The Usefulness of the Anaerobic Threshold in the Assessment and Prognostic Evaluation of the Patient With Dyspnea

Rosalinda Madonna, MD,[1] Roberto Bolli, MD,[2] Raffaele De Caterina, MD[1]
[1]Institute of Cardiology, G. D'Annunzio University, Chieti, Italy; [2]Institute of Molecular Cardiology, University of Louisville, Louisville, KY

The anaerobic threshold (AT) is defined as the oxygen consumption level above which energy production becomes determined by anaerobic metabolism, which causes a sustained increase in lactate and metabolic acidosis. The AT, as measured by cardiopulmonary stress testing, is ubiquitously used to determine the prognosis and diagnosis of cardiovascular and respiratory diseases. This measurement can help clinicians in the functional evaluation of patients and as guidance for rehabilitation and therapy. This article reviews the pathophysiological aspects and methods of measurement of the AT during a cardiopulmonary stress test, and its clinical use in assessing cardiac and respiratory diseases.

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KEY WORDS

Anaerobic metabolism • Anaerobic threshold • Lactate threshold • Heart failure • Coronary artery disease

Anaerobic metabolism is characterized by the enzymatic phosphorylation of substrates (in the Krebs cycle and glycolysis), leading to the synthesis of adenosine triphosphate (ATP) in the absence of oxygen. This occurs when the oxygen supply is insufficient to deoxidize a hydrogen ion with a nicotinamide adenine dinucleotide ion.[1] Under these circumstances, the production of pyruvic acid and lactate exceeds the rate of metabolism of these molecules in the Krebs cycle, resulting in lactic acid accumulation in the blood and tissues. The accumulation of lactate and glycolytic intermediates in the muscle and/or blood, and not merely the evidence of their increased synthesis,

marks the beginning of anaerobic metabolism. Because the net accumulation of lactate may arise not only from increased production but also from insufficient removal from the blood, anaerobic metabolism may occur even at rest.[2]

The term *anaerobic threshold* (AT) was first proposed in 1964 by Wasserman and McIlroy[3] to indicate the transition point from predominantly aerobic to anaerobic metabolism. It is usually expressed in units of oxygen consumption (VO_2) or as a percentage of maximum oxygen consumption (VO_2 max).[1] In untrained healthy people, lactic acid starts to accumulate when 40% to 60% of the maximum aerobic capacity is reached. Therefore, the average value of the AT in normal subjects is between 40% and 60% of their VO_2 max.[1] As lactic acid accumulates, it is buffered by serum bicarbonate according to the following reaction:

$$H + La^- + HCO_{3^-} \leftrightarrow H_2O + CO_2 + La^-$$

This causes an increased excretion of carbon dioxide, which leads to reflex hyperventilation. In other words, the anaerobic threshold is the point where ventilation (VE) increases disproportionately in comparison with VO_2 and work, and this occurs at 40% to 60% of VO_2 max in untrained healthy subjects. In trained subjects, the AT can reach 80% of VO_2 max. Below the AT, the production of carbon dioxide is proportional to oxygen consumption. Above the AT, carbon dioxide is produced in excess of oxygen consumption.[4]

This article examines the methods of AT measurement during exercise and its diagnostic value in specific groups of patients with respiratory and cardiovascular diseases, describes the concept of AT and the mechanisms that determine the nonlinear relationship between ventilatory response and exercise, and reviews the prognostic value of the integrated analysis of AT and VO_2 peak during the cardiopulmonary stress test.

Methods of Measurement of the AT

The AT can be determined by monitoring the lactic acid and/or bicarbonate levels in arterial and venous blood (lactate threshold), or by measuring, during a cardiopulmonary stress test, the increase in VO_2 and carbon dioxide production (VCO_2) and its effects on VE: that is, the ventilatory anaerobic threshold (VAT).

The conventional method used to determine the VAT is the V-slope analysis.[5] Other methods are based on calculating the following:

…the anaerobic threshold is the point where ventilation increases disproportionately in comparison with VO_2 and work, and this occurs at 40% to 60% of VO_2 max in untrained healthy subjects.

- VE/VO_2, which identifies the relationship between ventilation and oxygen consumption;
- VE/VCO_2, which identifies the relationship between ventilation and carbon dioxide production;
- The respiratory quotient (VCO_2/VO_2), which relates carbon dioxide production to oxygen consumption; and
- The difference between the arterial and end-tidal volume of oxygen [P (a - ET) O_2] and carbon dioxide [P (a - ET) CO_2] during exercise.[6]

The AT is reached when the response to the increase in VCO_2 is no longer accompanied by an increase in VE/VO_2 and P (a - ET) O_2 in the absence of changes in VE/VCO_2 and P (a - ET) CO_2. This is due to the fact that an increase in VE at the beginning of the exercise is related to the VCO_2 concentration: this is the isocapnic phase of exercise, in which metabolic acidosis has not yet developed. As the exercise continues over time, the resulting increase in lactic acidosis causes a further increase in VE, with an associated increase in VE/VCO_2 and a decrease in P (a - ET) CO_2. This corresponds to an excess of VCO_2 relative to VO_2, and a respiratory quotient (VCO_2/VO_2) > 1. From a practical point of view, the AT corresponds to the nadir of VE/VO_2 and P (a - ET) O_2 in the presence of a stable VE/VCO_2 and P (a - ET) CO_2 and a VO_2/VCO_2 of approximately 1. The method described above is based on the ventilatory response that results from the increase in VCO_2 concentration. It can be altered in case of loss of breath control and/or in the presence of mechanical lung diseases.[7]

The V-slope calculation[8] can simplify the method described above and permits the manual identification of the VAT. The V-slope method requires breath-to-breath sampling and data processing using mathematical calculations. This method is based on the principle that below the AT there is a linear relationship between VO_2 and VCO_2, whereas above the AT the increase in VCO_2 due to lactic acidosis produces an additional change in the VCO_2/VO_2 slope. This slope before the AT is equal to 1 and corresponds to the line of identity, which is parallel to the hypotenuse of an isosceles triangle, the sides of which are VO_2 (x axis) and VCO_2 (y axis). After reaching the AT, VCO_2/VO_2 deviates from the line of identity and the VO_2 value. The inflection point therefore represents the VAT.

