Oxygen Utilization and Ventilation During Exercise in Patients with Chronic Cardiac Failure

KARL T. WEBER, M.D., GARY T. KINASEWITZ, M.D.,
JOSEPH S. JANICKI, PH.D., AND ALFRED P. FISHMAN, M.D.

SUMMARY **Muscular work requires the integration of cardiopulmonary mechanisms for gas exchange and O_2 delivery. In patients with chronic cardiac failure, the response of these mechanisms may be impaired, and the pattern of O_2 utilization ($\dot{V}O_2$) and gas exchange during exercise would thus provide an objective assessment of the severity of heart failure. Accordingly, rates of air flow, O_2 uptake, CO_2 elimination and minute ventilation were determined during progressive treadmill exercise in 62 patients with stable heart failure. Exercise cardiac output, systemic O_2 extraction and lactate production were measured directly in 40 patients with heart failure of varying severity. As the severity of heart failure increased from class A to D, there was a progressive decrease in exercise capacity (from 1157 ± 154 to 373 ± 157 seconds) and maximum $\dot{V}O_2$ (23 ± 3.1 to 8.4 ± 1.5 ml/min/kg). These decreases corresponded with the reduced maximum cardiac output and stroke volume during exercise. The appearance of anaerobic metabolism (580 ± 17 to 157 ± 7 seconds of exercise) and the corresponding anaerobic threshold (17 ± 0.34 to 7.1 ± 1.5 ml/min/kg), determined noninvasively, were reproducible and correlated with the rise in mixed venous lactate concentration. No apparent untoward effects were experienced during or after the progressive exercise test. We conclude that the measurement of respiratory gas exchange and air flow during exercise is an objective, reproducible and safe noninvasive method for characterizing cardiac reserve and functional status in patients with chronic cardiac failure.**

AT REST, patients with heart disease often display normal cardiac performance. To elicit an abnormality in ventricular function, a physiologic stress, such as exercise, is required. This concept is well recognized clinically, when the severity of cardiac failure is traditionally evaluated in terms of information that relates levels of exertion with the appearance of breathlessness or fatigue. A more quantitative approach based on the pathophysiologic response to progressive exercise would be valuable for assessing the severity of cardiac disease and the functional capacity.

Muscular work elicits a complex interplay of diverse physiologic mechanisms designed to ensure that O_2 delivery is commensurate with O_2 demand. The heart, lung and O_2 carrying capacity of the blood participate in these adjustments. In patients with heart disease, cardiac output may not rise appropriately during exercise. The O_2 delivery system is then compromised, and the aerobic capacity is thus reduced. Determination of O_2 utilization during exercise, measured by the collection of expired air, provides an objective assessment of functional capacity in normal subjects and in patients with valvular heart disease.[1-4] However, enthusiasm for using this method to evaluate patients with chronic failure irrespective of cause and severity is tempered by the relative uncertainty of correlating respiratory gas exchange with cardiac function, the perceived hazards of exposing the patient with heart failure to exercise testing,[5] and the complexity of determining O_2 uptake.[6] The introduction of rapidly responding O_2 and CO_2 analyzers, however, has facilitated the noninvasive determination of respiratory gas exchange during exercise.[7] Using this approach,[8] we delineated the pattern of O_2 utilization, CO_2 elimination and ventilation during progressive treadmill exercise, thereby characterizing the severity of cardiac failure. We also assessed the hemodynamic response to upright exercise, correlating the noninvasive determinations of aerobic capacity with measurements of cardiac output, O_2 extraction and lactate production.

Methods

Patients

Sixty-two outpatients 19 years of age or older (mean 52 years, range 19–79 years), with chronic, stable clinical class I to IV heart failure as defined by New York Heart Association (NYHA) criteria (nine in class I, 19 in class II, 20 in class III and 14 in class IV) were selected for this study. The population included 27 males and 35 females. The degree of circulatory dysfunction was objectively graded according to the maximum O_2 uptake ($\dot{V}O_2$ max) achieved during exercise.[9, 10] On this basis, four classes were defined: functional class A, > 20 ml/min/kg (five patients); class B, 16–20 ml/min/kg (14 patients); class C, 10–15 ml/min/kg (19 patients); and class D, < 10 ml/min/kg (24 patients). We used the designations A to D in place of the NYHA clinical classifications of I to IV to avoid confusion.

The spectrum of cardiac disease included idiopathic cardiomyopathy in 15 patients, chronic mitral incompetence in 18, aortic incompetence in six, chronic mitral and aortic incompetence in four, mitral stenosis in two, ischemic heart disease in 10, and primary pulmonary hypertension in one patient. Five patients had prosthetic valve replacement. Two valve replacements were performed for chronic mitral regurgitation

From the Cardiovascular-Pulmonary Division, Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

Supported in part by program project grant HL-08805, NHLBI, NIH, and by NIH grant M01 RR00040 to the Clinical Research Center of the Hospital of the University of Pennsylvania.

Drs. Weber and Janicki are the recipients of Research Career Development Awards HL00187 and HL00411, respectively, from the NHLBI.

Address for correspondence: Karl T. Weber, M.D., 807 Gates Building, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, Pennsylvania 19104.

Received June 9, 1980; revision accepted September 11, 1981.
Circulation 65, No. 6, 1982.

(1975), one for aortic regurgitation (1979), and two for aortic stenosis (1966 and 1975). One patient had valvulotomy for congenital pulmonary stenosis in 1964.

The functional status of these patients had been clinically stable for at least 6 months before exercise evaluation. Thirteen patients had chronic atrial fibrillation; the rest were in sinus rhythm. Except for all class A patients, six class B and four class C patients, radiographic cardiomegaly, as estimated by a cardiothoracic ratio greater than 50%, was present in all patients. Class B, C and D patients were maintained on digitalis and diuretics for at least 6 months before exercise testing.

Patients were not exercised if they had symptomatic aortic stenosis, angina pectoris requiring antianginal medications other than occasional nitroglycerin, exercise-induced angina or ventricular arrhythmias. The presence of significant intrinsic pulmonary disease was excluded by history and by routine spirometry, using lung volumes, flow rate and maximal voluntary ventilation and the criteria of Morris et al.[11]

A control group was composed of nine males without cardiovascular disease or major medical illness (mean age 38 years, range 23–52 years). These normal subjects did not routinely engage in a regular exercise program or in strenuous physical activity.

Method of Exercise Testing

A programmable treadmill (Quinton) was used for the exercise studies. The treadmill program[8] consisted of 2-minute stages of graded exercise similar to that proposed by Naughton and Haider.[12] The program provided progressive increments in muscular work for patients with cardiac failure of varying severity. Cuff blood pressure, the ECG (modified V_5), and heart rate were monitored in the standing position before and throughout the exercise period and during recovery. All patients were studied in the air-conditioned (21–23°C) exercise facility at least 2 hours after a light meal. Patients exercised until severe fatigue or dyspnea made them unable to continue. Forty-three patients had a second exercise test within days to weeks of their first test.

