

Relation Between $\dot{V}E/\dot{V}CO_2$ Slope and Maximum Phonation Time in Chronic Heart Failure Patients

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Abstract: This study aimed to determine the relation between the regression slope relating minute ventilation to carbon dioxide output ($\dot{V}E/\dot{V}CO_2$ slope) and maximum phonation time (MPT), and the MPT required to attain a threshold value for $\dot{V}E/\dot{V}CO_2$ slope of ≤ 34 in chronic heart failure (CHF) patients.

This cross-sectional study enrolled 115 CHF patients (mean age, 54.5 years; men, 84.9%). $\dot{V}E/\dot{V}CO_2$ slope was assessed during cardiopulmonary exercise testing (CPX). Thereafter, patients were divided into 2 groups according to exercise capacity: $\dot{V}E/\dot{V}CO_2$ slope ≤ 34 ($\dot{V}E/\dot{V}CO_2 \leq 34$ group, $n = 81$) and $\dot{V}E/\dot{V}CO_2$ slope > 34 ($\dot{V}E/\dot{V}CO_2 > 34$ group, $n = 34$). For MPT measurements, all patients produced a sustained vowel/a:/ for as long as possible during respiratory effort from the seated position.

All subjects showed significant negative correlation between $\dot{V}E/\dot{V}CO_2$ slope and MPT ($r = -0.51$, $P < 0.001$). After adjustment for clinical characteristics, MPT was significantly higher in the $\dot{V}E/\dot{V}CO_2 \leq 34$ group vs $\dot{V}E/\dot{V}CO_2 > 34$ group (21.4 ± 6.4 vs 17.4 ± 4.3 s, $F = 7.4$, $P = 0.007$). The appropriate MPT cut-off value for identifying a $\dot{V}E/\dot{V}CO_2$ slope ≤ 34 was 18.12 seconds.

An MPT value of 18.12 seconds may be a useful target value for identifying CHF patients with a $\dot{V}E/\dot{V}CO_2$ slope ≤ 34 and for risk management in these patients.

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Abbreviations: AUC = area under the curve, BNP = brain natriuretic peptide, CHF = chronic heart failure, CI = confidence interval, CPX = cardiopulmonary exercise testing, $FEV_{1.0}$ = forced expiratory volume in 1 second, FVC = forced vital capacity, MPT = maximum phonation time, NYHA = New York Heart Association, peak VO_2 = peak oxygen uptake, ROC = receiver-operating characteristic, SD = standard deviation, $\dot{V}E/\dot{V}CO_2$ slope = regression slope relating minute ventilation to carbon dioxide output.

INTRODUCTION

Chronic heart failure (CHF) patients generally fatigue easily due to a low exercise capacity resulting from a low peak oxygen uptake (peak VO_2), an important index of morbidity and mortality that is assessed by symptom-limited cardiopulmonary exercise testing (CPX).^{1,2} Low peak VO_2 , a leading cause of hospitalization and predictor of mortality in cardiac patients, adversely affects health status and can impair health-related quality of life.^{3,4} The regression slope relating minute ventilation to carbon dioxide output ($\dot{V}E/\dot{V}CO_2$ slope) is widely used as an index of exercise capacity in CHF patients, and a value of > 34 is a strong predictor of mortality.⁵⁻⁷

As in other several countries, the number of cardiac patients with cardiovascular disease in Japan is increasing and has become a growing public health problem as the general population ages and the prevalence of cardiac disease in the elderly or those complicated by several diseases or disabilities increases.^{8,9} However, the ability to evaluate exercise capacity with CPX is limited due to cost and assessability.

Maximum phonation time (MPT) is widely used to evaluate maximum vocal capabilities of outpatients with functional or organic dysphonia and also healthy subjects because it is non-invasive, quick, and inexpensive.^{10,11} MPT has also been used to objectively assess the degree of severity of dysphonia and to determine effects of voice therapy.^{10,11} Our previous study showed a positive correlation between both MPT and peak VO_2 and MPT and other pulmonary functions, such as inspiratory muscle pressure, expiratory muscle pressure, and percent predicted forced vital capacity (FVC). Furthermore, MPT was a significant predictor of peak VO_2 in CHF outpatients.¹² In addition, peak VO_2 and MPT indices were found to decrease

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as disease severity, as assessed by New York Heart Association (NYHA) functional class, worsened.¹³

Presently, little is known about the relation between $\dot{V}E/\dot{V}CO_2$ slope and MPT or the threshold level of MPT in CHF patients with a $\dot{V}E/\dot{V}CO_2$ of ≤ 34 , a value associated with increased mortality. We hypothesized that negative correlations will exist between $\dot{V}E/\dot{V}CO_2$ slope and MPT and that there will be significant differences in the MPT of CHF patients with a $\dot{V}E/\dot{V}CO_2$ slope of ≤ 34 vs >34 . Thus, the purpose of the present study was to investigate the relation between $\dot{V}E/\dot{V}CO_2$ slope and MPT variables, the differences in MPT at the $\dot{V}E/\dot{V}CO_2$ slope threshold value of 34, and the length of MPT required to attain a $\dot{V}E/\dot{V}CO_2$ slope of ≤ 34 in CHF patients.

