UNIVERSITA' DEGLI STUDI DI PARMA

Dottorato di Ricerca in Fisiopatologia Respiratoria Sperimentale

XXII Ciclo

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CARDIOPULMONARY RESPONSE TO EXERCISE IN HEALTH AND DISEASE

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ABSTRACT

Exercise leads to increased metabolic request and this represents a challenge for the cardiopulmonary system, which must guarantee O_2 and CO_2 transfer and exchange. Ventilation (V_E) and circulation are responsible for gas transfer, whereas gas exchange is due to both pulmonary and cellular diffusion.

At rest, muscle work is limited to that of the heart and the respiratory and bowel muscles. During exercise limb muscles work is added and leads to an increase in adenosine triphosphate (ATP) request and oxygen consumption ($V'O_2$) and carbon dioxide production ($V'CO_2$). As the exercise intensifies, the aerobic metabolism can not supply all the ATP quantity requested. Consequently, the anaerobic metabolism takes over, leading to increased lactic acid output.

In healthy sedentary subjects, who perform a maximal exercise, V_E values range from 5-10 L/min at rest to 80-100 L/min at peak of exercise. Cardiac output (CO) increases linearly as external work increases, from 4-6 L/min at rest to 20 L/min at peak of exercise. In healthy sedentary subjects the factors which lead to exercise limitation are reaching the maximal CO, and consequently the maximal capacity of gas transfer to tissues, and depletion of glycogen stocks.

In heart and respiratory diseases, the cardiopulmonary exercise test (CPET) provides an overall assessment of functional capacity and allows to evaluate disease severity, prognosis and therapeutic interventions. Both in respiratory and cardiac patients exercise intolerance reflects integrated abnormalities of the ventilatory, cardiovascular, peripheral muscle, and neurosecretory systems. The

CPET is able to identify which dysfunctional component impacts exercise capacity to the greatest extent.

ABBREVIATIONS

$A\text{-}aDO_2$ = alveolar-capillary oxygen gradient

AT = anaerobic threshold

ATP = adenosine triphosphate

CaO_2 = arterial oxygen content

CO = cardiac output

CPET = cardiopulmonry exercise test

CvO_2 = venous oxygen content

EELV = end-expiratory lung volume

EILV = end-inspiratory lung volume

HF = heart failure

HR = heart rate

PO_2 = oxygen partial pressure

RR = respiratory rate

SV = stroke volume

T_E = expiratory time

T_I = inspiratory time

VC = vital capacity

$V'CO_2$ = carbon dioxide production

V_D = dead space

V_E = ventilation (L/min)

$V'O_2$ = oxygen consumption

V_T = tidal volume

Exercise physiology

Exercise leads to increased metabolic request and this represents a challenge for the cardiopulmonary system, which must guarantee O_2 and CO_2 transfer and exchange. At the same time, in the face of increased metabolic demands the objective of the cardiorespiratory system is to minimize the increase in work performed by the heart and respiratory muscles.

Gas transport and exchange at rest

Ventilation (V_E) and circulation are responsible for gas transfer, whereas gas exchange is due to both pulmonary and cellular diffusion [1,2] (fig.1). V_E can be considered as the product of respiratory rate (RR) and tidal volume (V_T). V_E supplies continuously O_2 to the lungs and removes CO_2 to the atmosphere. A part of the lungs, called dead space (V_D), does not participate to gas exchange. Dead space comprises conduction airways (anatomic dead space) and alveoli with low or no perfusion (alveolar dead space). Pulmonary diffusion is responsible for O_2 and CO_2 exchange between alveoli and pulmonary blood vessels. The exchange occurs because of passive diffusion, which is determined by the barometric gradients of O_2 and CO_2 (60-65 mmHg for O_2 and 5 mmHg for CO_2) [1], diffusivity (CO_2 is twenty-fold more diffusible than O_2), surface (70 m^2) and thickness (0,4-2 μ) of the alveolar-capillary interface. The transit time of red cells through pulmonary vessels is 0.75 seconds and O_2 diffusion occurs in 0,25 seconds. At the end of the exchange, the barometric

gradients between alveoli and pulmonary blood vessels are 5-10 mm Hg for O_2 and 0 for CO_2 [3].

