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Ventilatory efficiency and exercise tolerance in 101 healthy volunteers

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Abstract The ventilatory equivalent for CO_2 defines ventilatory efficiency largely independent of metabolism. An impairment of ventilatory efficiency may be caused by an increase in either anatomical or physiological dead space, the latter being the most important mechanism in the hyperpnoea of heart failure, pulmonary embolism, pulmonary hypertension and the former in restrictive lung disease. However, normal values for ventilatory efficiency have not yet been established. We investigated 101 (56 men) healthy volunteers, aged 16–75 years, measuring ventilation and gas exchange at rest ($n = 64$) and on exercise (modified Naughton protocol, $n = 101$). Age and sex dependent normal values for ventilatory efficiency at rest defined as the ratio ventilation:carbon dioxide output ($\dot{V}_E:\dot{V}CO_2$), exercise ventilatory efficiency during exercise, defined as the slope of the linear relationship between ventilation and carbon dioxide output ($\dot{V}_E$ vs $\dot{V}CO_2$ slope), oxygen uptake at the anaerobic threshold and at maximum ($\dot{V}O_{2AT}$, $\dot{V}O_{2max}$, respectively) and breathing reserve were established. Ventilatory efficiency at rest was largely independent of age, but was smaller in the men than in the women [$\dot{V}_E:\dot{V}CO_2$ 50.5 (SD 8.8) vs 57.6 (SD 12.6) $P < 0.05$]. Ventilatory efficiency during exercise declined significantly with age and was smaller in the men than in the women (men: ($\dot{V}_E$ vs $\dot{V}CO_2$ slope $= 0.13 \times \text{age} + 19.9$; women: $\dot{V}_E$ vs $\dot{V}CO_2$ slope $= 0.12 \times \text{age} + 24.4$). The $\dot{V}O_{2AT}$ and $\dot{V}O_{2max}$ were 23 (SD 5) and 39 (SD 7) ml $O_2 \cdot kg \cdot min^{-1}$ in the men and 18 (SD 4) and 32 (SD 7) in the women, respectively, and declined significantly with age. The $\dot{V}O_{2AT}$ was reached at 58 (SD 9)% $\dot{V}O_{2max}$. Breathing reserve at the end of exercise was 41% and was independent of sex and age. It was concluded from this study that ventilatory efficiency as well as peak oxygen uptake are age and sex dependent in adults.

Key words Ventilation · Exercise physiology · Ventilatory efficiency · Normal values · Oxygen uptake

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Introduction

The matching of ventilation and perfusion in the lungs is the primary determinant of ventilatory efficiency. This has been defined as the slope of the relationship between ventilation ($\dot{V}_E$) and carbon dioxide output ($\dot{V}CO_2$) during exercise (Reindl and Kleber 1996) and the $\dot{V}_E:\dot{V}CO_2$ ratio at rest. Its impairment has been recognized to contribute importantly to hyperpnoea and dyspnoea (Kleber et al. 1995; Reindl and Kleber 1996). The $\dot{V}_E$ versus $\dot{V}CO_2$ slope has been measured during cardiopulmonary exercise tests, yielding in addition values for oxygen uptake at the anaerobic threshold ($\dot{V}O_{2AT}$) and at maximal exercise (Weber et al. 1986) further to characterize patients with cardiac or pulmonary impairment of exercise capacity (Sullivan et al. 1988; Buller and Poole-Wilson 1990; Sullivan and Cobb 1990).

The interpretation of the results of exercise tests requires knowledge of the normal response (see Wasserman et al. 1986). Hitherto data reported have referred to the $\dot{V}_E:\dot{V}CO_2$ ratio at rest (White et al. 1983; MacGowan et al. 1995), at peak exercise (Davies et al. 1991; Hayashida et al. 1993), or at different levels of exercise

(Hansen et al. 1984; Clark et al. 1992; Treese et al. 1994). Normal values of the $\dot{V}_E$ versus $\dot{V}CO_2$ slope have been reported from only a few healthy volunteers from selected groups. Data using cycle exercise tests have been reported by Brischetto et al. (1984), Metra et al. (1992) and Wada et al. (1993), treadmill data have been reported by Lewis et al. (1992), Clark and Coats (1993) and Clark et al. (1994), and data in children by Cooper et al. (1987). The aim of our study was to acquire normal values for ventilatory efficiency and to establish correlations with age and sex.