METHODS

Participants

This single-center cross-sectional study included stable CHF patients who underwent CPX in the laboratories at St. Marianna University School of Medicine Hospital. A total of 115 consecutive CHF patients (mean age, 54.5 years; men, 84.9%) were included. Patient inclusion criteria included age >30 years old, prior completion of CPX, and the ability to measure MPT. NYHA functional class IV patients were excluded as were those with neurological, peripheral vascular, orthopedic, or pulmonary disease (percent predicted FVC $<80\%$ or percent predicted forced expiratory volume in 1 second [FEV_{1,0}] $<70\%$). NYHA classification was determined in all patients by an independent physician.

Measures

We evaluated patient characteristics that included age, sex, body mass index (BMI), etiology of heart failure, and medications. A cardiologist assessed cardiac function by ultrasound measurement of left ventricular ejection fraction and disease severity by brain natriuretic peptide (BNP) concentration.¹⁴ The present study was approved by the St. Marianna University School of Medicine Institutional Committee on Human Research. Written informed consent was obtained from each patient.

$\dot{V}E/\dot{V}CO_2$ Slope

All 115 patients underwent symptom-limited CPX via a ramp protocol on a cycle ergometer (Strength Ergo 8; Fukuda Denshi Co., Tokyo, Japan) during stable CHF. Testing consisted of an initial rest period of 3 minutes on the ergometer, 3 minutes of warm-up at a 20-W load, and exercise to maximal exertion with a linear load increase of 1 W every 6 seconds. A 12-lead ECG was monitored continuously throughout CPX, and heart rate was determined from the ECG R-R interval. VE and $\dot{V}CO_2$ were measured throughout the exercise period with an aero monitor (AE-300S; Minato Ikagaku Co., Tokyo, Japan), and calculations were performed on a personal computer.¹⁴

The exercise testing endpoint was determined according to guidance from the American Heart Association¹ and criteria of the American College of Sports Medicine¹⁵ and included leg fatigue, shortness of breath, or respiratory exchange ratio >1.10 . No patient had chest pain, ischemic ST changes, or serious arrhythmia during CPX. The $\dot{V}E/\dot{V}CO_2$ slope was determined by using linear regression analysis of minute ventilation and carbon dioxide production obtained during the entire exercise period. After CPX, we divided the patients into two

groups according to exercise capacity: $\dot{V}E/\dot{V}CO_2$ slope of ≤ 34 ($\dot{V}E/\dot{V}CO_2 \leq 34$, $n=81$) and $\dot{V}E/\dot{V}CO_2$ slope of >34 ($\dot{V}E/\dot{V}CO_2 >34$, $n=34$).

MPT

MPT was measured with a stopwatch with the patient in the seated position before CPX. Patients were asked to produce a sustained vowel/a:/ for as long as possible and were verbally encouraged during this effort. The method, variability, and reliability of this measurement were previously described.^{10–13} Trials were assessed by a physical therapist. Three consecutive trials were allowed with a 15-second break between each trial. The highest value measured was considered the index of MPT (second) in the present study.

Statistical Analysis

Results are expressed as mean \pm standard deviation (SD). First, correlation of $\dot{V}E/\dot{V}CO_2$ slope and MPT was performed with Pearson's correlation coefficient in all patients. Parametric and Chi-square tests were then used to analyze differences between the two groups. The unpaired *t* test was used to test for differences in clinical characteristics between the two groups. To compare MPT between the two groups, one-way analysis of covariance (ANCOVA) was performed with the variables as covariates if there were any differences in clinical characteristics. Choice of covariates was guided by Chi-square analyses and *t* tests, which indicated significant differences between the $\dot{V}E/\dot{V}CO_2 \leq 34$ and $\dot{V}E/\dot{V}CO_2 >34$ groups in the values of the clinical characteristics. Finally, a receiver-operating characteristic (ROC) curve^{16–18} was constructed by means of plotting the true-positive rates (sensitivity) against false-positive rates (1-specificity) following calculation of the sensitivity of MPT for a $\dot{V}E/\dot{V}CO_2$ slope of ≤ 34 to determine the best cut-off value. The area under the curve (AUC) was also calculated and is shown with 95% confidence interval (CI). A *P* value of <0.05 was considered significant. Statistical analyses were performed with SPSS 17.0J statistical software (SPSS Japan, Inc., Tokyo, Japan).