The cardiovascular system transfers O_2 from lungs to tissues and viceversa for CO_2. The cardiac output (CO), which can be considered as the product of stroke volume (SV) and heart rate (HR), pushes the blood from the heart to the circulatory system. The volume of O_2 transferred each minute to the tissues equals to the product of CO and arterial O_2 content (CaO_2). A part of the transferred oxygen is released to tissues, whereas another one returns to the heart. The quantity of O_2 which returns to the heart is equal to the product of CO and venous O_2 content (CvO_2). The difference between these two components [$CO(CaO_2)-(CvO_2)$] represents O_2 consumption ($V'O_2$) by tissues. Cellular diffusion allows gas exchange between blood vessels and cells, where oxygen consumption ($V'O_2$) and carbon dioxide production ($V'CO_2$) are 250 mL/min and 200 mL/min respectively, at rest.

Physiologic response to exercise

At rest, muscle work is limited to that of the heart and the respiratory and bowel muscles. During exercise limb muscles work is added and leads to an increase in adenosine triphosphate (ATP) request and $V'O_2$ and $V'CO_2$ (fig. 2). As the exercise intensifies, the aerobic metabolism can not supply all the ATP quantity requested. Consequently, the anaerobic metabolism takes over, leading to increased lactic acid output. The anaerobic metabolism is less efficient than the

aerobic one, since the glycolytic oxidative process produces 36 ATP molecules, in contrast to the anaerobic one, which produces only two.

Normally, during a progressively incremental exercise $V'O_2$ increases nearly linearly as external work increases, up to seven to eight-fold the rest value (fig. 3). $V'CO_2$ varies in line with $V'O_2$, but overtakes $V'O_2$ increase above the point of anaerobic threshold (AT) (fig. 3). In normal individuals the AT occurs at about 50% ± 10 of maximal $V'O_2$. In general, after the AT is reached, subjects may complain of dyspnoea and/or leg fatigue. In order to support the augmented metabolic demands of exercising muscles, V_E and CO increase during exercise.

At the beginning of exercise V_E increases before a significant increase in $V'O_2$ and $V'CO_2$, then increases linearly until the AT [4,5] (fig. 4). Afterward, the rise in V_E is superior to that of the workload, in order to balance the $V'CO_2$ increase due to the anaerobic metabolism (fig. 4). In healthy sedentary subjects, who perform a maximal exercise, V_E values range from 5-10 L/min at rest to 80-100 L/min at peak of exercise. The rise in V_E with exercise is associated with an increase in both depth and frequency of breathing (fig. 4). In health, increases in V_T are primarily responsible for increases in ventilation during low levels of exercise. As exercise progresses, both V_T and RR increase until 70 to 80% of peak exercise; thereafter RR predominates [1]. Younger adults typically increase V_T by three- to fivefold whereas in older adults V_T tends to increase two- to four-fold (from 0.5-1.0L at rest, which is 10% of vital capacity, to 2.3-3.0 L, which is 50% of vital capacity) [6]. In healthy subjects, the increase in V_T is due to both a

decrease in end-expiratory lung volume (EELV), but predominantly to an increase in end-inspiratory lung volume (EILV) through a decrease in the inspiratory reserve volume [7]. RR typically increases one- to three-fold in most subjects (from 12-16 apm to 40-50 apm). The increase in RR with exercise reflects a decrease in both inspiratory (T_I) and expiratory (T_E) time. Typically, however, at the moderate to higher ventilatory demands, a greater fractional decrease is noted in T_E, so that T_I/T_{tot} increases from 0.4 at rest to 0.5-0.55 at maximal exercise.