Cohen-Solal and colleagues[9] compared the reproducibility of the following four methods in order to identify the VAT in patients with New York Heart Association (NYHA) class II or III heart failure: (1) *crossing* (the point of intersection between the VO_2 and VCO_2 curves), (2) the *respiratory quotient* (the change in VCO_2/VO_2 slope vs time), (3) the *equivalent ventilation* (VE/VO_2 and VE/VCO_2), and (4) the V-slope. In this study, the methods of VAT measurement with the best reproducibility were the equivalent ventilation method and the crossing method, which exhibited variabilities of 7.3% and 5.5%, respectively.[9] For the V-slope method the variability was between 7% and 10%.[9] In healthy subjects, there is a good reproducibility in measuring the VAT by a conventional method of equivalent ventilation, with an interobserver variability of $< 16\%$.[10]

The AT in the Pathophysiological Assessment of Respiratory and Cardiovascular Diseases

During a cardiopulmonary stress test, measurement of the AT plays an important role, along with other parameters such as VO_2, VCO_2, heart rate, blood pressure, minute ventilation, respiratory rate, respiratory equivalent, ventilator reserve, and end-tidal volume at rest, during exercise, and at peak exercise.

The AT and VO_2 are components of the flow chart that is used for the initial assessment of patients with dyspnea (Figure 1). This flow chart uses measurements taken during the exercise in order to deduce the underlying pathophysiology. Although such a flow chart is not necessarily ideal in all instances and should always be used with some degree of flexibility, it establishes a pathophysiological method for interpreting cardiopulmonary exercise tests. Table 1 provides expected changes of key variables in a variety of clinical conditions impairing work tolerance.

The diagnostic strategy in this flow chart foresees the need to determine whether the VO_2 is decreased or normal, and whether the VAT is reduced or normal. Based on this initial assessment, a patient is classified into one of the following three diagnostic categories: (1) normal VO_2, (2) low VO_2 with a normal VAT, and (3) low VO_2 with a low VAT.[1]

Figure 1. Flow chart for the initial assessment of the cause of exercise limitation. The analysis starts with the measurement of peak oxygen consumption (VO_2 peak) and continues with anaerobic threshold evaluation. AT, anaerobic threshold; BPCO, chronic obstructive pulmonary disease; CAD, coronary artery disease; PAD, peripheral artery disease; PPH, primary pulmonary hypertension; RR, respiratory reserve; VD/VT, ratio of the dead space (VD) to the tidal volume (VT); VE/VCO_2, ventilatory equivalent of CO_2; VO_2, oxygen consumption. Heart diseases include coronary, valvular, myocardial, and congenital heart disease.

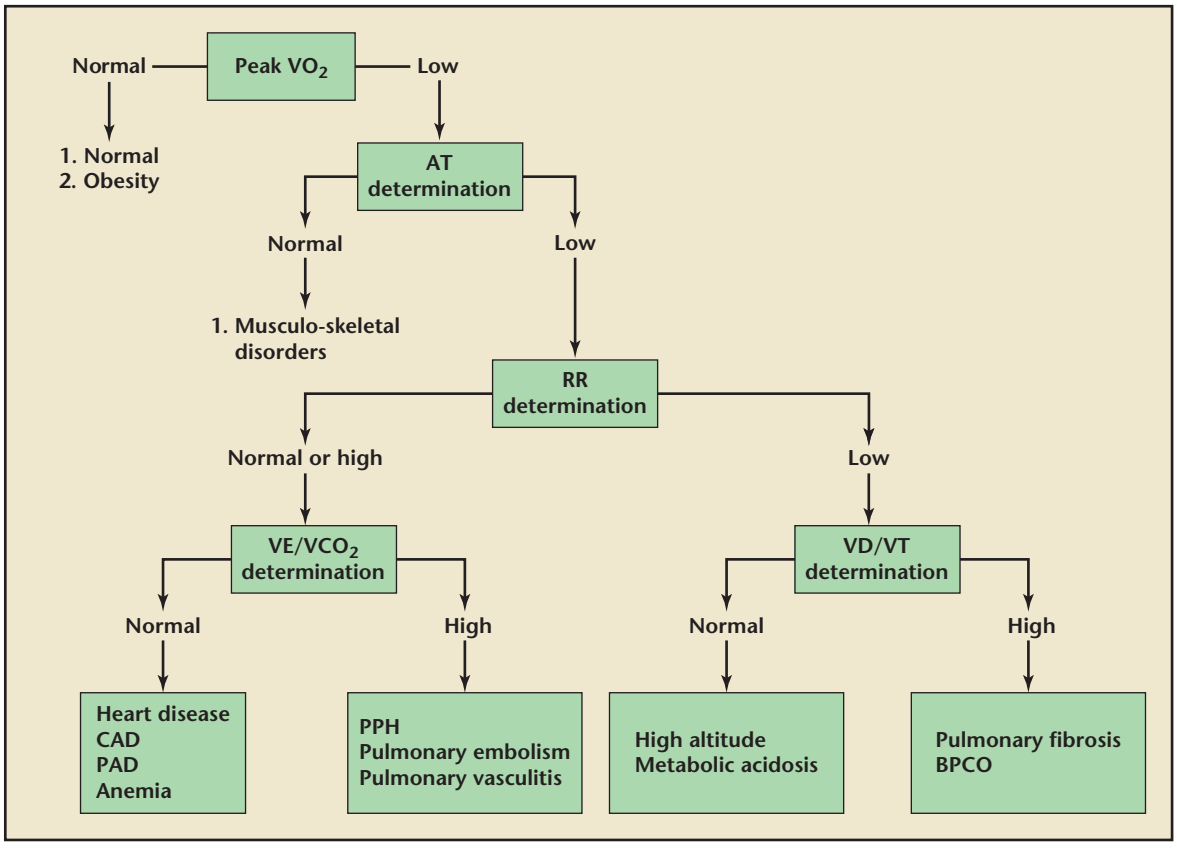


TABLE 1

Expected Changes of Key Variables in Clinical Conditions Impairing Exercise Tolerance

Disorder	VO_2 Peak	AT	O_2 Pulse	$\triangle VO_2/\triangle WR$	VD/VT	$P(a - ET)CO_2$	$P(A - a)O_2$	VE/VCO_2
Obesity	Low	Low	Normal to high	Normal	Normal	Normal	Normal	Normal
PAD	Low	Low	Normal	Low	Normal	Normal	Normal	Normal
CAD	Low	Low	Low	Normal at low work rates with slope above AT	Normal	Normal	Normal	Normal
CHF	Low	Low	Low	Gradually slows down near VO_2 peak	High	Normal	Normal	High
Valvular heart disease	Low	Low	Low	Low	Normal	Normal	Normal	Normal
Pulmonary vascular disease	Low	Low	Low	Shallow toward maximum WR	High	High	High	High
Obstructive lung disease	Low	Low	Low	Low	High	High	High	High
Restrictive lung disease	Low	Low	Low	Low	High	High	High	High
Defects in hemoglobin content	Low	Low	Low	Normal	Normal	Normal	Normal	Normal

Defects in hemoglobin content: anemia, carboxyhemoglobin, haemoglobinopathies.

