



Διαγνωστική προσέγγιση πνευμονικής υπέρτασης



Εργοσπιρομετρία



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Φυσιολογία της άσκησης

Βασικές αρχές

ΚΥΚΛΟΦΟΡΙΚΟ

Αύξηση HR, BP συσταλτικότητας και μείωση των ολικών περιφερικών αντιστάσεων

➡ **Αύξηση CI x 4-6 φορές**

ΑΝΑΠΝΕΥΣΤΙΚΟ

Αύξηση κυψελιδικού αερισμού ➡ **Αύξηση πρόσληψης οξυγόνου (VO_2)**

Να σημειωθεί ότι η διέγερση του ΣΝΣ ξεκινά κατά τη διάρκεια της αναμονής του ατόμου για την άσκηση (μικρού βαθμού αύξηση της καρδιακής συχνότητας και του αριθμού των αναπνοών).

Υποβάλλοντας ένα υγιές άτομο σε άσκηση παρατηρείται μέγιστη διέγερση του ΣΝΣ και απελευθέρωση κατεχολαμινών:

Exercise Pathophysiology in Patients With Primary Pulmonary Hypertension

Xing-Guo Sun, MD; James E. Hansen, MD; Ronald J. Oudiz, MD; Karlman Wasserman, MD, PhD

Background—Patients with primary pulmonary hypertension (PPH) have a pulmonary vasculopathy that leads to exercise intolerance due to dyspnea and fatigue. To better understand the basis of the exercise limitation in patients with PPH, cardiopulmonary exercise testing (CPET) with gas exchange measurements, New York Heart Association (NYHA) symptom class, and resting pulmonary hemodynamics were studied.

Methods and Results—We retrospectively evaluated 53 PPH patients who had right heart catheterization and cycle ergometer CPET studies to maximum tolerance as part of their clinical workups. No adverse events occurred during CPET. Reductions in peak O₂ uptake ($\dot{V}O_2$), anaerobic threshold, peak O₂ pulse, rate of increase in $\dot{V}O_2$, and ventilatory efficiency were consistently found. NYHA class correlated well with the above parameters of aerobic function and ventilatory efficiency but less well with resting pulmonary hemodynamics.

Conclusions—Patients with PPH can safely undergo noninvasive cycle ergometer CPET to their maximal tolerance. The CPET abnormalities were consistent and characteristic and correlated well with NYHA class. (*Circulation*. 2001;104:429-435.)

Key Words: oxygen ■ hypertension, pulmonary ■ ventilation ■ exercise ■ hemodynamics