CO increases with exercise, leading to an improved alveolar perfusion, so that the alveolar V_D decreases. At peak exercise the transit time of red cells through pulmonary vessels is 0.38 seconds, however, in healthy subjects gas exchange is still efficient. The alveolar-capillary O_2 gradient (A-aDO_2) may be amplified during intense exercise up to 20 mmHg [8,9]. Indeed, alveolar O_2 partial pressure (PO_2) increases with V_E, especially above the AT [10]. However, the arterial PO_2 does not vary, thus the A-aDO_2 increases [11]. Arterial PO_2 does not increase because of the low venous PO_2, due to high O_2 extraction from tissues.

CO increases linearly as external work increases, from 4-6 L/min at rest to 20 L/min in healthy sedentary subjects (fig. 5). Increases in CO are initially accomplished by increases in SV and HR, and then at moderate-to-high intensity exercise almost exclusively by increases in HR (fig. 5). The increase in CO is largely driven by vagal withdrawal and by increases in circulating or

neurally produced cathecolamines. In healthy subjects, the SV is 50-80 ml at rest and redoubles at peak exercise. HR increases nearly linearly with increasing $V'O_2$ up to 2.5-4 times as much as the rest value.

The exercise ends when intolerable perception of either leg fatigue or dyspnoea occurs. In healthy sedentary subjects the factors which lead to exercise limitation are reaching the maximal CO, and consequently the maximal capacity of gas transfer to tissues, and depletion of glycogen stocks [12,13].

Exercise limitations in heart failure

Heart failure (HF) is a multiorgan syndrome. The cardiopulmonary exercise test (CPET) provides an overall assessment of functional capacity and allows to evaluate disease severity, prognosis and therapeutic interventions. The CPET is also able to identify which dysfunctional component impacts exercise capacity in HF to the greatest extent. Several organs can be the limiting factor of exercise in HF [14]. As a consequence, there is not a single parameter at rest which can predict exercise capacity.

The heart is the organ from which HF starts. However, when HF is overt, it may not be the leading cause of exercise limitation. In the presence of exercise limitation a prevalence of cardiac dysfunction is suggested by a reduced $V'O_2$ at anaerobic threshold, a decreased HR difference between rest and peak exercise, a reduction in O_2 maximum pulse and a reduced slope of $V'O_2$/workload relationship [15,16]. Because of a reduction in oxygen delivery to the muscles, energy is provided by anaerobic pathways even at low workload, which determines an early AT. The difference between rest and peak exercise HR is reduced because resting HR is higher than in healthy subjects, unless patients are treated with β-blockers, and because peak exercise HR is low due to chronotropic incompetence or treatment. The O_2 pulse is clinically utilized as an index of SV. Infact, the O_2 pulse can be considered as the product of SV and arteriovenous O_2 difference, thereby being related to SV. A reduced

$V'O_2$/workload relationship slope through the exercise is an index of reduced CO response to exercise.

Moreover, alteration in peripheral circulation can contribute to limiting exercise capacity in HF, since fluid accumulates both inside the vascular wall and in the tissues, increasing the distance between capillary and mitochondria. However, no specific parameters derived from CPET can be used to suggest a peripheral circulatory alteration in HF.

HF patients develop a skeletal and respiratory myopathy, due to inactivity, malnutrition and increase of inflammatory status, which not only induces fatigue and dyspnoea, but also increases ventilation and peripheral vasoconstriction through an increased sympathetic activity [17,18]. Accordingly, elements which suggest that the peripheral muscles are the major cause of exercise limitation are symptoms such as leg fatigue and a reduced $V'O_2$/workload slope.