Methods

Subjects

A group of 101 healthy volunteers aged 16–75 [mean 37 (SD 14)] years performed cardiopulmonary exercise tests. Of the total 45 of them were women [body mass 60 (SD 8) kg, height 165 (SD 6) cm, and 56 were men 78 (SD 12) kg and 179 (SD 9) cm]. All the subjects were free of cardiovascular or pulmonary disease, were normal on physical examination, and during pulmonary function tests, and had normal rest and exercise electrocardiograms. This study was approved by the institution's Ethics Committee. Written informed consent was obtained from all the volunteers.

Rest $\dot{V}_E:\dot{V}CO_2$

In 64 subjects $\dot{V}_E:\dot{V}CO_2$ at rest was determined (29 women and 35 men) after 5 min of quiet standing. After reaching a steady-state with a plateau of 3 min of gas exchange [O_2 uptake ($\dot{V}O_2$), $\dot{V}CO_2$, partial pressure of end-tidal oxygen, partial pressure of end-tidal carbon dioxide, and $\dot{V}_E$] $\dot{V}_E:\dot{V}CO_2$ at rest was determined as the mean of $\dot{V}_E:\dot{V}CO_2$ over the last of these 3 min.

Exercise tests

In every subject, a symptom-limited cardiopulmonary exercise test was performed on a treadmill according to the modified Naughton protocol (see Weber et al. 1982). This is an incremental exercise test on a treadmill with 2-min stages and increments in both gradient and velocity simulating increments of about one metabolic equivalent (approximately 3.5 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$) per stage. A Medical Graphics cardiopulmonary exercise system (MG CPX/D) was used, and expired gas was sampled through a Rudolph mask. For each subject deadspace as specified was adjusted individually. The expiratory gas was collected and conveyed to a spirometer and to oxygen and carbon dioxide detectors. The $\dot{V}O_2$, $\dot{V}CO_2$, instantaneous expiratory gas concentration throughout the respiratory cycle and $\dot{V}_E$ were measured continuously breath-by-breath.

Breathing reserve

Before starting exercise, in all the subjects forced expiratory volume in 1 s was measured and multiplied by the factor 41 to provide maximal voluntary ventilation (MVV, see Miller et al. 1987). The ratio of maximal ventilation ($\dot{V}_{Emax}$) during exercise and MVV gave information on the breathing reserve at end of exercise.

Maximal oxygen consumption

Maximal oxygen uptake ($\dot{V}O_{2max}$) was defined as the highest $\dot{V}O_2$ measured, always occurring well beyond the anaerobic threshold and mostly at a constant $\dot{V}O_2$ despite increasing exercise intensity and increasing $\dot{V}CO_2$. The $\dot{V}O_2$ at the anaerobic threshold of gas exchange ($\dot{V}O_{2AT}$) was detected by the $\dot{V}$ slope method (see Beaver et al. 1981; Wasserman et al. 1994), supplemented by the simultaneous observation of end-tidal gas concentrations.

Ventilatory efficiency

Ventilatory efficiency during exercise was measured by plotting $\dot{V}_E$ against $\dot{V}CO_2$. These plots revealed linear relationships ($r = 0.98$–0.99). The ventilatory efficiency during exercise was represented by the slope of all $\dot{V}_E$ versus $\dot{V}CO_2$ values for each individual during incremental exercise. The nonlinear portion of this relationship after the onset of the acidotic drive to the ventilation (see Kleber et al. 1995) was excluded.

Statistical analysis

All data are expressed as means and standard deviation unless otherwise indicated. Differences between both sexes were assessed using the Mann-Whitney test. Multiple regression analyses, using linear, logarithmic, and exponential models of the relationships $\dot{V}_E:\dot{V}CO_2$ and $\dot{V}_E$ versus $\dot{V}CO_2$ slope, $\dot{V}O_{2max}$, $\dot{V}O_{2AT}$, maximal exercise respiratory rate, breathing reserve and age were performed. Since the fit was no better using logarithmic compared to exponential models we always used the linear fit. A P value <0.05 was considered statistically significant.