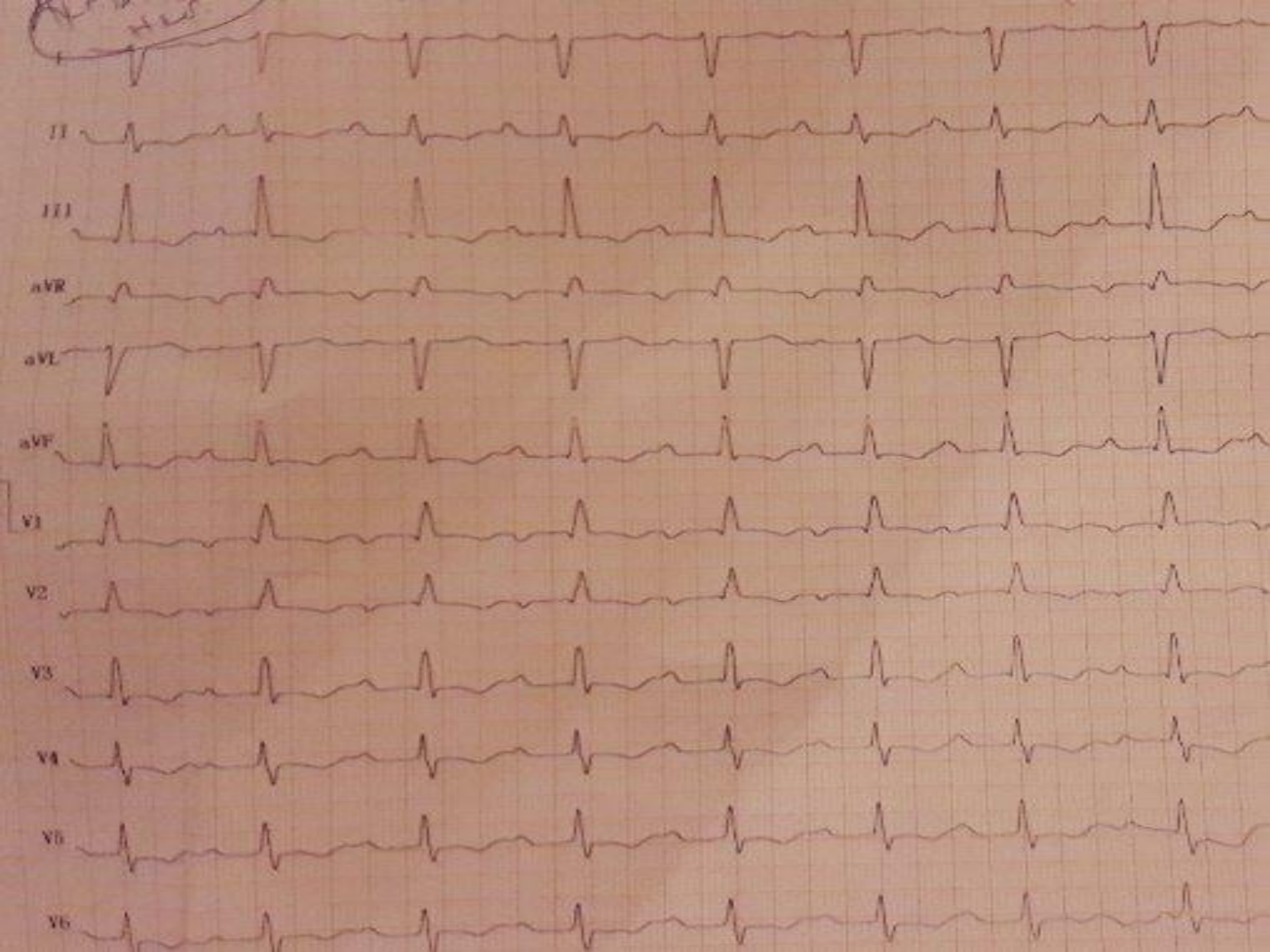
Patients with PAH mainly complain of **dyspnea and/or fatigue during exercise** due to:

- a. **HEART:** Impaired right ventricular systolic function, right ventricle dilatation and IVS systolic movement to the left lead to **decreased cardiac output** and oxygen supply to periphery.
- b. **LUNGS:** Increased PVR and subsequent decreased pulmonary vasodilator response lead to **inefficient lung gas exchange**.



Ιατρικό ιστορικό

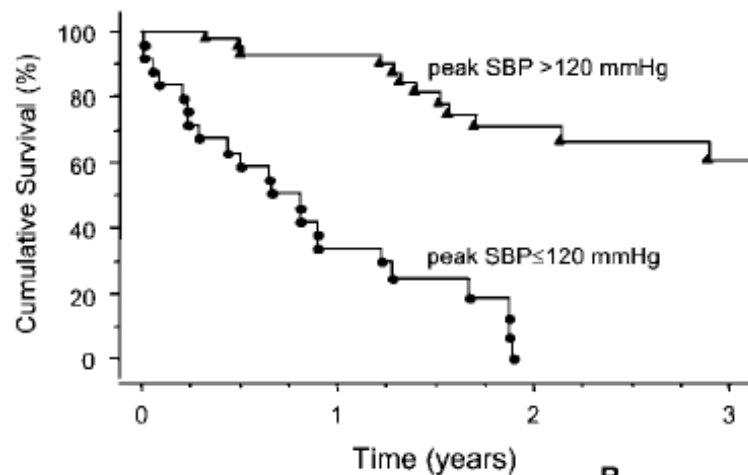
- Θήλυ, γεννηθείσα το 1969, καπνίστρια.
- Δύσπνοια προσπάθειας (2004).
- Καρδιολογική εκτίμηση (echo RVSP=55mmHg).
- Πνευμονολογική εκτίμηση (έναρξη βρογχοδιασταλτικών).
- Διάγνωση ΙΡΑΗ σε ηλικία 36 ετών (3/2005).
- **RHC: PAP= 76/36/49, PCWP= 8, PVR= 10 WU**
- Έναρξη Bosentan (7/2005)
- Παραπομπή στο Νοσοκομείο ΑΤΤΙΚΟΝ (2006)