In HF patients, respiratory function during exercise can be impaired because of mechanical and diffusion alterations [16]. The former is characterized by an increase in V_E due to reduction in V_T and increase in RR [19]. The increase in V_E is relative to work rate, $V'O_2$ and $V'CO_2$. As a consequence, HF patients may present an elevated ratio of ventilation to CO_2 production ($V_E/V'CO_2$) during exercise. The abnormal increase in $V_E/VC'O_2$ slope may be due to several factors, including the earlier onset of metabolic acidosis and a disproportionately high dead space from poor pulmonary perfusion [16,20].The parameters which

suggest lung mechanical alterations are increased V_E, reduced V_T, increased V_D/V_T ratio and increased RR. Also lung diffusion is altered in HF. Indeed, albeit the capillary blood volume increase during exercise, this is not enough to compensate the specific membrane diffusive capability reduction. This is likely due to increase in fibrosis and cellular content at the alveolar-capillary membrane. Furthermore, lung diffusion increase during exercise is blunt in HF patient.

Exercise limitations in respiratory patients

In respiratory patients exercise intolerance reflects integrated abnormalities of the ventilatory, cardiovascular, peripheral muscle, and neurosecretory systems [21]. Ventilatory limitation is often the predominant contributor to exercise intolerance, while at the same time cardiac and other physiological functions are operating below maximal capacity. One of the distinguishing features of respiratory patients is a reduced ventilatory reserve, signaling a significant ventilatory contribution to exercise limitation. The breathing strategy adopted by respiratory patients during exercise includes a higher RR and a lower V_T compared with healthy subjects.

In COPD patients the crucial abnormality is expiratory flow limitation (EFL) due to combined reduced lung recoil as well as airway narrowing. When EFL reaches a critical level, lung emptying becomes incomplete, EELV increases and patients experience air trapping [22,23,24]. This phenomenon is known as exercise dynamic hyperinflation. When breathing at a high dynamic EELV the pressure generating capacity of the inspiratory muscles and, thus, the ability to generate inspiratory flow, may be compromised [22]. An important mechanical consequence of dynamic hyperinflation is a limitation on V_T expansion during exercise. Moreover, in flow-limited patients, inspiration begins before tidal lung emptying is complete and the inspiratory muscles must first counterbalance the combined recoil at the lung and chest wall before inspiratory flow is initiated.

This phenomenon is associated with positive intrapulmonary pressures at the end of expiration and may have important implications for dyspnoea perception.

Peripheral muscle dysfunction is another potential cause of exercise intolerance [18,25,26,27]. Abnormalities of peripheral muscle structure and function, such as loss of muscle mass and mitochondrial compromised oxidative phosphorylation have been described [28]. Muscle biopsies have shown reduced capillarization, reduction in type 1 high oxidative, fatigue-resistant fibers and increase in type 2 fibers, which are characterized by low mechanical efficiency and increased fatigability [29].

In respiratory patients arterial hypoxemia during exercise commonly occurs, as a result of the effect of a fall in mixed venous O_2 tension on low ventilation-perfusion lung units, and shunting [30,31]. Both the ability to increase lung perfusion and to distribute inspired ventilation throughout the lungs during exercise is compromised. Resting physiological dead space is often increased, reflecting ventilation-perfusion inequalities, and fail to decline further during exercise. Inefficient ventilation due primarily to increased V_D/V_T and also hyperventilation due to hypoxemia and mechanoreceptor stimulation are usually observed throughout exercise. Hypoxemia not only contributes to the exaggerated ventilatory response, but may also contribute to reduced O_2 delivery primarily through a reduced O_2 content and also via hypoxic vasoconstriction.

Cardiovascular abnormalities are common and reflect pulmonary vascular and right ventricular dysfunction [32,33]. Pulmonary artery pressures and right ventricular afterload are generally higher than in healthy subjects, because of the increased vascular resistance. The left ventricular ejection fraction is generally preserved, whereas left ventricular diastolic function may be impaired due to ventricular interdependence; infact, increased tension or displacement of the right ventricle may impede left diastolic filling. Left ventricular afterload is also increased during exercise, because the left-ventricular transmural pressure gradient is increased as a result of progressively negative intrathoracic pressure generation. Consequently, in respiratory patients low peak HR responses are usually observed, thus HR reserve may be increased or normal and O_2 pulse reduced.