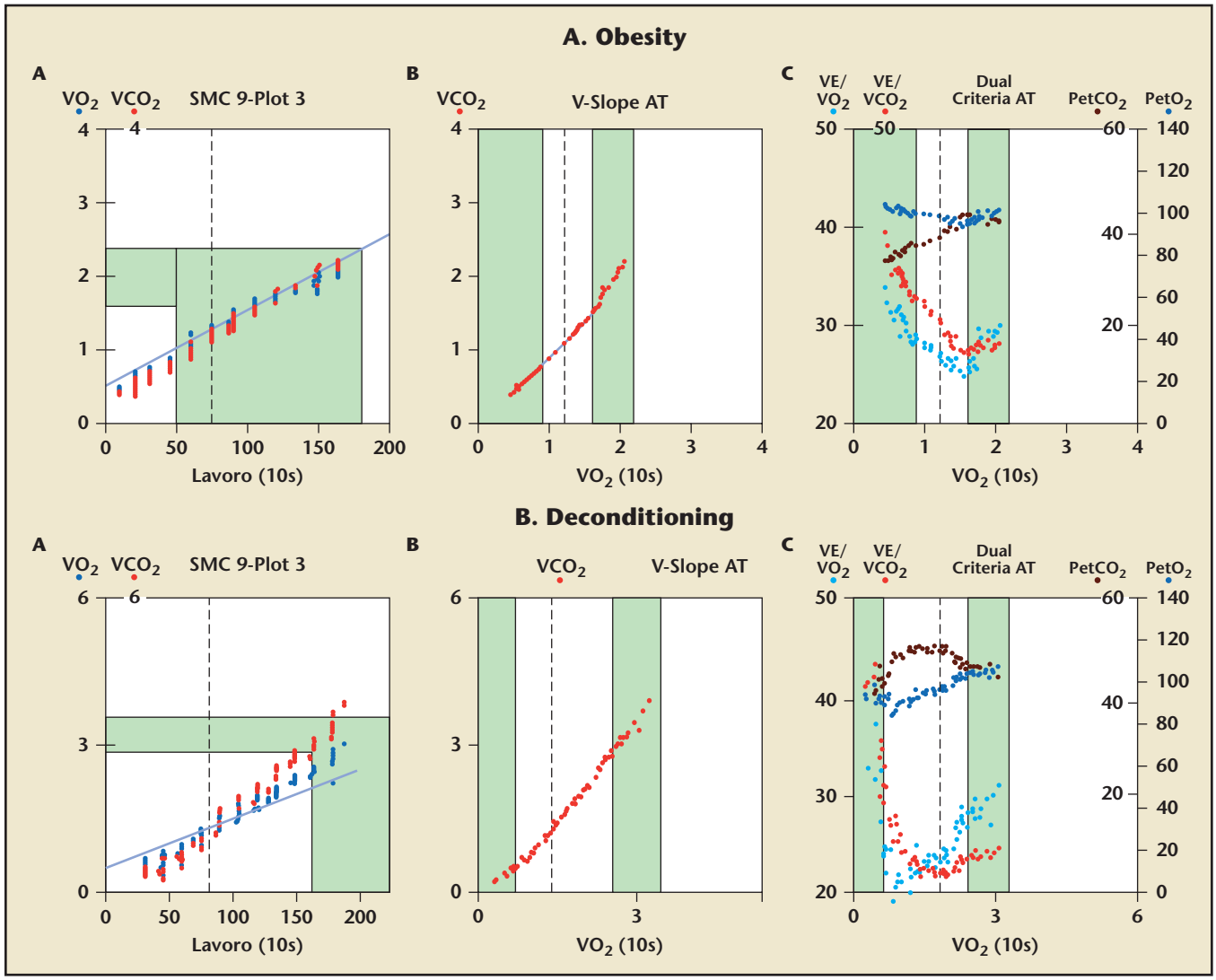
Criteria of normality: VO_2 peak $>$ 84% predicted; AT $>$ 40% VO_2 peak predicted; O_2 pulse $>$ 80%; VD/VT , 0.28; $>$ 0.30 for age $>$ 40 years; $P(A - a)O_2 < 35$ mm Hg; VE/VCO_2 , 34; $\triangle VO_2/\triangle WR > 10.3$ mL/min/W; $P(a - ET)CO_2$ 2-5 mm Hg. (Data from American Thoracic Society/American College of Chest Physicians.[32])

AT, anaerobic threshold; CAD, coronary artery disease; CHF, chronic heart failure; $P(A - a)O_2$, alveolar-arterial PO_2 difference; $P(a - ET)CO_2$, arterial end-tidal PCO_2 difference; PAD, peripheral arterial disease; VD, physiological dead space; VO_2 peak, highest O_2 uptake measured; VT, tidal volume; $\triangle VO_2/\triangle WR$, increase in VO_2 relative to increase in work rate.

