≤/> 35.7 (73% sensitivity/75% specificity), $P < 0.001$) in the BB group. Using the 1-yr threshold values, the hazard ratio for

TABLE 5. ROC curve analysis.

No-BB Group	ROC Area	*P* Value	95% CI	Optimal Threshold ($mL \cdot kg^{-1} \cdot min^{-1}$)	Sensitivity/Specificity
$VE/\dot{V}CO_2$ slope	0.82	<0.001	0.76–0.88	</≥ 36.0	77/73
Peak $\dot{V}O_2$	0.67	<0.001	0.59–0.75	≤/> 14.6	62/65
BB group					
$VE/\dot{V}CO_2$ slope	0.70	0.001	0.60–0.80	</≥ 34.3	70/69
Peak $\dot{V}O_2$	0.65	0.01	0.57–0.76	≤/> 14.8	63/59

ROC, receiver operating characteristic; BB, beta-blockade.

the $VE/\dot{V}CO_2$ slope increased to 14.3 (95% CI: 5.4–38.0. $P < 0.001$) in the no-BB group and 8.0 (95% CI: 2.2–29.4, $P < 0.001$) in the BB group.

DISCUSSION

The results of the present study indicate that CPX maintains prognostic value irrespective of BB use, supporting our hypothesis. Furthermore, the inclusion of HF subjects with preserved systolic function did not alter the prognostic characteristics of CPX variables. These findings both add to the existing body of literature in this area and introduce some needed, novel analyses.

Several investigators have examined the effect of BB use on the prognostic value of peak $\dot{V}O_2$, and the results of these studies have been mixed (9,22–25,31). Pohwani et al. (25) reported that peak $\dot{V}O_2$ was not a significant predictor of cardiac events in 103 subjects (48 receiving BB) diagnosed with HF. Shakar et al. (27) likewise reported that peak $\dot{V}O_2$ was not predictive of death or transplantation in 127 subjects receiving BB for at least 3 months. Other investigations, however, have found that peak $\dot{V}O_2$ maintains prognostic value (9,22–24,31), although a lower threshold value may be appropriate in patients receiving BB (22,24). These latter studies, which demonstrate that peak $\dot{V}O_2$ predicts outcome despite the presence of BB, were larger, with sample sizes exceeding 200. The results of the present study also indicate that BB did not negate the prognostic value of peak $\dot{V}O_2$ as a univariate predictor of mortality. Furthermore, we found that the optimal prognostic threshold value for peak $\dot{V}O_2$, as determined by ROC curve analysis, was strikingly similar between the no-BB and BB groups (~14 $mL \cdot kg^{-1} \cdot min^{-1}$). This is in contrast to the previous investigations advocating a lower peak $\dot{V}O_2$ threshold value in subjects receiving BB (22,24). Peterson et al. (23), however, reported that a peak $\dot{V}O_2$ threshold of 14 $mL \cdot kg^{-1} \cdot min^{-1}$ remained prognostically significant irrespective of BB, which is consistent with our findings. We do not consider this finding surprising, because previous investigations have found that BB does not alter aerobic capacity in HF (1,30). Additional work in other, larger HF groups—using a statistical tool such as the ROC curve, designed for defining threshold values with the highest level of sensitivity and specificity—is required to resolve this issue.