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FIGURES

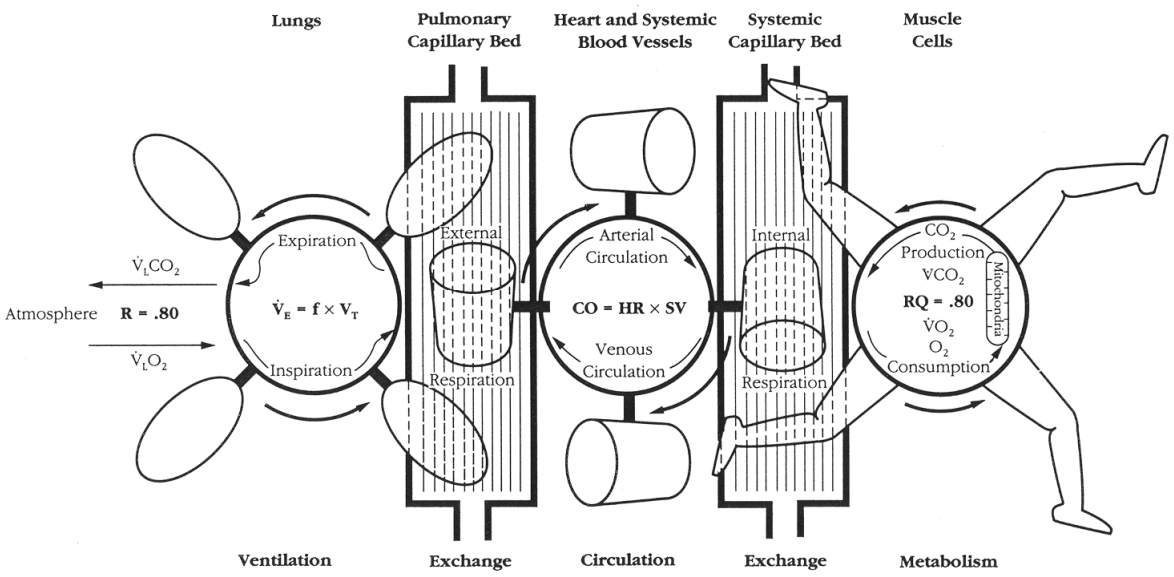

Figure 1. Relationship among physiologic mechanisms which support muscles work at rest.

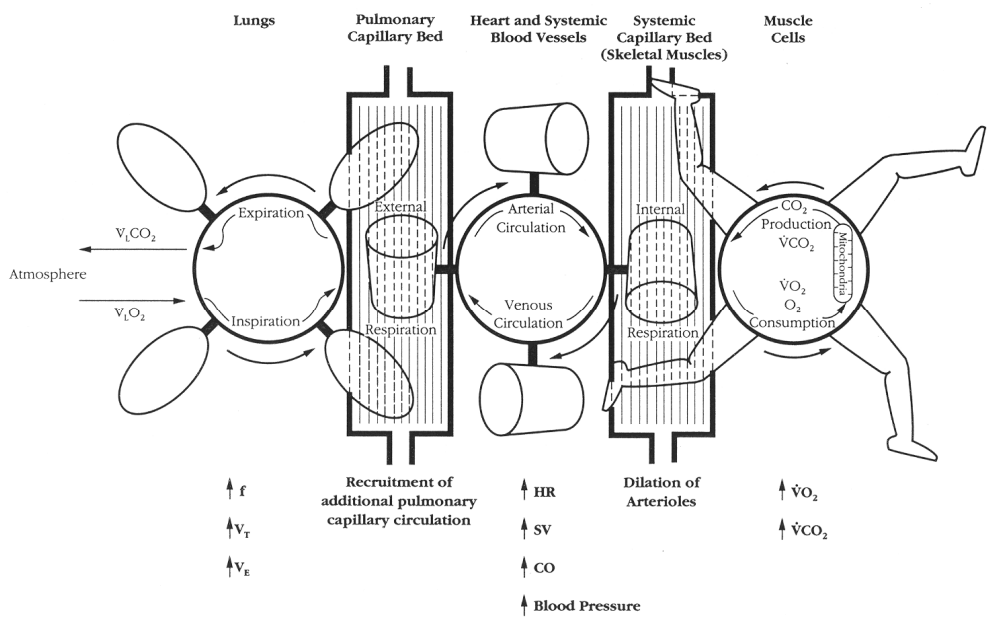

Figure 2. Physiologic response to exercise.