Results

$\dot{V}_E:\dot{V}CO_2$ at rest

The rest $\dot{V}_E:\dot{V}CO_2$ was 50.5 (SD 8.8) in the men versus 57.6 (SD 12.6) in the women ($P < 0.05$). There was no influence of age. However, there was more variation among the younger age groups. No value above 60 was observed over the age of 35 years in either the men or the women.

Ventilatory efficiency during exercise

Ventilatory efficiency during exercise was different in the men as compared to the women (Figs. 1, 2). The $\dot{V}_E$ versus $\dot{V}CO_2$ slope correlated highly significantly with age. Linear regression equations are shown in Table 1, and the relationships are displayed in Figs. 1 and 2. The difference in ventilatory efficiency between the men and the women was largely caused by a lower intercept (19.9 vs 24.4) of the regression curve, age factors being similar (0.13 vs 0.12). However, it could not be proved that the regressions were parallel (F value 0.055; $P > 0.8$). Dis-

Table 1 Linear regression equations for the minute ventilation ($\dot{V}_E$) versus carbon dioxide production ($\dot{V}CO_2$) slope

Regression equation	Standard error	Correlation coefficient	Probability
Men $\dot{V}_E$ vs $\dot{V}CO_2$ slope $= 0.13 \times$ age $+ 19.9$	2.89	0.43	0.0012
Women $\dot{V}_E$ vs $\dot{V}CO_2$ slope $= 0.12 \times$ age $+ 24.4$	3.25	0.53	0.0004

Fig. 1 Exercise ventilatory efficiency as a function of age in the men. $\dot{V}_E$ vs $\dot{V}CO_2$ slope: slope of the linear relationship between ventilation and carbon dioxide output during exercise. Regression: $\dot{V}_E$ vs $\dot{V}CO_2$ slope = 0.13 age + 19.9; $r = 0.43$; $P = 0.001$. *Straight lines* 95% prediction limit, *curvilinear lines* 95% confidence limit, *x axis* age in years, *y axis* $\dot{V}_E$ vs $\dot{V}CO_2$ slope in l/lCO_2

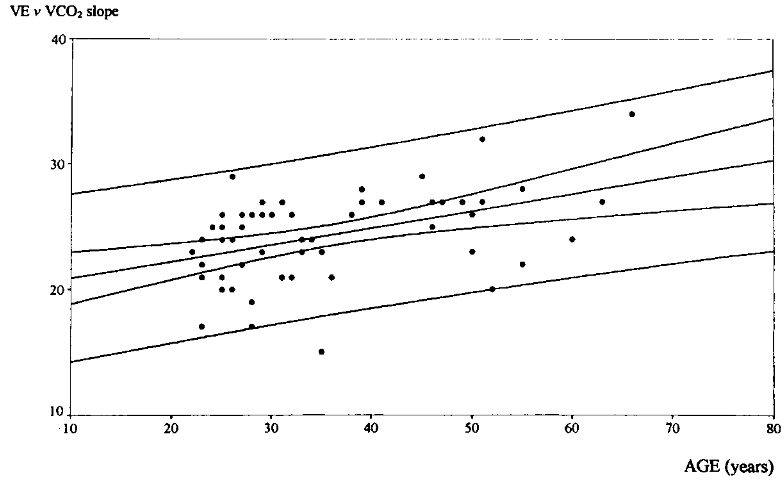


Fig. 2 Exercise ventilatory efficiency as a function of age in the women for abbreviations see Fig. 1. Regression: $\dot{V}_E$ vs $\dot{V}CO_2$ slope = 0.12 age + 24.4; $r = 0.53$, $P < 0.001$. *x axis* age in years, *y axis* $\dot{V}_E$ vs $\dot{V}CO_2$ slope in l/lCO_2