Exercise Intolerance in the Presence of a Normal VO_2

This case involves patients who complain of exercise intolerance, even though they have a normal maximal VO_2 (VO_2 peak). Possible explanations include simple anxiety; obesity, wherein even if the aerobic capacity is normal the oxygen demand is high because of the increased metabolic costs to overcome the aerobic capacity of the skeletal muscles (Figure 2, panel A); and early-stage pulmonary or cardiovascular disease, in which the disorder may not be sufficient to affect the VO_2 peak. In obese individuals, the VO_2 peak and AT are low relative to actual body weight, but usually normal relative to height[11] or to predicted weight or lean body mass.[12] Consequently, other cardiopulmonary variables are increasingly being studied to assess functional limitations in obese patients. deJong and associates[13] evaluated VE/VCO_2 as a measure complementary to VO_2 peak in morbidly obese patients referred for bariatric surgery. In that study, VO_2 peak inversely correlated with the body mass index (BMI), whereas VE/VCO_2 did not. The authors concluded that VE/CO_2 is a BMI-independent measure that may serve as an adjunctive cardiorespiratory variable when assessing the functional status of morbidly obese patients. Deconditioning, which is defined as the inability to exercise, and is a condition that can be seen in patients with little

Figure 2. Representative graphs that show the VO_2/work curve and three methods for the measurement of the anaerobic threshold (AT) (ventilatory equivalent of O_2 and CO_2; P [a – ET] O_2; and the V-slope) in obese subjects (**A**, showing a normal VO_2, VO_2/work, and ventilator AT [VAT]); and in the presence of deconditioning (**B**, showing a normal VO_2 and VO_2/work with a reduced VAT). Charts in panel A represent the volume of oxygen consumption (VO_2 in *blue*) and the volume of carbon dioxide produced (VCO_2 in *red*) plotted as a function of the work rate for an exercising subject. The V-slope plot of VCO_2 versus VO_2 is shown in panel B, wherein the diagonal line is at 45° (slope = 1). The AT is defined as the point at which the VCO_2 begins to increase faster than the VO_2 and the slope of the plot becomes steeper than 1. Charts in panel C depict the ratio of VE/VO_2 (ventilatory equivalent of O_2 in *red*) and VE/VCO_2 production (ventilatory equivalent of CO_2 in *sky blue*) versus oxygen consumption (VO_2). End-tidal CO_2 pressure ($PetCO_2$) and end-tidal VO_2 pressure ($PetO_2$) versus oxygen consumption (VO_2) are represented in *violet* and *blue*, respectively. Original data courtesy of the Cardiology Division, Cardiopulmonary Stress Test Laboratory, University Hospital SS. Annunziata, Chieti, Italy.



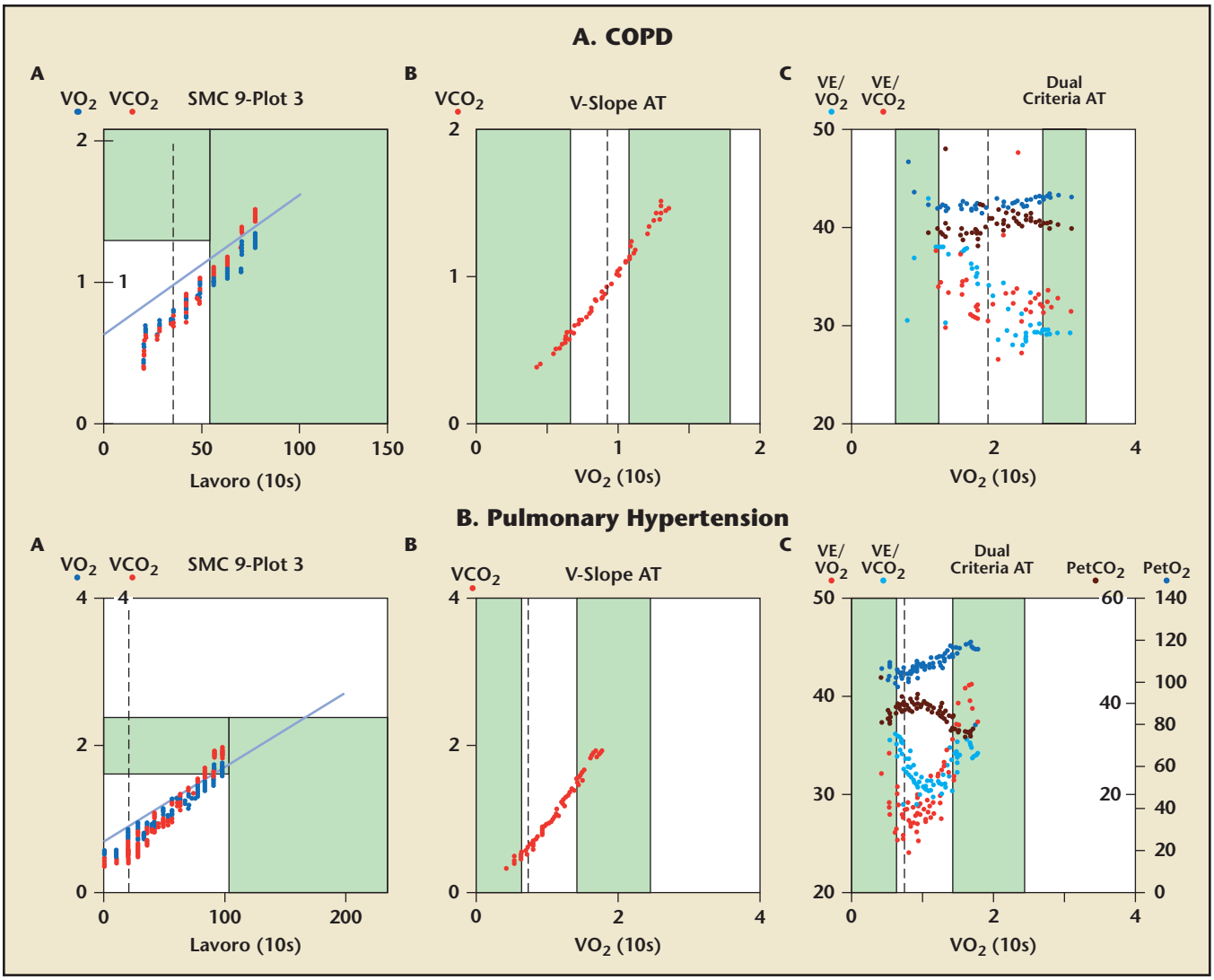


Figure 3. Representative graphs showing the VO_2/work curve and three methods for measuring the anaerobic threshold (AT) in patients with primary pulmonary disease (chronic obstructive pulmonary disease [COPD]) (**A**, characterized by a reduced VO_2 and normal VO_2/work, reduced VAT, reduced respiratory rate (RR), and increased VD/VT); and pulmonary hypertension (**B**, showing a reduced VO_2, normal VO_2/work, reduced VAT, normal RR, and increased VE/VCO_2). Original data courtesy of the Cardiology Division, Cardiopulmonary Stress Test Laboratory, University Hospital SS. Annunziata, Chieti, Italy.