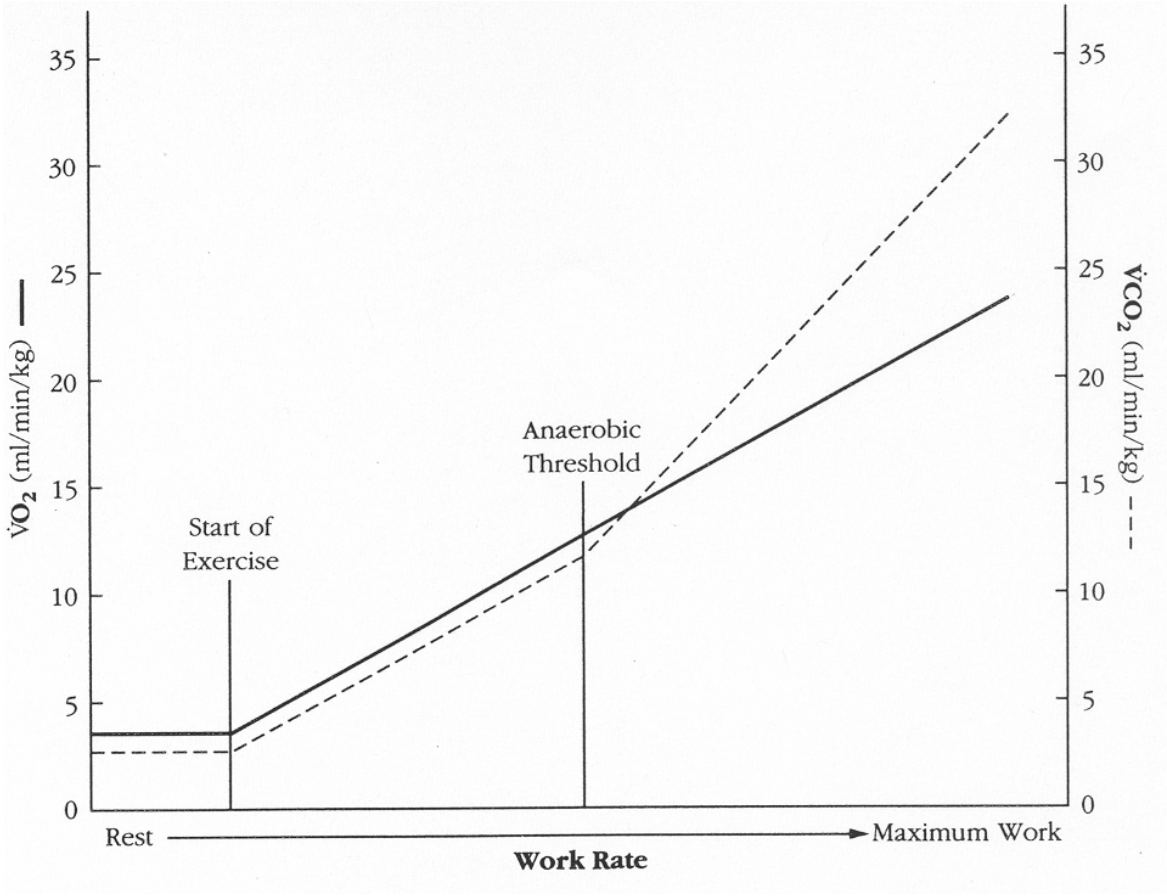

Figure 3. Metabolic parameters during a progressively incremental maximal exercise.