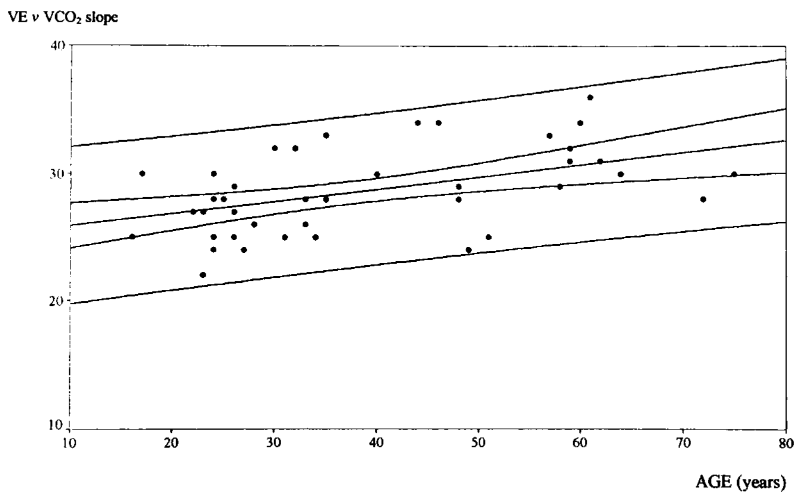
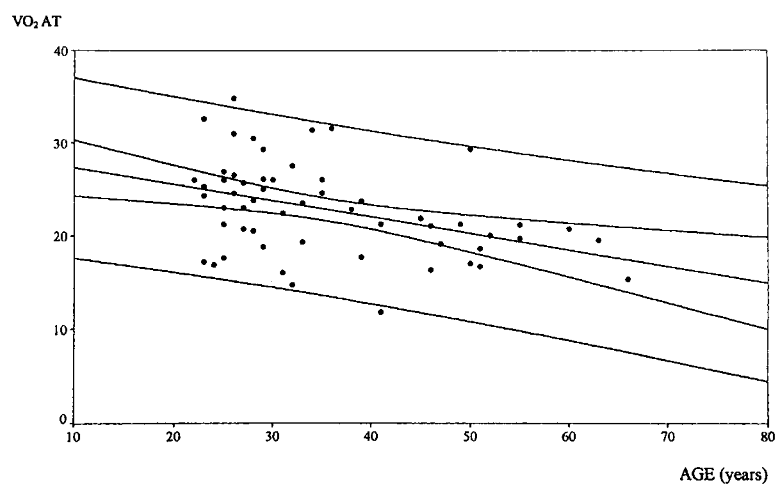


Fig. 3 Oxygen uptake at anaerobic threshold $\dot{V}O_{2AT}$ ($ml \cdot min^{-1} \cdot kg^{-1}$) as a function of age in men. Regression: $\dot{V}O_{2AT} = -0.17$ age + 28.6; $r = -0.41$; $P < 0.01$; *x axis* age in years, *y axis* $\dot{V}O_{2AT}$ in $ml \cdot kg^{-1} \cdot min^{-1}$



regarding the influences of age, the men had a $\dot{V}_E$ vs $\dot{V}CO_2$ slope of 24.5 (SD 3.6) and the women of 28.7 (SD 3.3) (difference $P < 0.001$).

$\dot{V}O_2$ during exercise

All 101 volunteers exercised until exhaustion. The $\dot{V}O_{2AT}$ and $\dot{V}O_{2max}$ max revealed a significant age dependency (in the men $r = -0.41$ and -0.59 respectively, $P < 0.01$ and 0.001 respectively; in the women

$r = -0.52$ and -0.67 respectively, $P < 0.001$ in both). Detailed results are given in Figs. 3–6 and average values for all age groups are shown in Table 2. Regression curves of the men and women were significantly different ($P < 0.001$). Exponential regression curves did not fit significantly better than the linear ones. Anaerobic threshold was reached at 58 (SD 9)% of $\dot{V}O_{2max}$ and this did not vary with age ($r = -0.21$; n.s.) or sex [men 59 (SD 10)%; women 57 (SD 8)%].