Expired O_2 and CO_2 and the rate of air flow were measured at rest (standing) and throughout the exercise period using a breathing apparatus consisting of a mouthpiece, nose clamp and a low-resistance two-way valve (Hans-Rudolph; dead space 90 ml). A pneumotachograph was calibrated daily using a rotameter, and the signal for air flows up to 350 l/min was linear. Expired air from the valve chamber, sampled at a constant rate of 500 ml/min, passed through a heated conduit to the fast responding O_2 and CO_2 analyzers (Beckman OM11 and LB2, respectively). The gas analyzers were coupled in series to ensure a constant air flow through both analyzers and to minimize the amount of air removed via this route. Consequently, a fixed delay or lag times of 0.475 second and 0.36 second occurred between the onset of expiration and the sampling of expired O_2 and CO_2 content, respectively. It was possible to account for these delays during computer analysis of the data. The analyzers were calibrated daily using room air and several gases of known concentration (17% O_2 and 3% CO_2; 11% O_2 and 7% CO_2). To provide additional validation of the analyzer and flow data, 30-second gas collections were also obtained for all patients at rest and during the last 30 seconds of various stages of exercise. Data were recorded on analog tape (Hewlett-Packard recorder) for subsequent digitization (125 samples/sec/channel) on a PDP 10 computer.

Derivations

Basic gas and flow measurements during exercise were corrected for ambient temperature, barometric pressure and water vapor. The following measurements were derived on a breath-by-breath basis: minute ventilation ($\dot{V}E$, l/min); O_2 uptake ($\dot{V}O_2$, ml/min/kg) and CO_2 production ($\dot{V}CO_2$, ml/min). Because body weight, not surface area, determines O_2 uptake during exercise, and because the measurement of body weight is the more accurate of the two, $\dot{V}O_2$ was normalized for body weight. Maximum $\dot{V}O_2$ ($\dot{V}O_2$ max) was considered to have been achieved when $\dot{V}O_2$ increased < 1 ml/min/kg over that produced by the previous work load.[4] We also measured the ventilatory equivalent (VEQ), or $\dot{V}E/\dot{V}O_2$; the ventilatory gas exchange ratio (R), or $\dot{V}CO_2/\dot{V}O_2$; and O_2 pulse, or the ratio $\dot{V}O_2$ and heart rate.

Anaerobic Threshold

In patients with cardiac disease, the delivery of O_2 to the tissues is impaired because cardiac output cannot increase adequately to meet the increasing need for O_2. Increments in metabolic demand with progressive exercise are therefore accompanied by anaerobic metabolism and the production of lactate by skeletal muscle. Lactate is buffered by the body's bicarbonate pool, and therefore CO_2 production increases. The increased production is accompanied by an increase in minute ventilation ($\dot{V}E$) to maintain eucapnia; consequently, the $\dot{V}CO_2/\dot{V}O_2$ ratio increases rapidly. The onset of anaerobic metabolism can therefore be detected during progressive exercise as the point at which R (i.e., $\dot{V}CO_2/\dot{V}O_2$) begins to rise disproportionately to $\dot{V}O_2$.[13–15] The corresponding $\dot{V}O_2$ at the onset of anaerobic metabolism defines the anaerobic threshold of these patients. The anaerobic threshold was determined to the nearest 50 seconds by visual inspection of the computer display of measured and derived variables obtained after exercise (fig. 1). In accordance with the suggestions of Wasserman et al.,[15] anaerobic threshold was identified by three measured variables — nonlinear increase in $\dot{V}E$, a nonlinear increase in $\dot{V}CO_2$, and an increase in end-tidal O_2 relative to invariant end-tidal CO_2 — and a derived variable — an increase in R, derived as $\dot{V}CO_2/\dot{V}O_2$. We also used another derived variable, VEQ, the ratio of $\dot{V}E/\dot{V}O_2$. During exercise, we could determine when this point was reached from the response in end-tidal O_2 relative to end-tidal CO_2, which could be monitored from the digital display of the gas

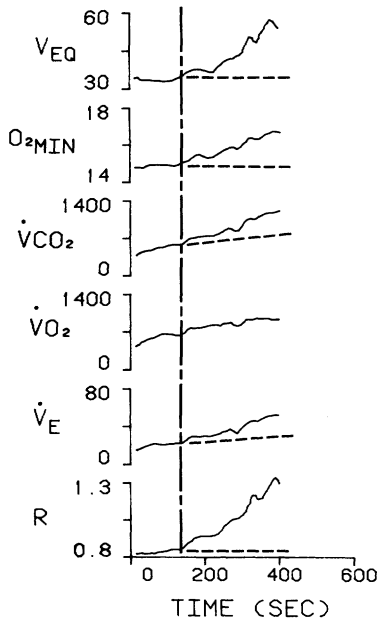

FIGURE 1. *Breath-by-breath analysis of gas exchange and air flow during upright treadmill exercise for a class D patient. O_2 min = end-tidal O_2; see text for other abbreviations. The vertical broken line indicates the onset of anaerobic metabolism; the horizontal broken lines indicate the linear extension of each variable.*

analyzers. All patients were exercised beyond the onset of their anaerobic threshold to ensure that maximal levels of exercise were achieved.

Exercise Hemodynamics

Forty patients with heart failure of varying etiology and severity (four class B, 11 class C and 25 class D) were admitted to the Clinical Research Center of the Hospital of the University of Pennsylvania for elective right-heart catheterization. Radionuclide ejection fraction (± SD) was 51 ± 32%, 24 ± 9% and 24 ± 13% in these class B, C and D patients, respectively. After each patient gave written consent, a flotation catheter was advanced into the pulmonary artery through an antecubital vein. The patients were then transported by wheelchair to the exercise facility.

An adjustable arm affixed to the support railing of the treadmill held a Statham P23ID transducer, positioned at mid-heart level to measure pulmonary artery and occlusive, or wedge, pressure during upright exercise. Throughout exercise, the position of the transducer remained constant within the plane of the mid-heart. Pulmonary capillary wedge pressure and cardiac output (Fick principle) were measured during the last 60 seconds and the last 30 seconds, respectively, of each stage of exercise. A sample of mixed venous blood was obtained during the last 30 seconds of each exercise stage; a portion was immediately placed in iced 8% perchloric acid for lactate determination,[16] while the remainder was used for determining venous O_2 content. Arterial O_2 content was derived from percent O_2 saturation and O_2 combining capacity, while O_2 extraction was calculated as the ratio of arteriovenous O_2 difference and arterial O_2 content. Stroke volume was calculated by dividing cardiac output by heart rate.

Statistical Analysis

Patients were classified according to their maximum O_2 uptake. The combined results for all patients are presented as mean ± SD. Interclass comparisons of resting data at any given stage of exercise were calculated by one-factor analysis of variance and by the modified t test.[17] Significance of the interclass exercise response of each variable was assessed by regression line analysis and the resulting slope was tested for significance. To determine significant interclass differences among these responses, comparisons of regression line slopes and intercepts between classes were made using the method of Brownlee.[18] Minimal acceptable significance for all comparisons was taken to be, according to the Bonferroni method, $p < 0.05/k$, where k is the number of comparisons performed.[17] Thus, if the four classes of patients were compared with the normal group, p would have to be less than 0.0125 for any of the differences to be considered statistically significant.