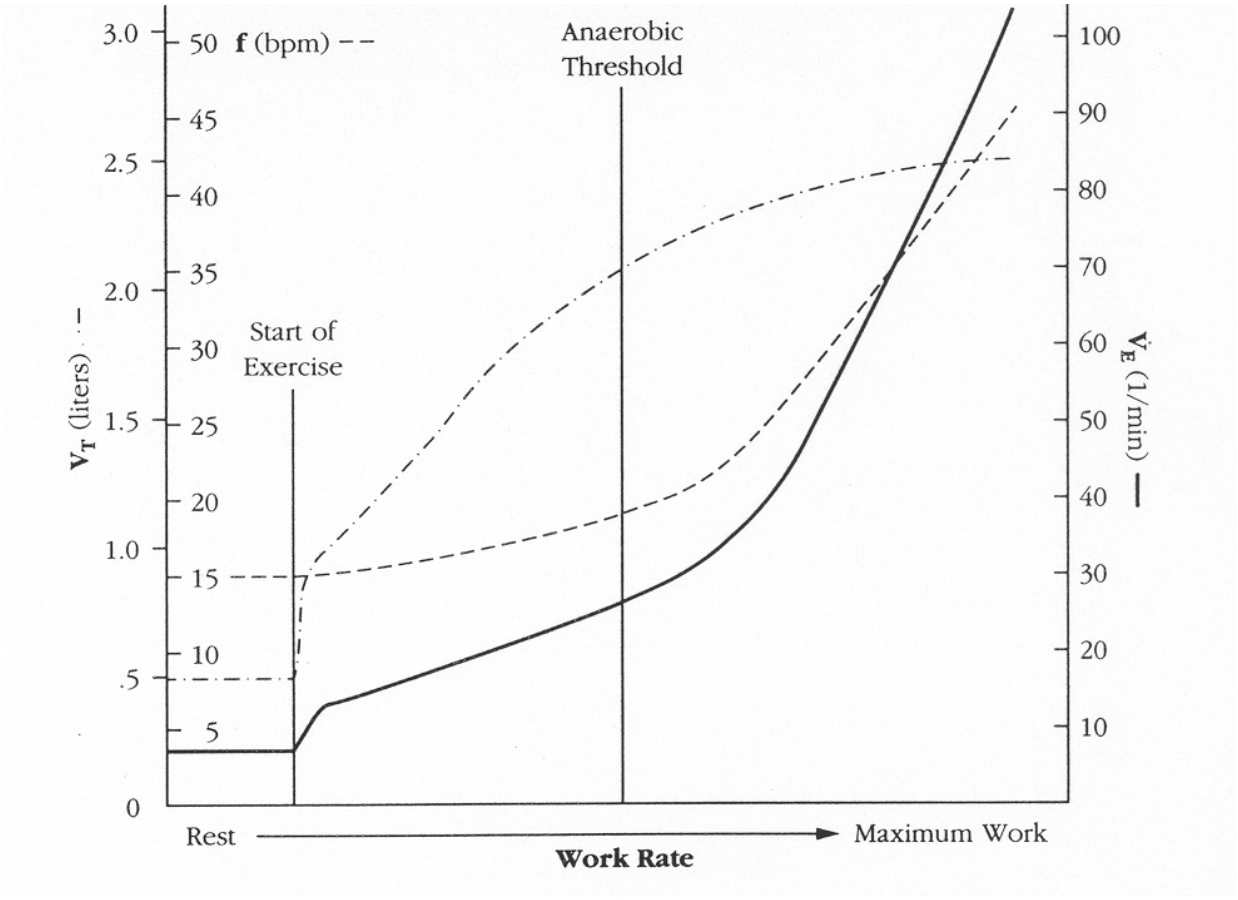

Figure 4. Ventilatory parameters during a progressively incremental maximal exercise.