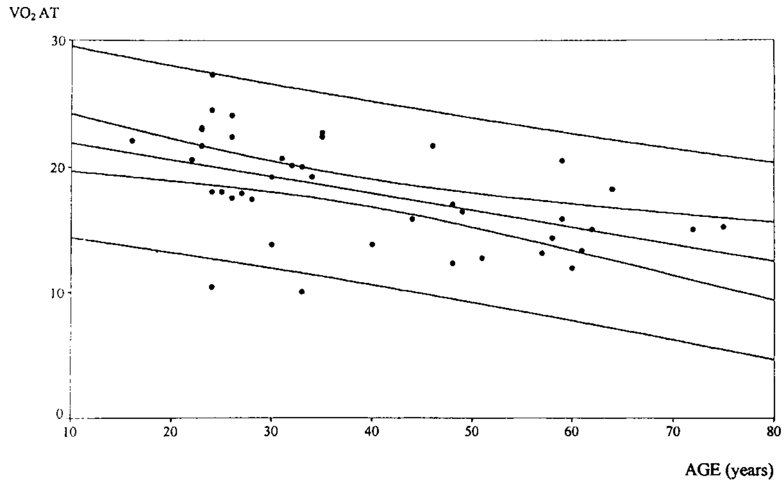


Fig. 4 Oxygen uptake at $\dot{V}O_{2AT}$ as a function of age in women, for abbreviations see Fig. 3. Regression: $\dot{V}O_{2AT} = -0.16$ age + 24.2. $r = -0.52$; $P < 0.001$; *x axis* age in years, *y axis* $\dot{V}O_{2AT}$ in $ml \cdot kg^{-1} \cdot min^{-1}$

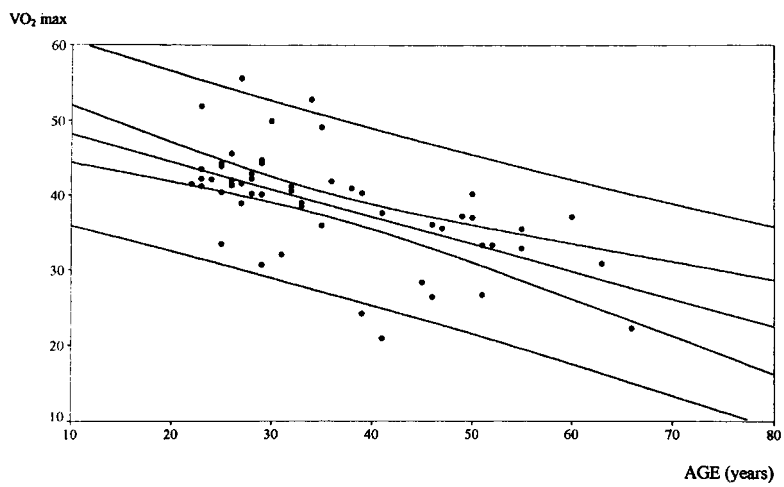


Fig. 5 Maximal oxygen uptake as a function of age in men. $\dot{V}O_2$ maximal oxygen uptake $ml \cdot kg^{-1} \cdot min^{-1}$. Regression: $\dot{V}O_{2max} = -0.36$ age + 51.5. $r = -0.59$, $P < 0.001$. *x axis* age in years, *y axis* $\dot{V}O_{2max}$ in $ml \cdot kg^{-1} \cdot min^{-1}$

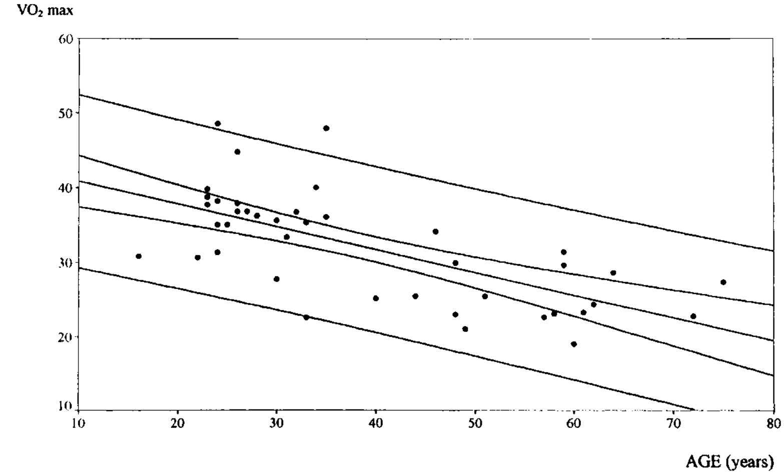


Fig. 6 Maximal oxygen uptake $\dot{V}O_{2max}$ as a function of age in women, for abbreviations see Fig. 5 Regression: $\dot{V}O_{2max} = -0.34$ age + 44.6; $r = -0.67$; $P < 0.001$ *x axis* age in years, *y axis* $\dot{V}O_{2max}$ in $ml \cdot kg^{-1} \cdot min^{-1}$

Table 2 Oygen uptake at anaerobic threshold ($\dot{V}O_{2AT}$) in men and women $\dot{V}O_{2max}$ maximal O_2 uptake