physical training, may also lead to a low AT despite the presence of normal ventricular systolic function and functional capacity (Figure 2, panel B).[1,14]

Exercise Intolerance in the Presence of a Low VO_2 and Normal VAT

In this case, even if the VO_2 peak that is recorded during exercise is low, the anaerobic threshold is normal. These patients did not perform a maximal physical effort or suffered from musculoskeletal disorders and, thus, had severe exercise limitations.[14]

Exercise Intolerance With a Low VO_2 and Reduced VAT

In the flow chart of disorders that are characterized by a low VO_2 peak and reduced VAT, the respiratory reserve provides the first branching point. Patients with low VO_2 peak and low VAT, and also with a low respiratory reserve can be thus further divided into two classes according to the ratio of the dead space (VD) to the tidal volume (VT), or VD/VT. If the ratio of the VD to VT is high, the presence of a primary pulmonary disease (eg, pulmonary fibrosis or chronic obstructive pulmonary disease) can be suspected (Figure 3, panel A). If the ratio is normal, hyperventilation, chronic metabolic acidosis, or the adaptation to a high altitude may be present.

In patients with a normal or high respiratory reserve, low VO_2 peak, and low VAT, the second branching point in the decision-making algorithm depends on the equivalent ventilation for carbon dioxide. If the VE/VCO_2 is high, the disease is in the pulmonary vascular bed due to primary pulmonary vascular disease (primary pulmonary hypertension) (Figure 3, panel B) or secondary vascular disease

(pulmonary embolism, vasculitis, or connective tissue disease). In these situations, the pathogenesis of a low VAT is given by a reduced oxygen saturation of the arterial blood (of hemoglobin; SaO_2) at exercise peak, that disappears at rest. This occurs because the reduction in the pulmonary vascular bed leads to a decrease in the time that the erythrocytes spend in the pulmonary capillaries during exercise when the cardiac output increases, thereby preventing effective oxygen diffusion from the alveoli to the blood. Patients with a primary disease of the pulmonary vascular bed are different from those with left ventricular (LV) dysfunction, because in the latter case there is an increased VD/VT and an increased difference in CO_2 tension between the arterial and venous blood, which indicates the presence of a mismatch between ventilation and perfusion. These patients do not have hypoxemia (their SaO_2 is normal) or an increase in the alveolar-arterial oxygen gradient. This disparity is due to slow blood flow in the pulmonary vascular bed, which is typical of conditions with LV dysfunction. Unlike primary pulmonary vascular disease, such conditions allow an adequate diffusion time for erythrocytes in contact with the alveolar surface and good oxygenation of the blood. In general, all diseases that affect the oxygen transport chain from the ambient air to the mitochondria in skeletal muscle during exercise can influence the VAT behavior.

If the VE/VCO_2 is normal, we can exclude a disease in the lung or the pulmonary circulation; however, the following conditions need to be considered: a reduced coronary reserve, where exercise determines the onset of myocardial ischemia and abnormal global and segmental ventricular wall motion, with a consequent poor peripheral tissue perfusion that results in the early use of glycolysis for ATP synthesis (Figure 4, panel A); heart disease (ischemic heart disease or primary cardiomyopathy), which causes heart failure with reduced stroke volume, decreased heart rate, and inadequate peripheral tissue perfusion (Figure 4, panel B); peripheral arterial obstructive disease, in which the onset of pain causes submaximal exercise; increased peripheral resistance, which affects the amount of arterial blood flow in the peripheral tissues leading to an early VAT; and anemia or hemoglobinopathies characterized by a low oxygen-carrying capacity of the blood. In the latter case, the hematocrit and oxygen pulse can help identify different conditions. All cardiovascular diseases determine a change in the oxygen transport chain (typically in chronic heart failure [CHF]) and may lead to a pathological VAT (ie, $<$ 40% of the predicted VO_2 max).[1] In a certain percentage of patients with CHF and periodic breathing, the VAT cannot be measured.[15]

Patients with a primary disease of the pulmonary vascular bed are different from those with left ventricular dysfunction, because in the latter case there is an increased VD/VT and an increased difference in CO_2 tension between the arterial and venous blood, which indicates the presence of a mismatch between ventilation and perfusion.

In patients with CHF, the VAT has a role in defining their prognosis. Gitt and colleagues[16] have observed that the risk of death is five times greater within 6 months after the first detection of a VAT $<$ 50% of the predicted VO_2 max and a $VE/VCO_2 > 34$. In patients with coronary heart disease (detection of one or more coronary arteries with a diameter stenosis $>$ 50% on a coronary angiogram) and in the absence of a previous myocardial infarction, the VAT correlates with the extension of stress-inducible myocardial ischemia.[17]

Prognostic Value of the Integrated Measurement of AT and VO_2 Peak During a Cardiopulmonary Stress Test

Several investigations have examined exercise-derived AT and VO_2 peak as predictors of outcomes in patients with CHF due to LV systolic dysfunction.[18] Matsumura and colleagues[19] and Itoh and colleagues[20] showed that AT and VO_2 peak correlated with symptom scores, as measured by the NYHA class. In the study by Itoh and colleagues,[20] the mean AT was 90% $\pm$ 15%, 77% $\pm$ 14%, and 60% $\pm$ 12% of the predicted values for NYHA class I, class II, and class III, respectively. AT correlated only weakly with the resting LV ejection fraction measured by echocardiography and angiography. Weber[21] suggested a classification based on VO_2 peak and AT, whereby heart failure patients are divided in class A (VO_2 peak $>$ 20 mL/kg/min; AT $>$ 14 mL/kg/min), class B (VO_2 peak 16-20 mL/kg/min; AT 11-14 mL/kg/min), class C (VO_2 peak 10-15 mL/kg/min; AT 8-11 mL/kg/min), and class D (VO_2 peak $<$ 10 mL/kg/min; AT $<$ 8 mL/kg/min). Koike and associates[22] have similarly linked exercise capacity to a symptoms score. In these patients, VO_2 peak, AT, the ratio of the increase in VO_2 to the increase in work rate ($\Delta VO_2/\Delta$work rate), and maximum work rate decreased as NYHA class increased. In 181