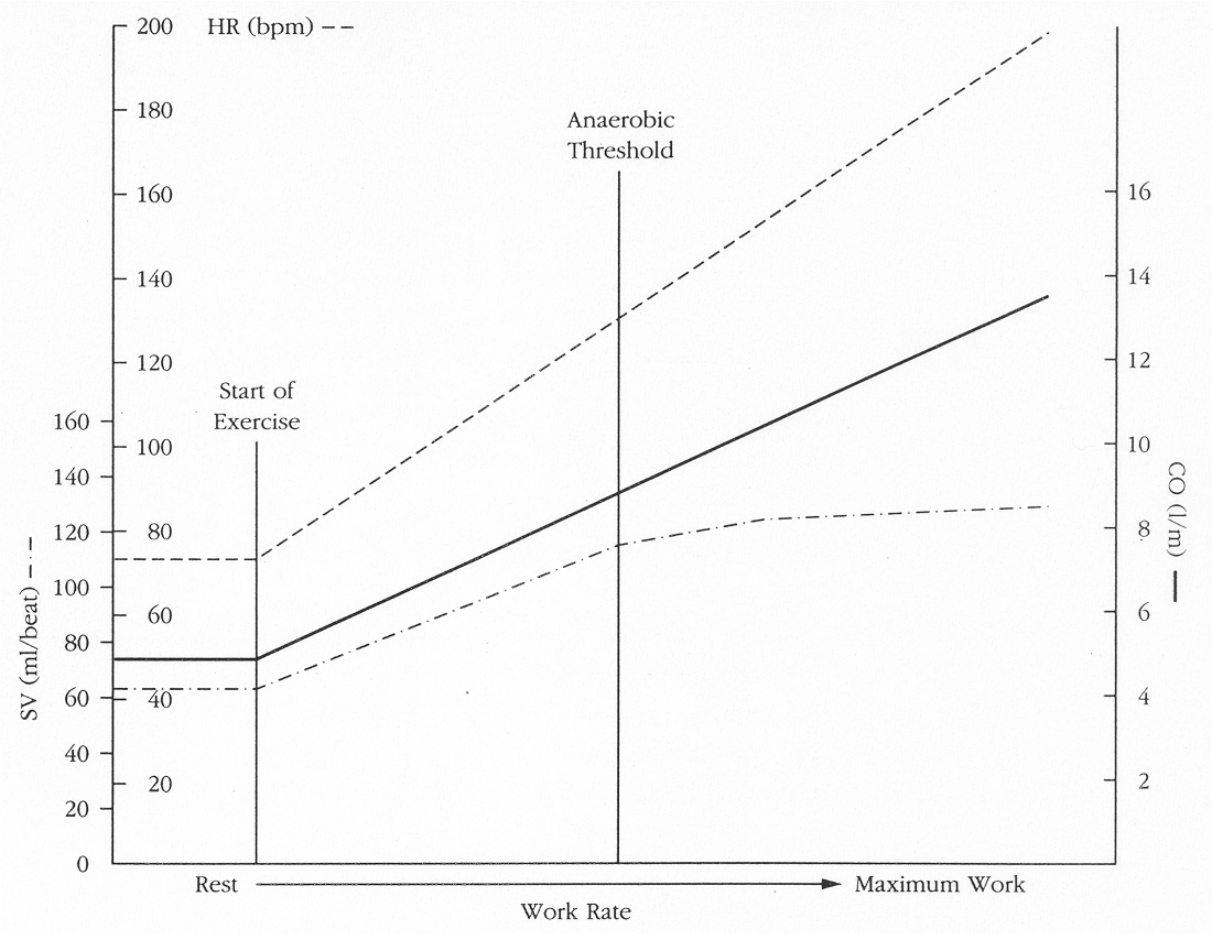

Figure 5. Cardiovascular parameters during a progressively incremental maximal exercise.

PAPERS

During her Doctorship Dr Panagiota Tzani has published the following papers relative to exercise capacity:

1. **P. Tzani**, M.F. Piepoli, F. Longo, M. Aiello, W. Serra, A.R. Maurizio, D. Olivieri, A. Chetta. “Resting Lung Function in the Assessment of the Exercise Capacity in Patients with Chronic Heart Failure”. *Am J Med Sci* 2010; in press.
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