Results

Hemodynamic Response to Exercise

The average (± SD) cardiac index for class B, C and D patients as measured in the standing position before exercise was 2.23 ± 0.24, 2.01 ± 0.41 and 1.81 ± 0.51 l/min/m², respectively (NS). With progressive increments in muscular work expressed as a percentage of maximal O_2 uptake (fig. 2), the response in cardiac output was significantly ($p < 0.01$) different between the classes (table 1). Exercise cardiac output in class B and C patients was obtained by a significant ($p < 0.01$) increment in stroke volume (fig. 2) and in heart rate.

TABLE 1. *Upright Hemodynamic Data at Standing Rest and Maximal Exercise*

	CI (l/min/m²)		SVI (ml/m²)		LVFP (mm Hg)		O_2 Ext (%)	
Class	R	E	R	E	R	E	R	E
B (n = 4)	2.23 ± 0.24	7.81 ± 0.95	26 ± 3	49 ± 5	8 ± 6	23 ± 12	33 ± 8	75 ± 2
C (n = 11)	2.01 ± 0.41	4.68 ± 1.1	23 ± 6	36 ± 11	19 ± 6	37 ± 9	39 ± 9	71 ± 5
D (n = 25)	1.81 ± 0.51	3.04 ± 0.48	22 ± 7	26 ± 4	24 ± 7	40 ± 11	48 ± 10	75 ± 8

Values are mean ± SD.
CI = cardiac index; SVI = stroke volume index; LVFP = left ventricular filling pressure from pulmonary wedge or diastolic pressure; O_2 Ext = oxygen extraction; R = upright standing rest; E = maximal upright exercise.

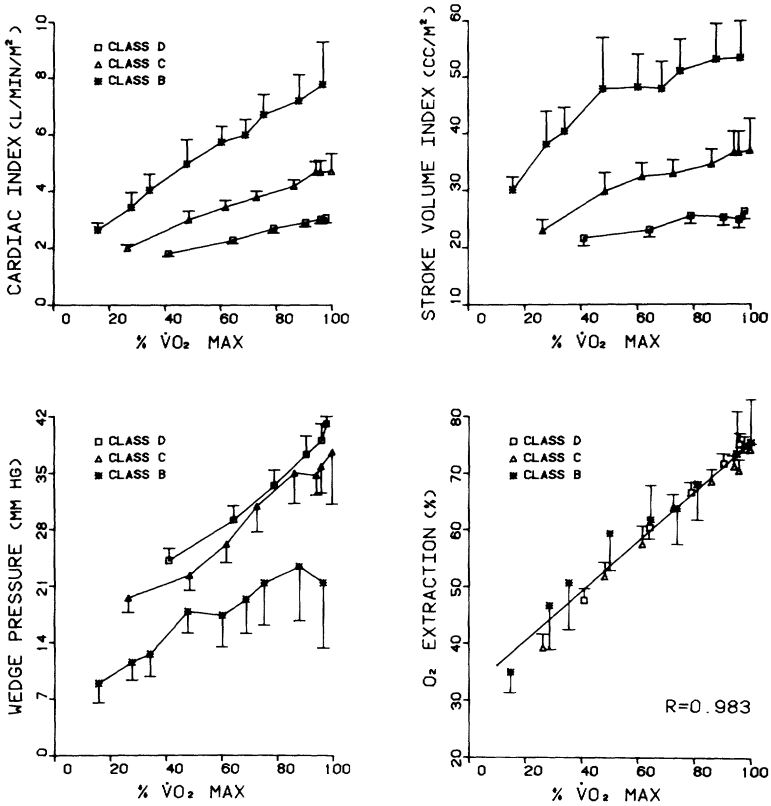

FIGURE 2. *The response in cardiac function and systemic O_2 extraction as a function of normalized work (percent maximum O_2 uptake, % $\dot{V}O_2$ max) for class B, C and D patients.*

Class D patients showed an insignificant rise in stroke volume throughout exercise and were entirely dependent upon their heart rate response to raise cardiac output. Resting heart rate (84 ± 5, 91 ± 13 and 85 ± 16 beats/min) as well as the slopes of the heart rate response to exercise did not differ between classes B, C and D.

In classes C and D, left ventricular filling pressure was elevated at rest (19 ± 6 and 24 ± 7 mm Hg, respectively). During exercise, filling pressure increased at a similar rate ($p < 0.01$) in both groups (fig. 2). The peak pressure at maximal exercise was 37 ± 9 and 40 ± 11 mm Hg for classes C and D, respectively. In class B patients, filling pressure was normal at rest and rose during exercise, but not to the level observed in class C or D (table 1).

Resting systemic O_2 extraction was greater ($p < 0.02$) in class D than in class B or C patients (48 ± 10% vs 33 ± 8% or 39 ± 9%, respectively). No interclass difference in the response of O_2 extraction to progressive increments in exercise could be demonstrated (fig. 2). The maximal values were greater than 70% in each class. Maximal O_2 extraction (≥ 70%) occurred at 80% of maximal O_2 uptake.

Measured at rest, mixed venous lactate was greater ($p < 0.05$) in class D (8.7 ± 2.9 mg%) than in class C (6.7 ± 1.7 mg%) or class B (7.2 ± 0.6 mg%). Anaerobic metabolism and lactate production became apparent in both groups at 70% of their aerobic capacity (fig. 3). This rise in lactate concentration occurred earlier during exercise in class D patients (fig. 3). The exponential rise in lactate concentration above 12 mg% (2 SD above resting control values for this laboratory) occurred at approximately 150 seconds of exercise in class D, compared with 314 seconds in class C and 465 seconds in class B.

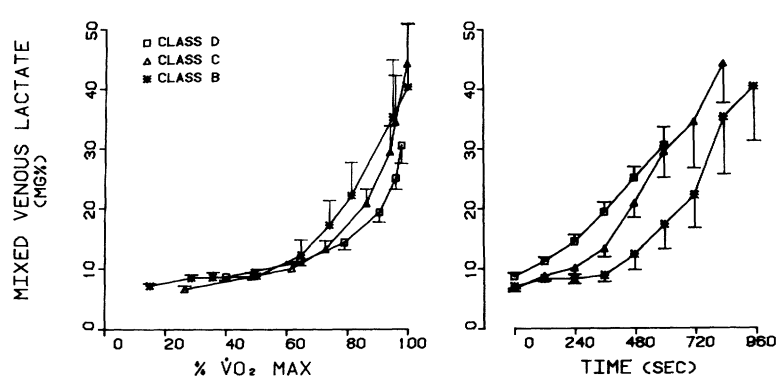

FIGURE 3. *The rise in mixed venous lactate concentration is shown as a function of normalized work (% $\dot{V}O_2$ max) and treadmill time for the patients shown in figure 2.*