	$\dot{V}O_{2AT}$ (ml · kg^{-1} · min^{-1})		$\dot{V}O_{2max}$ (ml · kg^{-1} · min^{-1})	
	mean	SD	mean	SD
Women	18.0	4.2	32.2	7.4
Men	22.8	5.0	38.8	7.2

Ventilation

The $\dot{V}E_{max}$:MVV was uninfluenced by age or sex [0.58 (SD 0.132) in the men vs 0.593 (SD 0.108) in the women], leaving a breathing reserve of roughly 0.40 at the end of exercise. The respiratory rate at maximal exercise showed a wide range of 25–60 breaths · min^{-1}. There was no age or sex dependency [men 35 (SD 6) vs women 38 (SD 9) breaths · min^{-1}].

Discussion

It has been demonstrated that $\dot{V}_E$ is mainly driven by partial pressure of carbon dioxide in arterial blood (P_aCO_2, Wasserman et al. 1986). After the onset of anaerobic metabolism, the additional CO_2 derived from the buffering of lactate by bicarbonate ions leads to stimulation of $\dot{V}_E$ keeping P_aCO_2 close to normal limits. The efficiency of $\dot{V}_E$ independent of aerobic/anaerobic metabolism is therefore best measured as the $\dot{V}_E:\dot{V}CO_2$ or their slope during incremental exercise. This relationship remains particularly close until the occurrence of metabolic acidosis, which further stimulates $\dot{V}_E$ by decreasing the P_aCO_2 setpoint.

The impairment of ventilatory efficiency is caused by an increase in either anatomical or physiological dead space or by a decrease in the P_aCO_2 setpoint. Anatomical deadspace is raised particularly by increases in respiratory rate as in diseases with low tidal volumes and restrictive lung diseases. An increased physiological deadspace is the most important feature of the hyperpnoea in heart failure, pulmonary embolism and pulmonary hypertension. A decrease in the P_aCO_2 setpoint has been found in metabolic acidosis as a compensatory mechanism, and indirectly in cyanotic heart disease compensating for the CO_2 shunt (Wasserman et al. 1986). Given the large differences in ventilatory efficiency between health and disease – up to fivefold increases in $\dot{V}_E:\dot{V}CO_2$ have been described (Metra et al. 1992; Kleber et al. 1995) – it is important to establish normal values in a larger group of healthy volunteers.

Ventilatory efficiency

Only small numbers of healthy subjects have been investigated regarding ventilatory efficiency. Sullivan et al. (1988) have found the $\dot{V}_E:\dot{V}CO_2$ at rest to be around 36 and to decrease with exercise to 30. Cooper et al. (1987) have measured $\dot{V}_E:\dot{V}CO_2$ in children and described an age dependency of the differences (Δ), Δ $\dot{V}_E$ versus Δ $\dot{V}CO_2$ (identical to our $\dot{V}_E$ vs $\dot{V}CO_2$ slope) with body mass, height and age, which are interdependent in children. Hayashida et al. (1993) have described 37 normal subjects, aged 24–67 years, but measured ventilatory equivalents only at peak exercise. At peak exercise a further ventilatory drive due to acidosis is present and the $\dot{V}_E:\dot{V}CO_2$ is influenced by non-pulmonary factors such as a decrease in the P_aCO_2 setpoint. Hansen et al. (1984) have reported that in 77 men, mean age 54 years, they found a $\dot{V}_E:\dot{V}CO_2$ of 39 ± 10 at rest and of 29 ± 4 at anaerobic threshold (AT). Slight differences between our data and those in the literature might be explained by the influence of body posture. Our resting $\dot{V}_E:\dot{V}CO_2$ values were obtained in an upright, standing position, which would decrease perfusion of the apex of the lungs and thus render $\dot{V}_E$ less efficient. Treese et al. (1994) have found in