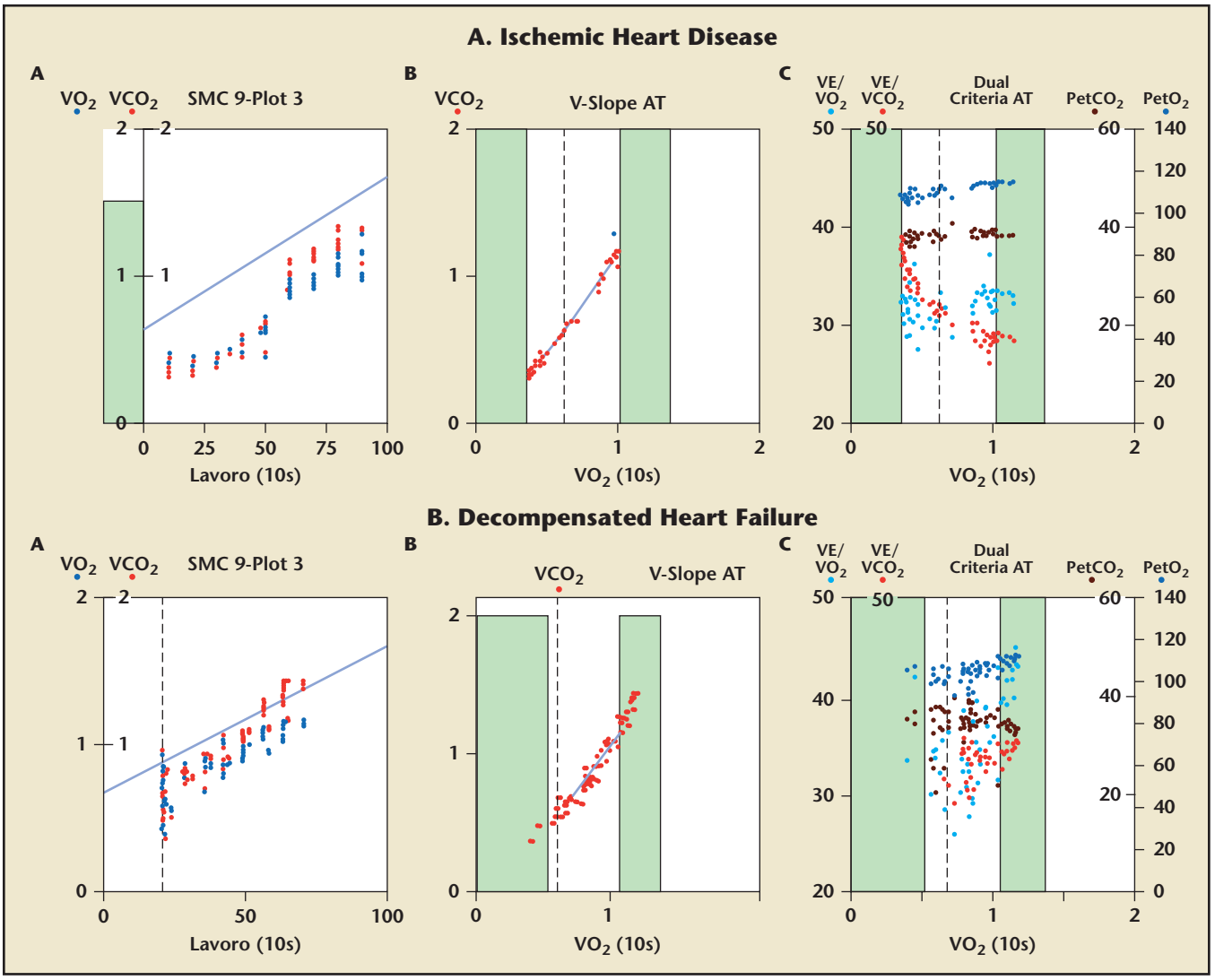


Figure 4. Representative graphs showing the VO_2/work curve and three methods for measuring the anaerobic threshold (AT) in patients with ischemic heart disease (**A**, showing a reduced VO_2 and VO_2/work plot, with slope flattening and the appearance of a double slope, reduced ventilatory AT (VAT), normal respiratory rate (RR), and normal VE/VCO_2); and chronic heart failure (**B**, showing a reduced VO_2 and VO_2/work plot with slope flattening in the absence of a double slope, reduced VAT, normal RR, and normal VE/VCO_2). Original data courtesy of the Cardiology Division, Cardiopulmonary Stress Test Laboratory, University Hospital SS. Annunziata, Chieti, Italy.

ambulatory patients with NYHA class II to III, Stelken and associates[23] observed that VO_2 peak and AT were significantly different in survivors and nonsurvivors when compared at 12 and 24 months. A total of 89 patients with VO_2 peak $<$ 50% of the predicted value had 1- and 2-year survival rates of 74% and 43%, respectively. The study by Mancini and coworkers[24] is the cornerstone of the documentation of the prognostic power of VO_2 peak in patients who are candidates for heart transplantation. In this study, 116 male CHF patients were divided into group 1 (VO_2 peak $<$ 14 mL/kg/min), and these had been accepted for heart transplantation; group 2 (VO_2 peak $\geq$ 14 mL/kg/min), who had transplant deferred; and group 3 (VO_2 peak $<$ 14 mL/kg/min), with significant comorbidities that precluded heart transplantation. The 1-year survival rates in groups 1, 2, and 3 were 48%, 94%, and 47%, respectively. A VO_2 peak of $<$ 10 mL/kg/min was associated with significantly poorer predicted survival. The updated guidelines of American College of Cardiology/American Heart Association for the diagnosis and management of CHF in the adult[25] point out, however, that when VO_2 peak values are between 10 and 18 mL/kg/min, VO_2 peak is not enough to define prognosis in patients with heart failure. Indeed, there is no statistical difference in survival between heart failure patients with VO_2 peak between 10 and 14 mL/kg/min and those with VO_2 peak between 14 and 18 mL/kg/min. A cutoff of VO_2 peak $\leq$ 10 mL/kg/min is, however, used for cardiac transplant selection.[26] Other variables, such as the VO_2/work rate relationship, the VO_2/heart rate relationship, the VE/VCO_2 slope and the oxygen pulse, especially

when they are integrated with AT, have been more recently proposed as prognostic predictors more useful than VO_2 peak alone.[27,28] For instance, an AT of < 11 mL/kg/min (as determined by the V-slope method) together with VE/VCO_2 slope > 34 has been shown to be a better predictor of risk associated with early cardiac death than VO_2 peak alone in patients being prioritized for cardiac transplantation.[16]