Η προγνωστική σημασία της CPET στην Πνευμονική Υπέρταση

A

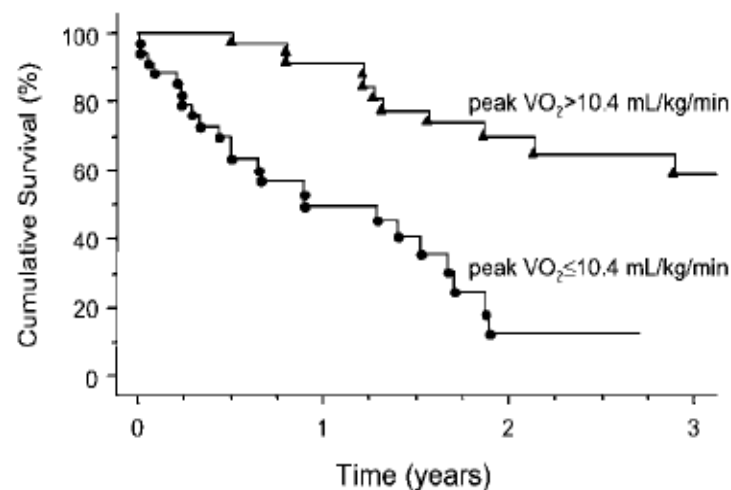


Background—Primary pulmonary hypertension (PPH) is a life-threatening disease. Prognostic assessment is an important factor in determining medical treatment and lung transplantation. Whether cardiopulmonary exercise testing data predict survival has not been reported previously.

Methods and Results—We studied 86 patients with PPH (58 female, age 46 ± 2 years, median NYHA class III) between 1996 and 2001 who were followed up in a tertiary referral center. Right heart catheterization was performed and serum uric acid levels were measured in all patients. Seventy patients were able to undergo exercise testing. At the start of the study, the average pulmonary artery pressure was 60 ± 2 mm Hg, average pulmonary vascular resistance was 1664 ± 81 dyne $\cdot$ s $\cdot$ cm $^{-5}$, average serum uric acid level was 7.5 ± 0.35 mg/dL, and average peak oxygen uptake during exercise (peak $\dot{V}O_2$) was 11.2 ± 0.5 mL $\cdot$ kg $^{-1}$ $\cdot$ min $^{-1}$. During follow-up (mean: 567 ± 48 days), 28 patients died and 16 underwent lung transplantation (1-year cumulative event-free survival: 68%; 95% CI 58 to 78). The strongest predictors of impaired survival were low peak $\dot{V}O_2$ ($P < 0.0001$) and low systolic blood pressure at peak exercise (peak SBP; $P < 0.0001$). In a multivariable analysis, serum uric acid levels (all $P < 0.005$) and diastolic blood pressure at peak exercise independently predicted survival ($P < 0.05$). Patients with peak $\dot{V}O_2 \leq 10.4$ mL $\cdot$ kg $^{-1}$ $\cdot$ min $^{-1}$ and peak SBP ≤ 120 mm Hg (ie, 2 risk factors) had poor survival rates at 12 months (23%), whereas patients with 1 or none of these risk factors had better survival rates (79% and 97%, respectively).

Conclusions—Peak $\dot{V}O_2$ and peak SBP are independent and strong predictors of survival in PPH patients. Hemodynamic parameters, although also accurate predictors, provide no independent prognostic information. (*Circulation*. 2002;106:319-324.)

B



Assessment of Survival in Patients With Primary Pulmonary Hypertension: Importance of Cardiopulmonary Exercise Testing
Roland Wensel, Christian F. Opitz, Stefan D. Anker, Jörg Winkler, Gert Höffken, Franz X. Kleber, Rakesh Sharma, Manfred Hummel, Roland Hetzer and Ralf Ewert
Circulation 2002;106:319-324; originally published online Jun 24, 2002;





Role of exercise testing in PAH management

Oudiz RJ, Semin Respir Crit Care Med 2005; 26(4):379-84.