RESULTS

Relation Between $\dot{V}E/\dot{V}CO_2$ Slope and MPT

The $\dot{V}E/\dot{V}CO_2$ slope correlated negatively with MPT in all patients ($r=-0.51$, $P<0.001$). A scatter plot showing the relations between $\dot{V}E/\dot{V}CO_2$ slope and MPT results for all CHF patients is presented in Figure 1.

Patient Clinical Characteristics

Patient characteristics and functional variables of the two groups based on $\dot{V}E/\dot{V}CO_2$ slope are summarized in Table 1. The characteristics were almost identical between the two groups except for those of age, BMI, BNP, and NYHA class.

Comparison of MPT Between Groups

Differences in MPT between groups according to exercise capacity in the CHF patients are shown in Table 2. After adjustment for the clinical characteristics of age and BMI, MPT in the CHF patients was found to be significantly higher in the $\dot{V}E/\dot{V}CO_2 \leq 34$ group than in the $\dot{V}E/\dot{V}CO_2 >34$ group A (MPT = 21.4 ± 6.4 vs 17.4 ± 4.3 s, respectively. $F=7.4$, $P=0.007$).

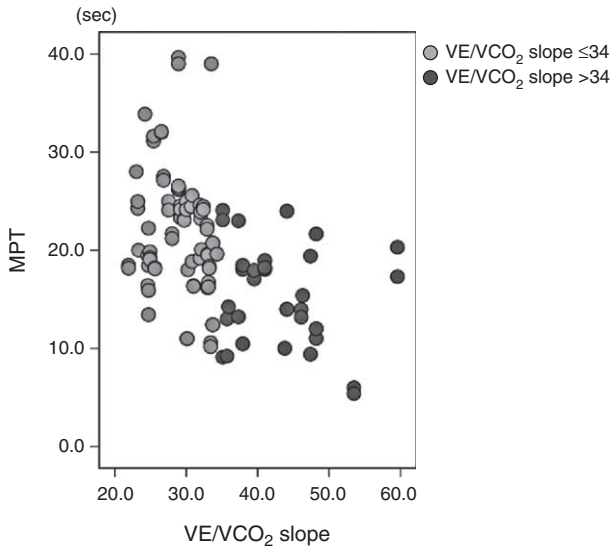


FIGURE 1. Relation between $\dot{V}E/\dot{V}CO_2$ slope and maximum phonation time (MPT). $\dot{V}E/\dot{V}CO_2$ slope correlated negatively with MPT in all patients ($r = -0.51$, $P < 0.001$).

Cut-Off Value of MPT

An ROC curve was constructed using the values of MPT and $\dot{V}E/\dot{V}CO_2$ slope of the CHF patients, and the cut-off value for MPT on the $\dot{V}E/\dot{V}CO_2$ slope of ≤ 34 or > 34 was calculated (Figure 2). The cut-off value for MPT identified by ROC analysis was determined to be 18.12 seconds, with a sensitivity of 0.79, 1-specificity of 0.23, and AUC value of 0.83 (95%CI: 0.74–0.92, $P < 0.001$).

DISCUSSION

The present study is the first, to our knowledge, to evaluate a possible relation between MPT and $\dot{V}E/\dot{V}CO_2$ slope in CHF patients. This study showed a significant negative correlation between $\dot{V}E/\dot{V}CO_2$ slope and MPT in CHF patients. The cut-off value for MPT associated with a $\dot{V}E/\dot{V}CO_2$ slope of ≤ 34 or > 34 was determined to be 18.12 seconds.

$\dot{V}E/\dot{V}CO_2$ slope is an independent prognostic predictor in heart failure patients, as is peak VO_2 .^{1,2,5–7} A decrease in the $\dot{V}E/\dot{V}CO_2$ slope results in improvement of dyspnea, walking distance, and peak VO_2 .^{1,2,5–7} Stepwise regression analysis in our previous study showed MPT to be a significant predictor of peak VO_2 in all CHF patients.¹² Therefore, we believe that MPT, in addition to other measurements of exercise capacity such as peak VO_2 and $\dot{V}E/\dot{V}CO_2$ slope, may be a useful method to predict and estimate exercise capacity in CHF patients.