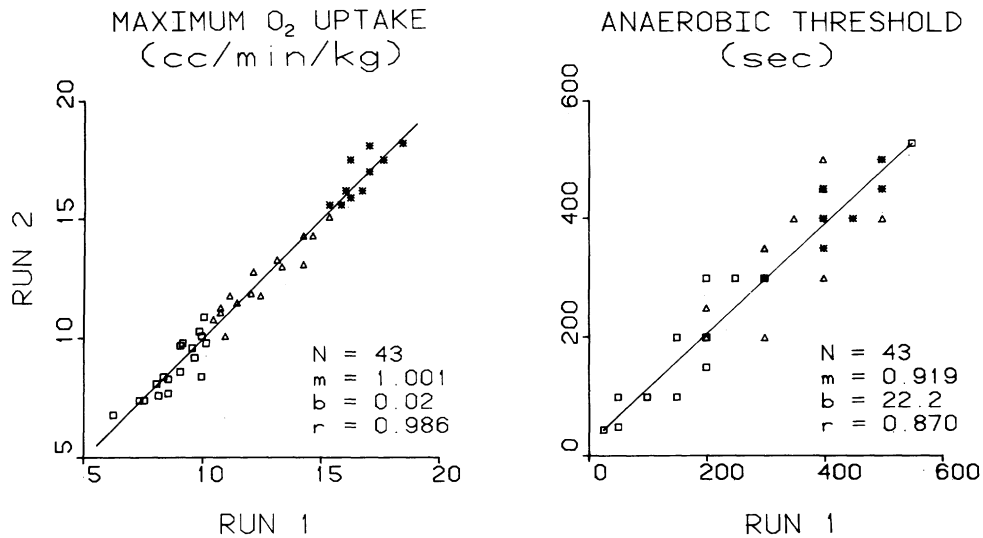

FIGURE 4. *The reproducibility in determining maximum O_2 uptake and the appearance of anaerobic threshold by the response in respiratory gas exchange is shown for 43 patients who had repeat exercise tests within days to weeks of their first exercise test. Symbols as in figure 3.*

Oxygen Utilization

Each functional class began exercising from the same level of resting $\dot{V}O_2$ (3.26 ± 0.87 ml/min/kg). The maximal level of $\dot{V}O_2$ achieved was 23.3 ± 3.1 ml/min/kg in class A (five patients); 16.5 ± 0.08 ml/min/kg in class B (14 patients); 12.2 ± 1.7 ml/min/kg in class C (19 patients); and 8.4 ± 1.5 ml/min/kg in class D (24 patients). The good reproducibility of the $\dot{V}O_2$ max determination, assessed within days to weeks of one another in 43 patients, is shown in figure 4.

The $\dot{V}O_2$ max was followed serially to monitor the functional capacity of these patients. Typical results are shown in figure 5 for representative class D and class C patients. In the class D patient, who had idiopathic cardiomyopathy, $\dot{V}O_2$ max was quite reproducible over a span of 5 months, extending from September 1980 to January 1981, indicating the stability of her functional capacity. On the other hand, the class C patient, who had aortic regurgitation and a paravalvular leak around her mitral valve prosthesis, deteriorated to functional class D status in December

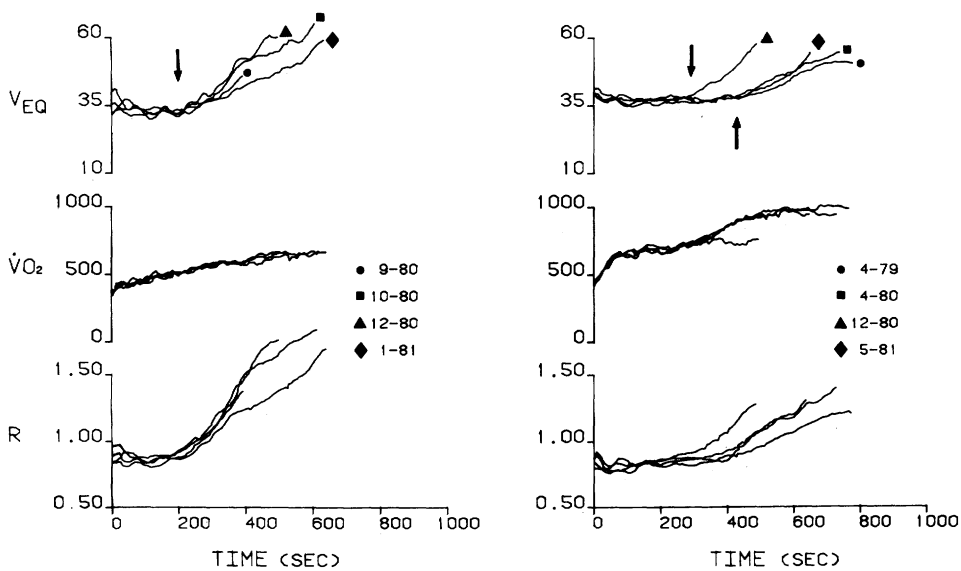

FIGURE 5. *The response in O_2 uptake ($\dot{V}O_2$, ml/min), respiratory gas exchange ratio (R) and ventilatory equivalent (V_{EQ}) are given for a class D patient (left) and a class C patient (right). In the class D patient, the response in $\dot{V}O_2$, R, and V_{EQ} are reproducible as well as the onset of anaerobic metabolism (arrow); over 5 months, but the duration of exercise varied. Hence, the measurement of treadmill time alone is more subjective. In the class C patient, $\dot{V}O_2$ and anaerobic threshold (arrows) indicate a decrease in functional capacity in December 1980. Each test can be identified by the symbols and the duration of exercise.*

TABLE 2. *Characteristics of Functional Class A and B Patients*

Pt	Age (years)	Sex	Weight (kg)	Etiology	NYHA	Rhythm	EC (sec)	$\dot{V}O_2$ max (ml/min/kg)	AT (sec/ [ml/min/kg])	ΔO_2 pulse
Class A										
1	35	M	73	AVR	2	NSR	1074	25.0	600/21.4	122
2	45	M	72	IHD	1	NSR	984	20.1	500/17.2	88
3	27	F	64	PR	1	NSR	1320	20.2	600/12.3	84
4	25	F	61	MR	2	NSR	1086	24.5	600/17.3	109
5	30	F	63	MR	1	NSR	1320	27.0	600/17.0	76
Mean ± SD	32 ± 9		67 ± 5				1157 ± 154	23.3 ± 3.1	580/17.0 ± 20/3.4	96 ± 20
Class B										
1	72	M	54	CM	2	NSR	906	16.7	500/11.1	57
2	54	F	67	AR/MVR	3	AF	711	16.1	400/12.1	42
3	77	F	51	AR	2	NSR	684	16.5	400/15.4	57
4	58	F	65	MR	2	NSR	837	18.3	400/13.8	56
5	66	F	55	CM	2	NSR	897	17.0	450/15.1	62
6	57	M	94	CM	1	NSR	1008	16.5	400/12.0	86
7	30	M	85	AR	1	NSR	1320	18.2	600/11.6	105
8	30	F	58	MR	1	NSR	1170	16.0	400/11.6	66
9	50	M	88	AR	2	NSR	1200	14.7	400/11.4	53
10	49	F	63	MR	1	NSR	1056	16.0	500/11.7	82
11	56	M	75	AVR	2	NSR	882	16.0	500/14.4	56
Mean ± SD	55 ± 17	± 17	69				970 ± 200	16.5 ± 0.7	450/12.7 ± 70/1.7	66 ± 17

Abbreviations: NYHA = New York Heart Association functional classification; EC = exercise capacity; AT = anaerobic threshold in time of appearance and corresponding O_2 uptake (ml/min/kg); ΔO_2 pulse = change in O_2 pulse from resting to end-exercise; HR = heart rate at end-exercise; MVV = maximum voluntary ventilation; VC = vital capacity; VT = tidal volume; f = respiratory rate; AVR, MVR = aortic and mitral valve replacement; IHD = ischemic heart disease; AR, MR and PR = aortic, mitral or pulmonic valvular regurgitation; CM = cardiomyopathy; $\dot{V}O_2$ max = maximal O_2 uptake; NSR = normal sinus rhythm; AF = atrial fibrillation.