- Exercise testing can aid the clinician in:
 - a. outlining **the nature** of a patient's exercise limitation,
 - b. noninvasively assessing **disease severity**,
 - c. establishing **prognosis** and
 - d. evaluating the **response to therapy**.

- The **change in exercise capacity parallels** other clinical indicators of **disease severity**, such as: a. survival, b. hemodynamic parameters and c. time to clinical worsening.

- The clinician uses various exercise modalities in evaluating and managing patients with PAH: a. 6MWT, b. CPET, c. Exercise Echocardiography.



Condition-Related Cardiopulmonary Exercise

Testing Indication

- Selection for Heart transplantation
- Systolic Heart Failure
- Heart Failure With Preserved Ejection Fraction
- Hypertrophic Cardiomyopathy
- Unexplained Exertional Dyspnea
- **Suspected or Confirmed PAH or Secondary PH**
- Confirmed COPD or Interstitial Lung Disease
- Suspected Myocardial Ischemia
- Suspected Mitochondrial Myopathy

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Eur Respir J 2015; 46: 903–975

TABLE 13 Risk assessment in pulmonary arterial hypertension

Determinants of prognosis ^a (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope ^b	Repeated syncope ^c
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak $\dot{V}O_2$ >15 ml/min/kg (>65% pred.) VE/ $\dot{V}CO_2$ slope <36	Peak $\dot{V}O_2$ 11–15 ml/min/kg (35–65% pred.) VE/ $\dot{V}CO_2$ slope 36–44.9	Peak $\dot{V}O_2$ <11 ml/min/kg (<35% pred.) VE/ $\dot{V}CO_2$ slope ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm ² No pericardial effusion	RA area 18–26 cm ² No or minimal, pericardial effusion	RA area >26 cm ² pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m ² SvO ₂ >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m ² SvO ₂ 60–65%	RAP >14 mmHg CI <2.0 l/min/m ² SvO ₂ <60%





0/120

9 8:39



Six minute walking test (6MWT)

BP, HR, Saturation
Borg Scale

Total walking meters
(600 m)

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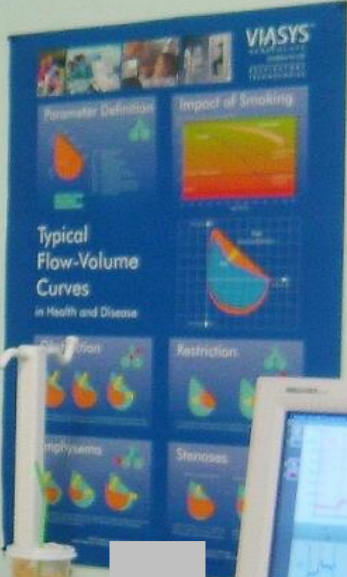




Figure 1 Cardiopulmonary exercise testing machine using the cycle ergometry. A non-rebreathing valve is connected to a mouthpiece with continuous ECG and blood pressure monitoring. Resuscitation equipment on hand. Informed consent was obtained for publication of this figure.







9 9:11

Βασικές μετρήσεις



VO₂ peak

Αναερόβιος ουδός (AT)

Αναπνευστικό πηλίκιο (VCO₂/VO₂)

>84% προβλεπόμενης τιμής

40%-80% προβλεπόμενης VO₂

1.05-1.30

Καρδιακή συχνότητα (HR)

Εφεδρεία καρδιακής συχνότητας (HRR)

O₂ παλμού (VO₂ peak/HR)

Αρτηριακή πίεση (BP)

>90% προβλεπόμενης τιμής

<15 bpm

>80%

<220/90 mm Hg

Αναπνευστική συχνότητα (BF)

Κατά λεπτό αερισμός (VE)

Αναπνευστική εφεδρεία (BR)

Κορεσμός O₂ (Sat)

<60 αναπνοές/min

lt/min

MVV-VE / MVV >20-40%

πτώση <4%

Κλίση VE/VCO₂

Κλίση O₂ ανάνηψης (O₂ recovery)

< 34

> 650

Διακύμανση βασικών μεταβλητών



	Καρδιακή ανεπάρκεια	Αναπνευστική ανεπάρκεια	Κακή φυσική κατάσταση
VO₂ peak	decreased	decreased	decreased
AT	decreased	normal/decreased	normal/decreased
Peak HR	normal	decreased	normal
BR	normal	decreased	normal
Saturation O₂	normal	decreased	normal