There were significant differences in the clinical characteristics of age, BMI, BNP, and NYHA class in the study patients. Both BNP and NYHA class increase as the severity of CHF increases, and these factors correlate negatively with exercise capacity.¹⁹ Thus, we believe that a $\dot{V}E/\dot{V}CO_2$ slope of > 34 reflects the severity of CHF as do BNP level and NYHA class. Consequently, these variables were excluded from the covariate analysis. After adjusting for age and BMI, MPT in the CHF patients found to be significantly higher in patients with a $\dot{V}E/\dot{V}CO_2$ slope of ≤ 34 than in those with $\dot{V}E/\dot{V}CO_2$ slope of > 34 (Table 2).

Yanagihara et al²⁰ reported that in normal subjects, average MPT was 30.2 seconds in men and 22.5 seconds in women. Hirano et al²¹ also studied normal subjects and reported an average MPT of 34.6 seconds in men and 25.7 seconds in women. These values were greater than those in our two CHF patient groups. Although MPT was significantly higher in the $\dot{V}E/\dot{V}CO_2 \leq 34$ group vs the $\dot{V}E/\dot{V}CO_2 > 34$ group, it was lower than that measured in normal Japanese subjects.

TABLE 1. Clinical Characteristics of the Patients

Characteristic	$\dot{V}E/\dot{V}CO_2$ Slope ≤ 34	$\dot{V}E/\dot{V}CO_2$ Slope > 34	<i>t</i> or χ^2 Value	<i>P</i> Value
No. of patients	81	34		
Age (years)	51.5 ± 8.9	61.3 ± 9.6	5.09*	<0.001
Male (%)	85.1	84.3	2.12	0.56
BMI (kg/m ²)	24.3 ± 5.0	20.6 ± 2.9	3.79*	<0.001
LVEF (%)	33.9 ± 11.4	30.5 ± 12.3	1.44*	0.15
BNP (pg/mL)	222.5 ± 177.1	336.0 ± 207.8	-2.73*	0.007
NYHA class (I/II/III)	26/49/6	4/19/11	13.96	<0.001
Etiology (%)				
Cardiomyopathy	53.1	47.2	4.92	0.17
Previous MI	16.1	14.7		
Arrhythmia	25.9	20.6		
CABG/VR	4.9	17.6		
Medications (%)				
β-blockers	79.8	82.1	0.69	0.21
ARB	42.5	46.8	0.49	0.30
ACEI	50.1	43.9	0.51	0.28
Diuretic	84.2	85.9	0.12	0.47

ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, BMI = body mass index, BNP = brain natriuretic peptide, CABG = coronary artery bypass grafting, LVEF = left ventricular ejection fraction, MI = myocardial infarction, NYHA = New York Heart Association, VR = valve replacement.

* *t* value.

TABLE 2. Differences in Maximum Phonation Time adjusted for Age and Body Mass Index

Variable	$\dot{V}E/\dot{V}CO_2$ Slope ≤ 34	$\dot{V}E/\dot{V}CO_2$ Slope >34	F Value	P Value
No. of patients	81	34		
Maximum phonation time (s)	21.4 \pm 6.4 (20.1–22.9)	17.4 \pm 4.3 (14.9–19.8)	7.4	0.007

Strength values are shown as mean \pm standard deviation (95% confidence interval). Independent variables of analysis of covariance: age and body mass index.

The cut-off value by ROC analysis for MPT in CHF patients having $\dot{V}E/\dot{V}CO_2$ slope of ≤ 34 was 18.12 seconds, with a sensitivity of 0.79, 1-specificity of 0.23, and AUC value of 0.83 (Figure 2). Because an AUC of 0.7 to 0.9 can be interpreted to indicate moderate accuracy,^{17,18} the AUC of 0.83 indicates moderate accuracy for this cut-off value.

Our previous study reported that an exercise capacity of <5 metabolic equivalents (METs) was related to mortality and impaired activities of daily living in elderly people and cardiac patients and equated to an MPT of approximately 18.27 seconds in CHF patients.¹² The MPT cut-off value in the present study was very close to the result from our previous study,¹² indicating that an exercise capacity of <5 METs and a $\dot{V}E/\dot{V}CO_2$ slope of >34 may be values associated with increased mortality.