1980, after a 20-month period of stability. Surgical correction of the paravalvular leak and aortic regurgitation was performed. Three months later, in May 1981, she had returned to functional class C status.

In all four groups, the heart rate response to progressive exercise was essentially linear, and no statistically significant interclass differences were seen either in the slope of the response or in the resting values. However, the exercise capacity, and thereby the level of muscular work attained, was different in each class. The maximal heart rate achieved at the end point of exercise, therefore, was also different for each class (tables 2–4). These findings were not altered by excluding from the analysis patients in atrial fibrillation. The $\dot{V}O_2$–heart rate relationship, or O_2 pulse, however, was different among the four classes; the more severe the impairment in cardiac performance, the lower the O_2 pulse. Similarly, the change in O_2 pulse from the onset to the end of exercise is smaller in the more compromised patient (tables 2–4).

Anaerobic Threshold

The onset of anaerobic metabolism during exercise, as determined by noninvasive respiratory gas exchange, was related to the functional capacity of the patient (tables 2–4, fig. 3). In class C and D patients, the anaerobic threshold occurred during modest levels of work within 339 ± 72 and 157 ± 74 seconds of exercise, and were significantly different ($p < 0.05$) from one another. This noninvasive estimate of anaerobiosis approximates the rise in mixed venous lactate concentration in class C and D patients. For class A and B patients, the anaerobic threshold was observed within 580 ± 20 and 450 ± 70 seconds of exercise, respectively, and again were significantly different ($p < 0.05$). For all four classes of cardiac patients, anaerobic threshold fell within 60–70% of $\dot{V}O_2$ max; the corresponding heart rate at the onset of anaerobic metabolism was 124 ± 7, 122 ± 11, 119 ± 13 and 112 ± 5 beats/min for classes A, B, C and D, respectively.

The reproducibility of the noninvasive determination of anaerobic metabolism for 43 patients is shown in figure 4 (SEE = 66). The slope and intercept of the regression line was not statistically different from 1.0 and 0, respectively.

Ventilatory Changes with Exercise

The maximal level of minute ventilation ($\dot{V}E$ max) achieved at the symptomatic end point of exercise was related to the exercise capacity of each patient. Maximum $\dot{V}E$ was 62 ± 18, 44 ± 19, 38 ± 17 and 29 ± 10 l/min for classes A, B, C and D respectively (table 5).

TABLE 2. *(Continued)*

HR (beats/min)	MVV (l/min/% predicted)	VC (l/% predicted)	VT (ml)	f (min)
162	—/—	—/—	1469	62
147	—/—	—/—	3522	27
147	116/97	4.0/110	1552	32
168	109/92	1.8/53	1070	52
186	103/90	2.7/78	1420	33
158 ± 22			1807 ± 977	41 ± 16
135	110/89	2.6/87	1158	34
131	43/46	2.2/66	1145	38
143	93/141	2.0/85	762	41
161	114/63	2.8/92	704	31
158	105/135	2.7/100	1016	35
155	—/—	—/—	2597	35
145	—/—	—/—	1856	35
184	103/90	2.7/78	1023	36
177	—/—	—/—	2048	50
141	83/76	2.8/86	1218	41
164	117/83	2.3/61	1089	42
154 ± 17	94/92 ± 28/45	2.5/86 ± 0.3/14	1329 ± 587	37 ± 7

In normal subjects, $\dot{V}E$ max was 72 ± 30 l/min at end-exercise. When $\dot{V}E$ was related either to the level of treadmill work or to $\dot{V}O_2$, however, class C and D patients had a significantly higher level of ventilation ($p < 0.01$) for any given level of work, including that at end-exercise (fig. 6). $\dot{V}E$, on the other hand, is more closely related to $\dot{V}CO_2$ (fig. 6) and reflects the proportionate increase in alveolar ventilation. Nonetheless, at any given level of CO_2 production, more severely affected patients had a higher $\dot{V}E$, indicating that more of their respiratory effort was expended in ventilating anatomic or physiologic dead space.

At lower levels of work, class A and B cardiac patients showed an increase in ventilation that was due mainly to an increase in tidal volume (VT). Later in exercise, the increment in VT became less apparent. The hyperbolic VT and $\dot{V}E$ relation is shown in figure 7. Maximal VT occupies approximately 50 ± 13% and 42 ± 15% of vital capacity in class A and B patients, respectively (table 4). The pattern of ventilation, respiratory frequency and VT that were used throughout exercise, however, differed for class C and D patients (fig. 7). These patients showed a higher respiratory rate and a lower VT than did class A and B patients. This pattern of rapid, shallow breathing was noted at all levels of muscular work. Because of the reduction in VT, dead space ventilation would be expected to occupy a relatively greater fraction of total ventilation. Since these patients also experienced less of an increase in VT with exercise, their wasted ventilation during exercise would be higher. The fraction of maximum voluntary ventilation (MVV) used to achieve maximum $\dot{V}E$ at end-exercise was also different between classes. The $\dot{V}E$ max/MVV ratio for class C and D patients (0.34 ± 0.31 and 0.37 ± 0.24, respectively) was less ($p < 0.01$) than that for class A and B patients (0.43 ± 0.02 and 0.52 ± 0.45), reflecting the diminished exercise capacity and lower $\dot{V}O_2$ max characteristic of the more compromised patient.

Discussion

The severity of cardiac failure is usually graded according to the level of physical activity that is associated with dyspnea or fatigue. A more objective method is obviously desirable. The noninvasive determination of maximal O_2 uptake and anaerobic threshold provide an objective, quantitative description of functional capacity and cardiac reserve.

At rest, cardiac output is normally some fraction of the maximal cardiac output that the heart can generate. Guyton and co-workers[19] used the terms "actual" and "permissible" to distinguish between resting and maximal (e.g., during exercise) cardiac output and to establish the concept of cardiac reserve. With a severe impairment in cardiac function, as in class D patients whose stroke volume fails to increase during exercise, the permissible and actual cardiac outputs are almost the same. Class C patients show a resting cardiac output similar to that of class D patients; but class C patients can raise cardiac output somewhat during exercise by a modest increase in stroke volume, as well as by an increase in heart rate. This would indicate that in group C patients, the heart has a reserve capacity, albeit a limited one. Class B patients, and by inference class A patients, must have an even greater cardiac reserve. These observations emphasize that the extent of the cardiac reserve can best be determined during physiologic stress, such as exercise.

Maximal O_2 uptake ($\dot{V}O_2$ max) is determined by maximal cardiac output and by maximal O_2 extraction. The respiratory system normally imposes no limitations on $\dot{V}O_2$ max.[20, 21] We have observed and others[22, 23] have reported that the extraction of O_2 by metabolizing tissues is not impaired in patients with heart disease. In fact, commensurate with the reduced systemic flow noted in class C and D patients, O_2 extraction is increased at rest and progresses to maximal levels with exercise. Hence, since O_2 extraction is unimpaired, maximum O_2 uptake primarily reflects the level of cardiac output achieved during exercise, and thereby cardiac reserve. Resting cardiac output, wedge pressure, ejection fraction, radiographic heart size, and history, on the other hand, do not reliably predict cardiac reserve.