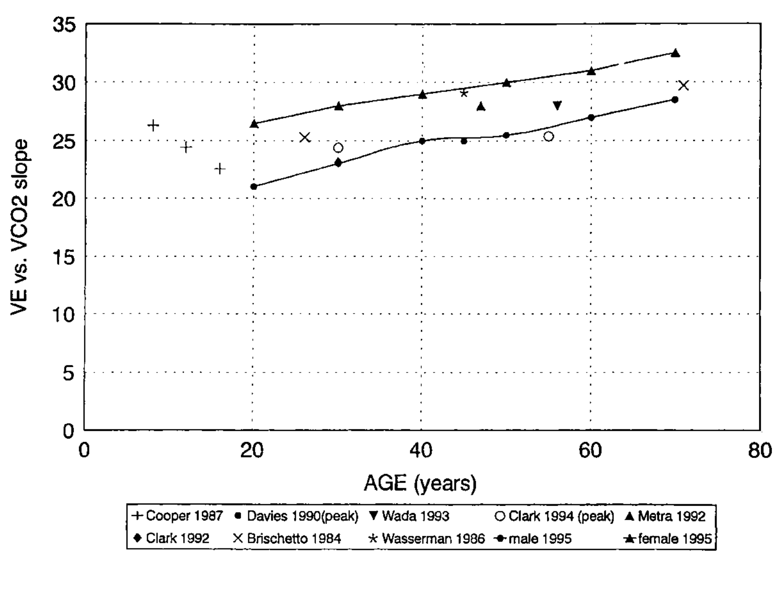


Fig. 7 $\dot{V}_E$ vs $\dot{V}CO_2$ slope as a function of age in comparison with the literature 1984–1995, for abbreviations see Figs. 1 and 5. *x axis* age in years, *y axis* $\dot{V}O_{2max}$ in ml · kg^{-1} · min^{-1}

39 healthy volunteers, aged 33–66 years a $\dot{V}_E : \dot{V}CO_2$ at the AT of 35 ± 8 in men and 39 ± 5 in women, corresponding well with our values for the $\dot{V}_E$ versus $\dot{V}CO_2$ slope for normal middle-aged persons (slope values are always somewhat smaller than minimal $\dot{V}_E : \dot{V}CO_2$ values due to the influence of the intercept of the relationship).

None of these studies has investigated the age dependency of ventilatory efficiency. Brischetto et al. (1984), however, have compared a group of 10 younger (22–37 years) and 10 older (76–79 years) persons and found significantly ($P < 0.05$) lower $\dot{V}_E$ versus $\dot{V}CO_2$ slopes in the younger, but have not looked at sex differences. By plotting the $\dot{V}_E$ versus $\dot{V}CO_2$ slopes or ratios against mean age of the populations investigated in studies published between 1984 and 1995, we have found that all data fit nicely with our present data, substantiating the age dependency over a wide range of populations (see. Fig. 7).

Although a decline in ventilatory efficiency with age seems obvious, the physiological basis remains unclear and needs further studies.

Exercise tolerance and age

The correlations between $\dot{V}O_2$, age, and sex have been identified in earlier large-scale studies both using treadmill (Bruce et al. 1973; Niederberger et al. 1974) and cycle exercise (Wasserman et al 1986; Astrand et al. 1973). The data presented here confirm these normal values.

We concluded from this study that as with $\dot{V}O_2$, ventilatory efficiency is different in men and women and declines with age in healthy adults. Although age dependency of ventilatory efficiency during exercise is less prominent than age dependency of $\dot{V}O_2$, normal values corrected for age and sex should be used in studies comparing health and disease.

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References

Astrand I, Astrand PO, Hallbäck I, Kilbom A (1973) Reduction in maximal oxygen uptake with age. J Appl Physiol 35:649–54

Beaver WL, Lamarra N, Wasserman K (1981) Breath-by-breath measurement of true alveolar gas exchange. J Appl Physiol 51:1662–75

Brischetto MJ, Millman RP, Peterson DD, Silage DA, Pack AI (1984) Effect of aging on ventilatory response to exercise and CO_2. J Appl Physiol 56:1143–50

Bruce RA, Kusumi F, Hosmer D (1973) Maximal oxygen intake and normographic assessment of functional aerobic impairment in cardiovascular disease. Am Heart J 85:546–562

Buller NP, Poole-Wilson PA (1990) Mechanism of the increased ventilatory response to exercise in patients with chronic heart failure. Br Heart J 63:281–283

Clark AL, Coats AJS (1993) Relationship between ventilation and carbon dioxide production in normal subjects with induced changes in anatomical dead space. Eur J Clin Invest 23:428–32

Clark A, Poole-Wilson PA, Coats AJS (1992) Relation between ventilation and carbon dioxide production in patients with chronic heart failure. J Am Coll Cardiol 20:1326–32