In recent years, several investigations have found that the $VE/\dot{V}CO_2$ slope is an even more powerful marker of risk than peak $\dot{V}O_2$ in patients with HF (5,10,11,16,18). The current findings indicate that the $VE/\dot{V}CO_2$ slope is a robust prognostic marker of risk, irrespective of BB use. The optimal threshold value for the $VE/\dot{V}CO_2$ slope was, however, somewhat lower in the BB group. Previous research has demonstrated that BB significantly lowers $VE/\dot{V}CO_2$ slope in patients with HF (1). Our finding of a lower prognostic threshold value for the $VE/\dot{V}CO_2$ slope in the BB group may reflect the impact that BB has on this CPX variable. Additional research investigating the impact of BB use on the prognostic utility of the $VE/\dot{V}CO_2$ slope is limited. Corra et al. (9) examined the prognostic value of the $VE/\dot{V}CO_2$ slope and peak $\dot{V}O_2$ in 272 subjects not receiving a BB agent and in 236 subjects receiving carvedilol. $VE/\dot{V}CO_2$ slope was the strongest prognostic variable in both the overall and the no-BB groups. Whereas $VE/\dot{V}CO_2$ slope was a significant univariate predictor of cardiovascular mortality or urgent transplantation in the BB group, it was removed from the multivariate regression, where peak $\dot{V}O_2$ was the only CPX variable retained. Our findings contrast with those of Corra et al. because although peak $\dot{V}O_2$ was a significant univariate predictor of cardiac-related events, it was removed from the multivariate regression, where $VE/\dot{V}CO_2$ slope was the only CPX variable retained. One of the primary reasons for this disparity in findings may be the differences in the way $VE/\dot{V}CO_2$ slope was calculated. Corra et al. (9) used data from the onset of exercise to the ventilatory threshold to calculate $VE/\dot{V}CO_2$ slope. Previous work by our group has found that using all data, from onset to maximal exercise, produces a prognostically superior $VE/\dot{V}CO_2$-slope calculation compared with a value excluding data past ventilatory threshold (4). A recent investigation by Bard et al. (7) supports our findings in that calculating the $VE/\dot{V}CO_2$ slope with all exercise data points is prognostically optimal. Therefore, we used all exercise data to calculate the $VE/\dot{V}CO_2$ slope in the present study. Perhaps using all of the exercise data to calculate the $VE/\dot{V}CO_2$ slope in the previous investigation reported by Corra et al. (9) would have altered the prognostic characteristics of this variable in the BB group.

Our group has previously demonstrated that limiting the follow-up period improved the prognostic strength of CPX variables (6), which has been confirmed herein among both the BB and no-BB groups. Area under the ROC curve and hazard ratios improved for both peak $\dot{V}O_2$ and the $VE/\dot{V}CO_2$ slope when limiting the tracking period to 1 yr after CPX. The results of the present study also support limiting the duration for which CPX data are clinically used for prognostic purposes, regardless of BB use.

Previous research has demonstrated that a lower peak $\dot{V}O_2$ (28,29) and higher $VE/\dot{V}CO_2$ slope (20,26) both reflect worsening cardiopulmonary function in patients with HF, which explains why both of these CPX variables possess univariate prognostic value. Whereas BB use clearly improves cardiac function and prognosis in the HF population, it is unlikely that the previously established relationship between CPX variables and cardiopulmonary physiology are altered. That is, individuals with a lower peak $\dot{V}O_2$ and an elevated $VE/\dot{V}CO_2$ slope are likely to have poorer cardiopulmonary function and, therefore, worse prognosis, irrespective of BB use. Thus, the fact that the majority of investigations, including the present study, have found that CPX has prognostic value, irrespective of BB use, is not surprising.

CPX has been an accepted clinical evaluation technique in the HF population for a number of years. Recently, the use of CPX as a prognostic tool has been questioned secondary to the increase in BB use. The results of the present study

indicate that CPX variables, particularly VE/$\dot{V}CO_2$ slope, are prognostically valuable in patients with HF, irrespective of BB use. Previous studies have reported that a VE/$\dot{V}CO_2$ slope cut point of approximately 34 is the best discriminator between favorable and poor prognosis in patients with HF (5,8). On the basis of our results, a cut point of 34 seems appropriate in HF patients who are prescribed a BB agent, if no time limit is applied to the tracking period. If the tracking period is limited to 1 yr after CPX, the VE/$\dot{V}CO_2$ slope cut point should be increased (to approximately 36) if the subject is receiving a BB agent.

Although several hundred subjects were included in this analysis, the sample size may be considered somewhat small. The current results must therefore be confirmed by additional investigations. A smaller group of subjects from each of the three centers did, however, make tracking medication history and events much more manageable and accurate. An additional weakness of this study was its retrospective design. However, given the clearly demonstrated benefit of BB use in the HF population, it would not be possible to conduct this type of study prospectively.

In conclusion, CPX seems to maintain prognostic value in patients with HF receiving BB therapy. The present study also provides further evidence that VE/$\dot{V}CO_2$ slope is a superior prognostic marker compared with peak $\dot{V}O_2$, a finding reported by several recent investigations not controlling for BB use (5,10,11,16,18). Thus, the use of CPX in patients with HF remains a valuable prognostic assessment tool in the BB era.

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