During exercise, an increase in cardiac output is accomplished by increases in both heart rate and stroke volume. Normally, the increase in stroke volume is most important during the transition from upright rest to submaximal levels of upright work;[24] maximal stroke volume is reached at approximately 40–50% of $\dot{V}O_2$. Heart rate contributes to cardiac output throughout exercise.[25] Despite their limited cardiac

TABLE 3. *Characteristics of Functional Class C Patients*

Pt	Age (years)	Sex	Weight (kg)	Etiology	NYHA class	Rhythm	EC (second)	$\dot{V}O_2$ max (ml/min/kg)	AT (sec/ [ml/min/kg])	ΔO_2 pulse
1	56	F	61	AR/MR	3	AF	534	11.6	300/9.5	14
2	47	M	55	MVR	3	AF	475	15.2	300/13.4	21
3	47	F	83	MR	3	NSR	466	11.5	300/9.7	35
4	62	M	79	CM	3	AF	399	12.0	200/10.2	45
5	45	F	64	AR	2	NSR	854	13.4	500/10.8	64
6	59	F	65	MR	2	NSR	666	14.2	300/13.1	70
7	40	F	48	IHD	2	NSR	534	10.4	300/8.7	58
8	55	M	80	CM	3	NSR	507	10.2	250/7.0	28
9	42	M	72	CM	3	NSR	525	13.1	300/12.8	47
10	41	M	74	CM	4	NSR	723	10.6	400/8.9	41
11	79	M	68	CM	3	NSR	810	10.6	400/10.8	31
12	50	M	66	MR	1	NSR	780	10.1	400/8.8	23
13	36	F	56	MR	2	NSR	612	11.8	350/9.3	58
14	48	M	96	CM	2	NSR	714	10.5	350/7.3	42
15	56	M	60	AVR	2	NSR	600	15.2	300/13.6	52
16	62	M	75	IHD	2	NSR	942	14.0	400/13.1	42
17	53	M	89	CM	2	NSR	720	14.5	400/11.9	32
18	19	F	76	MR	2	NSR	606	11.8	400/10.1	23
19	72	F	73	IHD	3	NSR	684	11.5	300/8.6	54
20	60	F	62	CM	3	NSR	738	14.0	300/6.9	67
Mean ± SD	50 ± 13		70 ± 13				644 ± 143	12.1 ± 1.8	339/10.4 ± 72/2.2	42 ± 16

Abbreviations: See table 2.

reserve, class C and D patients displayed an increase in heart rate during exercise that was statistically the same as that measured for either class A or B patients or for normal subjects. Therefore, the heart rate has only limited application to predicting $\dot{V}O_2$ max. Other limitations inherent in the use of heart rate measurement to assess O_2 intake in normal subjects have been reported.[26, 27]

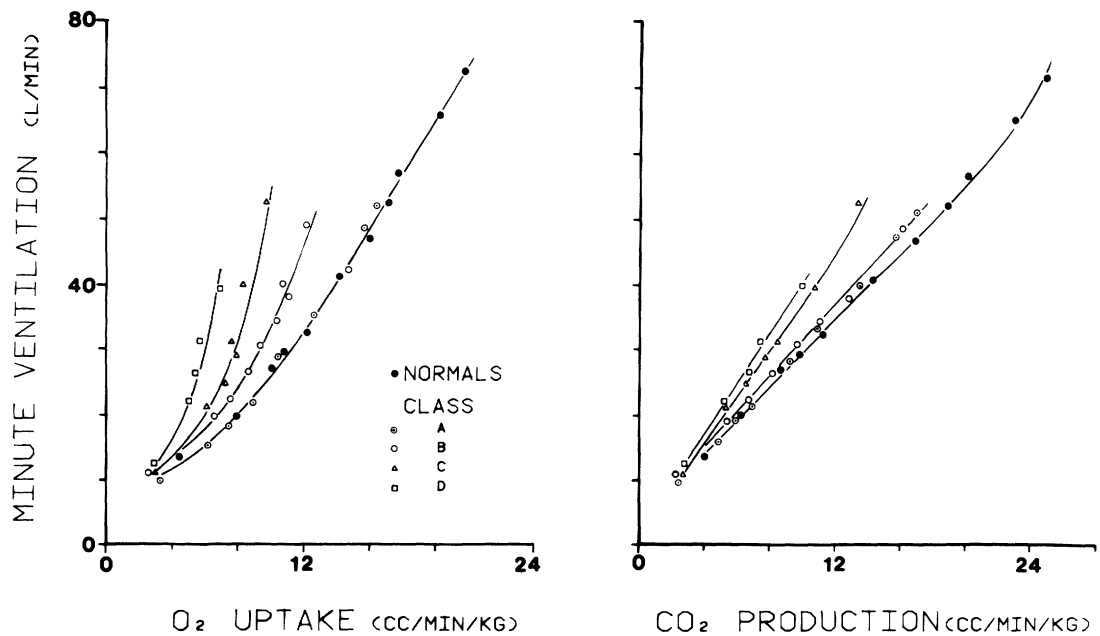

FIGURE 6. *The relationship between minute ventilation and O_2 uptake and CO_2 production for the four functional classes of cardiac patients and normal subjects. End-stage values are given.*

TABLE 3. *(Continued)*

HR (beats/min)	MVV (l/min/% predicted)	VC (l/% predicted)	VT (ml)	f (min)
156	101/89	1.2/40	620	30
164	— —	1.4/37	535	54
124	67/68	2.2/69	913	31
140	115/89	3.6/114	1034	29
107	67/68	2.4/76	800	38
118	96/100	2.5/77	946	30
111	110/107	1.8/60	480	21
121	132/96	2.3/73	1155	37
163	118/72	3.1/56	982	44
137	76/63	5.0/95	1905	43
111	122/110	2.5/108	855	36
153	110/76	3.5/89	1232	35
120	— —	3.3/108	775	52
135	— —	— —	1495	29
156	97/71	3.3/96	1234	33
144	— —	— —	1553	30
157	— —	— —	1316	58
152	— —	— —	1366	38
133	— —	— —	1212	24
144	76/91	3.3/95	1542	28
140 ± 18	99/85 ± 22/18	2.8/79 ± 1.5/27	1075 ± 376	36 ± 9

During progressive upright maximal exercise, the response in cardiac output, rather than the high pulmonary venous pressure, is responsible for symptomatic limitation. Richards et al.,[28] studying patients with mitral stenosis, reached a similar conclusion. Despite pulmonary venous congestion, patients did not cease exercising because of breathlessness. Wedge pressure, which was elevated in class C and D patients at rest, exceeded 30 mm Hg during submaximal levels of work. Wedge pressure and the work of breathing noncompliant, congested lungs may be more important during prolonged submaximal work, or in the supine position, rather than during short periods of maximal upright work.