Clark AL, Swan JW, Laney R, Conelly M, Somerville J, Coats AJS (1994) The role of right and left ventricular function in the ventilatory response to exercise in chronic heart failure. Circulation 89:2062–69

Cooper DM, Kaplan MR, Baumgarten L, Weiler-Ravell D, Whipp BJ, Wasserman K (1987) Coupling of ventilation and CO_2 production during exercise in children. Pediatr Res 21:568–72

Davies SW, Emery TM, Watling MIL, Wannamethee G, Lipkin DP (1991) A critical threshold of exercise capacity in the ventilatory response to exercise in heart failure. Br Heart J 65:179–183

Hansen JE, Sue DY, Wasserman K (1984) Predicted values for clinical exercise testing. Am Rev Respir Dis 129:S49–S55

Hayashida W, Kumada T, Kohno F, Noda M, Ishikawa N, Kambayashi M, Kawai C (1993) Post-exercise oxygen uptake kinetics in patients with left ventricular dysfunction. Int J Cardiol 38:63–72

Kleber FX, Reindl I, Wernecke KD, Baumann G (1995) Dyspnea in heart failure. In: Wasserman K (ed) Exercise gas exchange in heart disease. Futura, Armonk, NY., pp 95–107

Lewis NP, MacDougall IC, Willis N, Henderson AH (1992) The ventilatory cost of exercise in chronic heart failure and chronic renal anaemia. Q J Med 83:523–31

MacGowan GA, Murali S, Cecchetti A, Janosko K, Uretsky BF (1995) Ventilatory abnormalities predict survival in congestive heart failure. First International Meeting of the Working Group on Heart Failure, Amsterdam, April 1–4 (abstract)

Metra M, Dei Cas L, Panina G, Visioli O (1992) Exercise hyperventilation in chronic congestive heart failure, and its relation to functional capacity and hemodynamics. Am J Cardiol 70:622–28

Miller WF, Scacci R, Gast LR (1987) Laboratory evaluation of pulmonary function. Lippincott, Philadelphia, p 300

Niederberger M, Bruce RA, Kusumi F, Whitkanack S (1974) Disparities in ventilatory and circulatory responses to bicycle and treadmill exercise. Br Heart J 36:377–82

Reindl I, Kleber FX (1996) Exertional hyperpnea in patients with chronic heart failure is a reversible cause of exercise intolerance. Basic Res Cardiol 91[Suppl 1]:37–43

Sullivan MJ, Cobb FR (1990) The anaerobic threshold in chronic heart failure, relation to blood lactate, ventilatory basis, reproducibility, and response to exercise training. Circulation 81[Suppl II]:II47–II58

Sullivan MJ, Higginbottam MB, Cobb FR (1988) Increased exercise ventilation in patients with chronic heart failure: intact ventilatory control despite hemodynamic and pulmonary abnormalities. Circulation 77:552–559

Treese N, Akbulut Ö, Coutinho M, Epperlein S, Meyer J (1994) Halbliegende kardiopulmonale Belastung bei Herzgesunden mittleren Alters. Z Kardiol 83:138–45

Wada O, Asanoi H, Miyagi K, Ishikaza S, Kameyama T, Seto H, Sasayama S (1993) Importance of abnormal lung perfusion in excessive exercise ventilation in chronic heart failure. Am Heart J 125:790–98

Wasserman K, Hansen JE, Sue DY, Whipp BJ (eds) (1986) Principles of exercise testing and interpretation. Lea and Febiger, Philadelphia, pp 27–46

Wasserman K, Stringer WW, Casaburi R, Koike A, Cooper CB (1994) Determination of the anaerobic threshold by gas exchange: biochemical considerations, methodology and physiological effects. Z Kardiol 83 [Suppl III]:1–12

Weber KT, Kinasewitz GT, Janicki JS, Fishman AP (1982) Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. Circulation 65:1213–23

Weber KT, Janicki JS, McElroy PA (1986) Cardiopulmonary exercise (CPX) testing. Physiologic principles and clinical applications. Saunders, Philadelphia, pp 151–167

White DP, Douglas NJ, Pickett CK, Weil JV, Zwillich CW (1983) Sexual influence on the control of breathing. J Appl Physiol 54:874–879