Several previous studies have investigated higher $\dot{V}E/\dot{V}CO_2$ slopes in relation to mortality and cardiovascular events.^{5–7} Gitt et al⁵ reported that in 223 consecutive patients with CHF (mean age, 62.9 years; men, 86%), a combination of VO_2 of <11 mL/kg/min at anaerobic threshold and a $\dot{V}E/\dot{V}CO_2$ slope of >34 better identified patients at high risk for early death from CHF than did peak VO_2 alone. Ritt et al⁶ found that in 1167 heart failure patients, a $\dot{V}E/\dot{V}CO_2$ slope of >34 was an independent predictor of mortality. Recently, Myers et al²²

studied 2625 patients with heart failure (mean age, 56 years; men, 75%) who underwent CPX, and they developed a CPX score that was a composite of peak VO_2 , oxygen uptake efficiency slope, heart rate recovery, and $\dot{V}E/\dot{V}CO_2$ slope threshold of 34. The patients were followed for cardiovascular mortality and major cardiovascular events (death, transplantation, and left ventricular assist device implantation), and their results suggest that the composite CPX score is a valid approach for predicting the risk of adverse events in patients with heart failure. Thus, we believe that a $\dot{V}E/\dot{V}CO_2$ slope of >34 may be related to mortality in male and female CHF patients, and the cut-off value of 18.12 seconds for MPT reported here may also be useful as both an estimate of exercise capacity and as an index of mortality and cardiovascular events in CHF patients. Further studies are warranted to evaluate the effects of certain interventions, including that of a multi-disciplinary cardiac rehabilitation program, to improve MPT in CHF patients and whether these interventions will also result in improvement in activities of daily living, rate of cardiovascular events, and mortality.

Clinical implications of MPT include its possible use in the evaluation of CHF patients because it is non-invasive, quick, and inexpensive. Further, MPT might also be useful as an index of exercise capacity in CHF patients who cannot be evaluated by traditional CPX.

Study Limitations

The present study had several limitations, including its small sample size and cross-sectional study design. We investigated differences in MPT in relation to $\dot{V}E/\dot{V}CO_2$ slope assessed at only one time point; however, it would be of interest to also evaluate longitudinal changes in $\dot{V}E/\dot{V}CO_2$ slope and MPT in CHF patients. Because relatively few female CHF patients were studied, sex-related differences in MPT could not be assessed adequately. We did not directly measure the relation between risk factors and differences in MPT associated with exercise capacity, nor did we assess mortality, morbidity, or cardiovascular events. Although MPT measurement could be an inexpensive and useful method to predict or estimate exercise capacity for CHF patients, it has an important limitation in that it does not provide any other information on respiratory or cardiac metabolism. CPX, however, offers much more information allowing assessment of the integrative exercise responses involving the pulmonary, cardiovascular, hematopoietic, neuropsychological, and skeletal muscle systems. Future trials are needed to further evaluate the relation between MPT and these factors in CHF patients.

CONCLUSIONS

The present study showed a negative correlation between $\dot{V}E/\dot{V}CO_2$ slope and MPT in CHF patients. There were

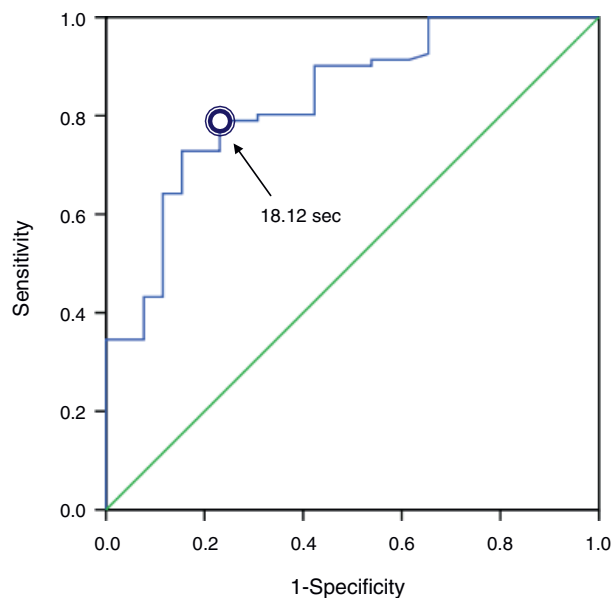


FIGURE 2. Cut-off value for maximum phonation time (MPT) on the $\dot{V}E/\dot{V}CO_2$ slope of ≤ 34 or >34 . The cut-off value for MPT identified by ROC analysis was determined to be 18.12 seconds, with a sensitivity of 0.79, 1-specificity of 0.23, and AUC value of 0.83 (95%CI: 0.74–0.92, $P < 0.001$).

differences in MPT in relation to the $\dot{V}E/\dot{V}CO_2$ slope threshold of 34 and mortality in CHF outpatients. Exercise capacity associated with a $\dot{V}E/\dot{V}CO_2$ slope of ≤ 34 was equivalent to an MPT of 18.12 seconds and, therefore, may be a useful target value for estimating exercise capacity and disease severity in and for risk management of CHF patients who cannot be evaluated by traditional CPX.

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