The $\dot{V}O_2$ max measured under highly standardized conditions is a stable and reproducible characteristic of the patient with cardiac failure. It is a useful index of the functional capacity of the cardiovascular system, as well as a measure of exercise response in cardiac output. To reach $\dot{V}O_2$ max, at least 50% of the muscle mass of the body must be exercised for a sufficient duration and at the proper intensity.[20] We chose upright incremental treadmill exercise to achieve these conditions. Using the simple measurements of respiratory gas exchange during exercise, we have determined $\dot{V}O_2$ max and ascertained the onset of anaerobic metabolism to characterize the severity of chronic cardiac failure. Wasserman and co-workers[14, 15] demonstrated the value of monitoring respiratory gas exchange during exercise to establish the anaerobic threshold in normal subjects and patients with cardiovascular disease. Our findings in a large group of patients with chronic cardiac failure underscore the value of this technique for characterizing the severity of chronic cardiac failure. However, we would not emphasize the exact time of exercise when anaerobic metabolism appeared, but rather its appearance relative to the level of work performed. Accordingly, variations in anaerobiosis exceeding one stage of exercise (fig. 5) would be considered significant or indicative of a change in functional status.

The safety of determining $\dot{V}O_2$ max and anaerobic threshold in cardiac patients with incremental exercise testing may be of concern. Over the past 3 years, we have performed hundreds of maximal exercise tests without incident. Many of our patients have been evaluated serially in the course of studying the efficacy of various pharmacologic modes of management.[8, 22] The determination of $\dot{V}O_2$ max has proved valuable in assessing the severity of cardiac failure, the aerobic and functional capacities of each patient, and the natural course of their disease. However, we have consistently excluded from our studies patients in whom maximal exercise testing would clearly be hazardous.

In patients with cardiac failure and pulmonary congestion, the VT at rest is small.[29] Stimulation of juxtacapillary receptors by interstitial congestion could be expected to alter the breathing pattern, thus increasing respiratory frequency and decreasing VT at any given level of ventilation.[30] The more severely affected class C and D patients achieved their increased $\dot{V}E$ during

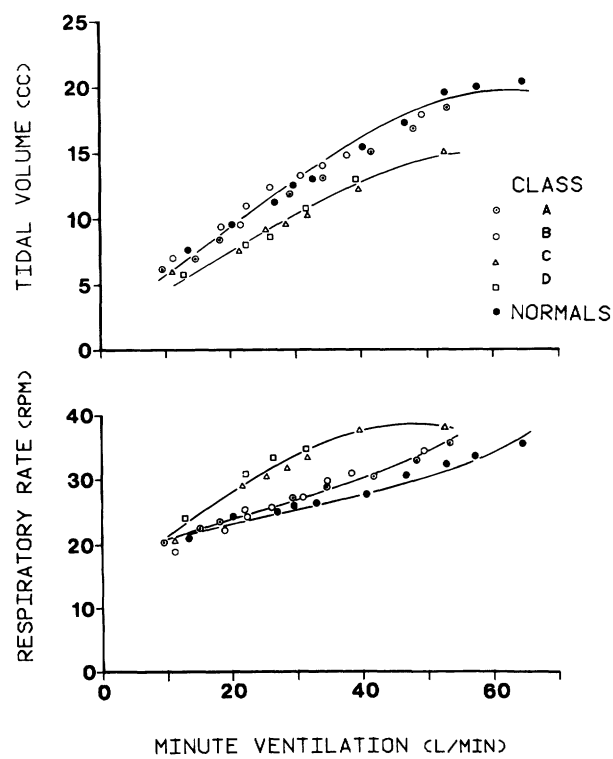

FIGURE 7. *The relationship between minute ventilation and tidal volume and respiratory rate for the four functional classes of cardiac patients and normal subjects.*

TABLE 4. *Characteristics of Functional Class D Patients*

Pt	Age (years)	Sex	Weight	Etiology	NYHA class	Rhythm	EC (sec)	$\dot{V}O_2$ max (ml/min/kg)	AT (sec/ [ml/min/kg])	ΔO_2 pulse
1	61	F	77	CM	4	NSR	180	8.3	100/7.7	30
2	64	F	48	AR/MR	4	AF	298	9.7	100/8.3	29
3	67	F	64	CM	4	NSR	160	8.4	150/7.5	21
4	58	F	55	MR	4	AF	220	7.5	100/5.7	22
5	55	F	61	AR/MR	3	NSR	600	9.9	200/8.2	38
6	73	F	78	AR	3	NSR	528	9.9	200/7.8	41
7	63	F	65	AR/MR	4	AF	612	9.4	300/8.6	11
8	48	M	89	IHD	4	NSR	477	9.3	200/8.3	30
9	57	M	65	IHD	3	NSR	588	9.7	300/8.4	29
10	66	F	62	MR	4	AF	318	8.6	200/8.2	51
11	31	F	70	PPH	4	NSR	384	6.0	150/5.6	4
12	45	M	59	CM	4	NSR	132	9.9	50/8.5	44
13	63	F	60	AR	3	NSR	282	8.4	100/7.8	39
14	64	M	76	IHD	3	NSR	306	5.6	150/5.1	29
15	56	F	60	MR	3	AF	500	9.1	200/7.6	19
16	29	F	55	AR/MS	2	NSR	540	8.3	200/6.0	29
17	58	M	52	MR	4	AF	312	7.2	100/5.4	29
18	52	M	110	CM	3	AF	594	6.1	250/4.6	17
19	52	F	55	MS	4	AF	384	8.3	200/6.7	29
20	55	F	77	MR	4	AF	312	6.4	150/5.8	7
21	46	F	75	MS	3	NSR	336	9.9	100/8.4	51
22	49	F	54	MR	3	NSR	228	9.9	50/5.8	23
23	23	M	60	AVR	3	NSR	282	7.5	50/6.9	23
24	75	M	69	IHD	4	NSR	240	4.8	150/4.0	15
Mean ± SD	53 ± 14		67 ± 14				373 ± 157	8.4 ± 1.5	157/7.1 ± 74/1.5	28 ± 12

Abbreviations: MS = mitral stenosis; PPH = primary pulmonary hypertension; others as in table 2.

TABLE 5. *Gas Exchange During Exercise*

	Class A	Class B	Class C	Class D
Max $\dot{V}E$ (l/min)	62 ± 18	44 ± 19	38 ± 17	29 ± 10
Max VEQ	38 ± 7	40 ± 8	45 ± 17	38 ± 15
Max $\dot{V}E/MVV$	0.43 ± 0.02	0.52 ± 0.45	0.34 ± 0.31	0.37 ± 0.24
Max VT (ml)	1807 ± 977	1329 ± 662	1075 ± 366	869 ± 333
Max VT/VC	0.50 ± 0.13	0.42 ± 0.15	0.38 ± 0.09	0.47 ± 0.20
Max $\dot{V}CO_2$ (l/min)	1863 ± 485	1390 ± 569	1001 ± 362	676 ± 211
Max R	1.15 ± 0.16	1.24 ± 0.26	1.16 ± 0.35	1.22 ± 0.34

Abbreviations: $\dot{V}E$ = maximum voluntary ventilation; Max VEQ = maximum ventilatory equivalent; Max $\dot{V}E/MVV$ = the ratio of maximum ventilation at end-exercise to maximum voluntary ventilation; Max VT = maximum tidal volume; Max VT/VC = maximum tidal volume at end-exercise to initial capacity; Max $\dot{V}CO_2$ = maximum CO_2 production; Max R = maximum ventilatory gas exchange ratio.

exercise with higher respiratory frequencies and with lower VT compared with class A and B patients. This pattern of rapid, shallow breathing minimizes the work and energy cost of breathing,[31] but anatomic dead space occupies a relatively greater portion of each VT. The result is more wasted ventilation, and this accounts for the progressively higher $\dot{V}E$ observed in cardiac patients at a given work load. Despite this less efficient distribution of $\dot{V}E$, class C and D patients used a smaller proportion of the MVV than did the less severely affected patients. This finding is consistent with the interpretation that cardiac response limits exercise capacity in patients with chronic cardiac failure.