Prognostic Preoperative Evaluation of Noncardiac Surgery by Cardiopulmonary Stress Test-Derived Variables

The updated guidelines of the European Society of Cardiology for preoperative cardiac risk assessment and perioperative cardiac management in noncardiac surgery[29] have indicated the cardiopulmonary stress test among preoperative noninvasive testing aimed at providing information on LV dysfunction and myocardial ischemia as a major determinant of adverse postoperative outcomes. This relies on the assumption that demands on the heart, lungs, and peripheral circulation to support the increased metabolic rate taking place perioperatively can be reproduced during exercise. Thus, a patient's capacity to increase oxygen delivery during exercise may correlate with the capacity to maintain organ system function after surgery. The guidelines have suggested VO_2 peak and AT are the most useful data from this test for the perioperative evaluation of noncardiac surgery. The thresholds for classifying patients as low risk for all noncardiac surgery are usually set at VO_2 peak > 15 mL/kg/min and a VO_2 at AT > 11 mL/kg/min. In a study of 204 patients undergoing lung resection, VO_2 peak > 20 mL/kg/min was a predictor of pulmonary complications, cardiac complications, and mortality, whereas VO_2 peak > 12 mL/kg/min was associated with a 13-fold higher rate of mortality.[30] McCullough and associates[31] assessed VO_2 peak in 109 bariatric patients undergoing laparoscopic Roux-en-Y gastric bypass surgery. In this study, patients were divided into tertiles based on their VO_2 peak. The authors observed the occurrence of complications (death, unstable angina, myocardial infarction, venous thromboembolism, renal failure, or stroke) in 16.6% of patients with VO_2 peak < 15.8 mL/kg/min (lowest tertile) and in only 2.8% of patients with VO_2 peak > 15.8 mL/kg/min. Hospital length of stay and 30-day readmission rates were highest in the lowest tertile. Table 2 summarizes the main studies that reported results on VO_2 peak and AT, finding them to be significant predictors in patients undergoing abdominal surgery.

...a patient's capacity to increase oxygen delivery during exercise may correlate with the capacity to maintain organ system function after surgery.

Conclusions

AT, measured with a variety of techniques, is useful in assessing hematological, respiratory, and cardiovascular diseases. Despite the existence of several methods for measuring the AT, each has different indications and reproducibility.

TABLE 2

Predictive Value of VO_2 Peak for Cardiopulmonary Complication After Abdominal Surgery

Study	Type of Surgery	Total Patients (N)	Outcome	Study Results
McCullough PA et al[31]	Roux-en-Y gastric bypass	109	Postoperative complications	Predictor (< 15.8 mL/Kg/min)
Carlisle and Swart[33]	AAA repair	130	Postoperative survival	Predictor (< 20 mL/Kg/min)
Epstein SK et al[34]	Hepatic transplantation	59	Postoperative survival	Predictor (< 60% predicted)
Forshaw MJ et al[35]	Oesophagectomy	78	Postoperative complications	Predictor (< 16 mL/Kg/min)
Nagamatsu Y et al[36]	Thoraco-laparotomy	52	Postoperative complications	Predictor (< 12 mL/Kg/min)
Nagamatsu Y et al[37]	Oesophagectomy	91	Postoperative complications	Predictor (< 13 mL/Kg/min)
Nugent AM et al[38]	AAA repair	36	Postoperative complications	Not a predictor[a]

[a]No significant difference between VO_2 peak 18.6 mL/Kg/min (complications group) and 21.8 mL/Kg/min (no complications group).
AAA, abdominal aortic aneurysm repair.

There is no doubt that the VAT plays a relevant role in interpreting the results obtained during a cardiopulmonary stress test. Higher values of carbon dioxide per unit of oxygen in patients with specific diseases that cause an inadequate oxygen supply to peripheral tissues indicate the presence of an early utilization of glycolysis as a means of ATP synthesis and, therefore, reflect an impairment in aerobic metabolism during exercise. Referring such patients for repeated cardiopulmonary stress tests over time would enable noninvasive and reproducible serial measurements of the VAT, thus allowing for proper monitoring of the disease and its therapy. ■

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References

1. Wasserman K, Hansen JE, Sue DY, et al. *Physiology of Exercise*. Lippincott Williams & Wilkins: Philadelphia, PA; 2005.
2. Svedahl K, Macintosh BR. Anaerobic threshold: the concept and methods of measurement. *Can J Appl Physiol*. 2003;28:299-323.
3. Wasserman K, McIlroy MB. Detecting the threshold of anaerobic metabolism in cardiac patients during exercise. *Am J Cardiol*. 1964;14:844-852.
4. Binder RK, Wonisch M, Corra U, et al. Methodological approach to the first and second lactate threshold in incremental cardiopulmonary exercise testing. *Eur J Cardiovasc Prev Rehabil*. 2008;15:726-734.
5. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol*. 1986;60:2020-2027.
6. Wasserman K, Beaver WL, Whipp BJ. Gas exchange theory and the lactic acidosis (anaerobic) threshold. *Circulation*. 1990;81(1 suppl):II14-II30.
7. Corrà U, Pistono M, Mezzani A, et al. Sleep and exertional periodic breathing in chronic heart failure: prognostic importance and interdependence. *Circulation* 2006;113:44-50.
8. Sue DY, Wasserman K, Moricca RB, Casaburi R. Metabolic acidosis during exercise in patients with chronic obstructive pulmonary disease. Use of the V-slope method for anaerobic threshold determination. *Chest*. 1988;94:931-938.
9. Cohen-Solal A, Zannad F, Kayanakis JG, et al. Multicentre study of the determination of peak oxygen uptake and ventilatory threshold during bicycle exercise in chronic heart failure. Comparison of graphical methods, interobserver variability and influence of the exercise protocol. The VO_2 French Study Group. *Eur Heart J*. 1991;12:1055-1063.
10. Simonton CA, Higginbotham MB, Cobb FR. The ventilatory threshold: quantitative analysis of reproducibility and relation to arterial lactate concentration in normal subjects and in patients with chronic congestive heart failure. *Am J Cardiol*. 1988;62:100-107.
11. Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis*. 1984;129(2 Pt 2):S49-S55.
12. Buskirk E, Taylor HL. Maximal oxygen intake and its relation to body composition, with special reference to chronic physical activity and obesity. *J Appl Physiol*. 1957;11:72-78.
13. deJong AT, Gallagher MJ, Sandberg KR, et al. Peak oxygen consumption and the minute ventilation/carbon dioxide production relation slope in morbidly obese men and women: influence of subject effort and body mass index. *Prev Cardiol*. 2008;11:100-105.
14. Capelli C, Antonutto G, Kenfack MA, et al. Factors determining the time course of VO2(max) decay during bedrest: implications for VO2(max) limitation. *Eur J Appl Physiol*. 2006;98:152-160.
15. Cohen-Solal A, Aupetit JF, Gueret P, et al. Can anaerobic threshold be used as an end-point for therapeutic trials in heart failure? Lessons from a multicentre randomized placebo-controlled trial. The VO2 French Study Group. *Eur Heart J*. 1994;15:236-241.
16. Gitt AK, Wasserman K, Kilkowski C, et al. Exercise anaerobic threshold and ventilatory efficiency identify heart failure patients for high risk of early death. *Circulation*. 2002;106:3079-3084.
17. Zafrir N, Fink G, Klainman E, et al. Relation between aerobic capacity and extent of myocardial ischemia in patients with normal cardiac function. *Am Heart J*. 1999;138:1088-1092.
18. Beniaminovitz A, Mancini DM. The role of exercise-based prognosticating algorithms in the selection of patients for heart transplantation. *Curr Opin Cardiol*. 1999;14:114-120.
19. Matsumura N, Nishijima H, Kojima S, et al. Determination of anaerobic threshold for assessment of functional state in patients with chronic heart failure. *Circulation*. 1983;68:360-367.
20. Itoh H, Taniguchi K, Koike A, Doi M. Evaluation of severity of heart failure using ventilatory gas analysis. *Circulation*. 1990;81(1 suppl):II31-II37.
21. Weber KT. Cardiopulmonary exercise testing and the evaluation of systolic dysfunction. In: Wasserman K, ed. *Exercise Gas Exchange in Heart Disease*. Armonk, NY: Futura Publishing; 1996:55-62.
22. Koike A, Hiroe M, Adachi H, et al. Anaerobic metabolism as an indicator of aerobic function during exercise in cardiac patients. *J Am Coll Cardiol*. 1992;20:120-126.
23. Stelken AM, Younis LT, Jennison SH, et al. Prognostic value of cardiopulmonary exercise testing using percent achieved of predicted peak oxygen uptake for patients with ischemic and dilated cardiomyopathy. *J Am Coll Cardiol*. 1996;27:345-352.
24. Mancini DM, Eisen H, Kussmaul W, et al. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation*. 1991;83:778-786.
25. Hunt SA. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol*. 2005;46:e1-e382.
26. Fleg JL, Piña IL, Balady GJ, et al. Assessment of functional capacity in clinical and research applications: an advisory from the Committee on Exercise, Rehabilitation, and Prevention, Council on Clinical Cardiology, American Heart Association. *Circulation*. 2000;102:1591-1597.
27. Arena R, Myers J, Abella J, et al. Development of a ventilatory classification system in patients with heart failure. *Circulation*. 2007;115:2410-2417.
28. Cattadori G, Salvioni E, Gondoni E, Agostoni P. Evaluation of noninvasive exercise cardiac output determination in chronic heart failure patients: a proposal of a new diagnostic and prognostic method. *J Cardiovasc Med (Hagerstown)*. 2011;12:19-27.

MAIN POINTS

- Anaerobic threshold (AT) can be determined by monitoring the lactic acid and/or bicarbonate levels in arterial and venous blood, or by measuring, during a cardiopulmonary stress test, the increase in oxygen consumption (VO_2) and carbon dioxide production (VCO_2) and their effects on ventilation (VE): that is, the ventilatory anaerobic threshold (VAT).
- During a cardiopulmonary stress test, measurement of the AT plays an important role, along with other parameters such as VO_2, VCO_2, heart rate, blood pressure, minute ventilation, respiratory rate, respiratory equivalent, ventilator reserve, and end-tidal volume at rest, during exercise, and at peak exercise.
- In general, all diseases that affect the oxygen transport chain from the ambient air to the mitochondria in skeletal muscle during exercise can influence the VAT behavior. If the VE/VCO_2 is normal, we can exclude a disease in the lung or the pulmonary circulation.
- A patient's capacity to increase oxygen delivery during exercise may correlate with the capacity to maintain organ system function after surgery.

29. Poldermans D, Bax JJ, Boersma E, et al. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery. *Eur Heart J*. 2009;30:2769-2812.
30. Brunelli A, Belardinelli R, Refai M, et al. Peak oxygen consumption during cardiopulmonary exercise test improves risk stratification in candidates to major lung resection. *Chest*. 2009;135:1260-1267.
31. McCullough PA, Gallagher MJ, Dejong AT, et al. Cardiorespiratory fitness and short-term complications after bariatric surgery. *Chest*. 2006;130:517-525.
32. American Thoracic Society/American College of Chest Physicians. ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med*. 2003;167:211-277.
33. Carlisle J, Swart M. Mid-term survival after abdominal aortic aneurysm surgery predicted by cardiopulmonary exercise testing. *Br J Surg*. 2007;94:966-969.
34. Epstein SK, Freeman RB, Khayat A, et al. Aerobic capacity is associated with 100-day outcome after hepatic transplantation. *Liver Transpl*. 2004;10:418-424.
35. Forshaw MJ, Strauss DC, Davies AR, et al. Is cardiopulmonary exercise testing a useful test before esophagectomy? *Ann Thorac Surg*. 2008;85:294-299.
36. Nagamatsu Y, Ono H, Hiraki H, et al. Evaluation of the exercise capacity recovery process after lung cancer surgery by exercise test and expire gas analysis [Article in Japanese] *Nihon Kyobu Geka Gakkai Zasshi*. 1994;42:228-232.
37. Nagamatsu Y, Shima I, Yamana H, et al. Preoperative evaluation of cardiopulmonary reserve with the use of expired gas analysis during exercise testing in patients with squamous cell carcinoma of the thoracic esophagus. *J Thorac Cardiovasc Surg*. 2001;121:1064-1068.
38. Nugent AM, Riley M, Megarry J, et al. Cardiopulmonary exercise testing in the pre-operative assessment of patients for repair of abdominal aortic aneurysm. *Ir J Med Sci*. 1998;167:238-241.