Acknowledgment

We express our appreciation to Lester Shelton, Thomas Nusbickel, Daniel Ward, Jerome Dowell and Mary Merlino for

TABLE 4. *(Continued)*

HR (beats/min)	MVV (l/min/% predicted)	VC (l/% predicted)	VT (ml)	f (min)
121	84/100	1.6/100	549	31
120	79/100	1.1/43	1891	39
104	— —	1.7/61	615	26
83	69/80	1.7/57	704	33
98	120/136	1.5/53	532	35
116	64/88	1.5/55	1114	23
141	24/30	1.5/56	911	28
135	104/63	3.4/65	1650	36
93	73/48	3.0/68	1231	23
99	80/104	2.5/98	741	37
131	— —	— —	1192	31
115	— —	— —	834	40
110	— —	— —	835	30
105	— —	— —	1289	39
148	90/102	1.9/66	1067	28
142	— —	— —	465	48
151	31/23	2.1/62	670	48
140	88/52	2.6/47	1454	42
110	— —	— —	560	45
135	49/41	1.1/40	587	33
106	92/91	3.8/110	983	31
114	98/103	2.4/82	567	46
139	— —	— —	848	39
80	90/81	2.9/128	849	37
120 ± 20	77/77 ± 30/32	2.2/70 ± 0.8/25	869 ± 333	35 ± 10

their technical assistance and to Susan Wahl and Judith Stofman for their secretarial assistance.

References

1. Harrison TR, Pilcher C: Studies in congestive heart failure. II. The respiratory exchange during and after exercise. J Clin Invest **8:** 291, 1930
2. Mitchell JE, Sproule BJ, Chapman CB: The physiological meaning of the maximal oxygen intake test. J Clin Invest **37:** 538, 1958
3. Donald KW, Bishop JM, Wade OL: A study of minute to minute changes of arterio-venous oxygen content difference, oxygen uptake and cardiac output and the rate of achievement of a steady state during exercise in rheumatic heart disease. J Clin Invest **33:** 1146, 1954
4. Chapman CB, Mitchell JH, Sproule BJ, Potter D, Williams B: The maximal oxygen intake test in patients with predominant mitral stenosis. Circulation **22:** 4, 1960
5. Wasserman K, Whipp BJ: Exercise physiology in health and disease. Am Rev Resp Dis **112:** 219, 1975
6. Bruce RA, Kusumi F, Hosmer D: Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. Am Heart J **85:** 546, 1973
7. Beaver WL, Wasserman K, Whipp BJ: On-line computer analysis and breath-to-breath graphical display of exercise function tests. J Appl Physiol **34:** 128, 1973
8. Weber KT, Kinasewitz GT, West JS, Janicki JS, Reichek N, Fishman AP: Long term vasodilator therapy with trimazosin in chronic failure. N Engl J Med **303:** 242, 1980
9. Donald KW: Exercise and heart disease. A study in regional circulation (Bradshaw Lecture). Br J Med **1:** 985, 1959
10. Patterson JA, Naughton J, Pietras RJ, Gunner RM: Treadmill exercise in assessment of the functional capacity of patients with cardiac disease. Am J Cardiol **30:** 757, 1972
11. Morris JF, Koski A, Johnson LC: Spirometric standards for healthy, nonsmoking adults. Am Rev Resp Dis **103:** 57, 1971
12. Naughton JP, Haider R: Methods of exercise testing. *In* Exercise Testing and Exercise Training in Coronary Artery Disease, edited by Naughton JP, Hellerstein HK, Mohler IC. New York, Academic Press, 1973, pp 79–91
13. Naimark A, Wasserman K, McIlroy MB: Continuous measurement of ventilatory exchange ratio during exercise: a test of cardiovascular function. J Appl Physiol **19:** 644, 1964
14. Wasserman K, McIlroy MB: Detecting the threshold of anaerobic metabolism in cardiac patients during exercise. Am J Cardiol **14:** 844, 1964
15. Wasserman K, Whipp BJ, Kogal SN, Beaver WL: Anaerobic threshold and respiratory gas exchange during exercise. J Appl Physiol **35:** 236, 1973
16. Henry RJ: Clinical Chemistry: Principles and Technics. New York; Harper and Row, 1968, pp 655–666
17. Wallenstein S, Zucker CL, Fleiss JL: Some statistical methods useful in circulation research. Circ Res **47:** 1, 1980
18. Brownlee KA: Statistical Theory and Methodology in Science and Engineering. New York, Wiley, 1965, pp 349–351
19. Guyton AC, Jones CE, Coleman TC: Circulatory Physiology: Cardiac Output and Its Regulation. Philadelphia, WB Saunders, 1973, pp 143–145
20. Rowell LB, Taylor HL, Wang Y: Limitations to prediction of maximal oxygen intake. J Appl Physiol **19:** 919, 1964
21. Jones NL, Campbell EJM, Edwards RHT, Robertson DG: Clinical Exercise Testing. Philadelphia, WB Saunders, 1975, p 27
22. Weber KT, Andrews V, Janicki JS, Wilson JR, Fishman AP: Amrinone and exercise performance in patients with chronic heart failure. Am J Cardiol **48:** 164, 1981
23. Zelis R, Longhurst J, Capone RJ, Mason DT: A comparison of regional blood flow and oxygen utilization during dynamic forearm exercise in normal subjects and patients with congestive heart failure. Circulation **50:** 137, 1974
24. Chapman CG, Fisher JN, Sproule BJ: Behavior of stroke volume at rest and during exercise in human beings. J Clin Invest **39:** 1208, 1960
25. Astrand PO, Cuddy TE, Saltin B, Stenberg J: Cardiac output during submaximal and maximal work. J Appl Physiol **19:** 268, 1964
26. Davies CTM: Limitations to the prediction of maximum oxygen intake from cardiac frequency measurements. J Appl Physiol **24:** 700, 1968
27. Hayward GW, Knott JM: The effect of exercise on lung distensibility and respiratory work in mitral stenosis. Br Heart J **17:** 303, 1955
28. Richards DGB, Whitfield AGW, Arnott WM, Waterhouse JAH: The lung volume in low output cardiac syndromes. Br Heart J **13:** 381, 1951
29. Paintal AX: Vagal sensory receptors and their reflex effects. Physiol Rev **53:** 159, 1973
30. Turino GM, Fishman AP: The congested lung. J Chronic Dis **9:** 510, 1959

Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure.

K T Weber, G T Kinasewitz, J S Janicki and A P Fishman

Circulation. 1982;65:1213-1223
doi: 10.1161/01.CIR.65.6.1213
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539