Prognostic characteristics of cardiopulmonary exercise testing in heart failure: comparing American and European models

Ross Arena^a, Marco Guazzi^b, Jonathan Myers^c and Mary Ann Peberdy^a

^aDepartment of Physical Therapy, Virginia Commonwealth University, Health Sciences Campus, Richmond, Virginia, USA, ^bCardiopulmonary Laboratory, Cardiology Division, University of Milan, San Paolo Hospital, Milan, Italy and ^cVA Palo Alto Health Care System, Cardiology Division, Stanford University, Palo Alto, California, USA.

Background Cardiopulmonary exercise testing (CPET) in the heart failure population is a standard of care in both American and European clinics, although the mode of exercise typically differs. The purpose of the present study was to compare the prognostic characteristics of peak oxygen consumption (VO_2) and the minute ventilation–carbon dioxide production (VE/VCO_2) slope between two independent heart failure groups.

Design and methods One hundred and two subjects underwent maximal exercise CPET using bicycle ergometry at San Paolo Hospital in Milan, Italy (SPH) and 105 subjects underwent treadmill CPET at Virginia Commonwealth University in Richmond, Virginia (VCU). Subjects were tracked for cardiac-related mortality for a 1-year period after CPET.

Results There were 13 cardiac-related deaths over the 1-year tracking period in both groups. Optimal prognostic threshold values for peak VO_2 were 12.9 ml O_2 /kg per min (sensitivity 81%, specificity 69%) in the SPH group and 12.0 ml O_2 /kg per min (sensitivity 74%, specificity 69%) in the VCU group. An optimal prognostic threshold value for the VE/VCO_2 slope was 34.4 in the SPH (sensitivity 61%, specificity 85%) and 34.5 in the VCU (sensitivity 64%, specificity 93%) groups.

Discussion The prognostic characteristics of peak VO_2 and the VE/VCO_2 slope were similar between the two centers. These results suggest that the mode of exercise does not greatly impact the prognostic utility of CPET responses in heart failure. They further suggest that prognostic guidelines for the application of CPET in heart failure may be applied globally, irrespective of differences in testing modality. *Eur J Cardiovasc Prev Rehabil* 12:562–567 © 2005 The European Society of Cardiology

Reproducibility of Peak Oxygen Uptake and Other Cardiopulmonary Exercise Testing Parameters in Patients With Heart Failure (from the Heart Failure and A Controlled Trial Investigating Outcomes of exercise training)

Daniel R. Bensimhon, MD^a, Eric S. Leifer, PhD^b, Stephen J. Ellis, PhD^c, Jerome L. Fleg, MD^b, Steven J. Keteyian, PhD^d, Ileana L. Piña, MD^e, Dalane W. Kitzman, MD^f, Robert S. McKelvie, MD, PhD^g, William E. Kraus, MD^h, Daniel E. Forman, MDⁱ, Andrew J. Kao, MD^j, David J. Whellan, MD^k, Christopher M. O'Connor, MD^c, and Stuart D. Russell, MD^{l,*}, for the HF-ACTION Trial Investigators

Peak oxygen uptake (pV_{O_2}) is an important parameter in assessing the functional capacity and prognosis of patients with heart failure. In heart failure trials, change in pV_{O_2} was often used to assess the effectiveness of an intervention. However, the within-subject variability of pV_{O_2} on serial testing may limit its usefulness. This study was designed to evaluate the within-subject variability of pV_{O_2} over 2 baseline cardiopulmonary exercise tests. As a substudy of the HF-ACTION trial, 398 subjects (73% men, 27% women; mean age 59 years) with heart failure and left ventricular ejection fraction $\leq 35\%$ underwent 2 baseline cardiopulmonary exercise tests within 14 days. Mean pV_{O_2} was unchanged from test 1 to test 2 (15.16 ± 4.97 vs 15.18 ± 4.97 ml/kg/min; $p = 0.78$). However, mean within-subject absolute change was 1.3 ml/kg/min (10th, 90th percentiles 0.1, 3.0), with 46% of subjects increasing and 48% decreasing on the second test. Other parameters, including the ventilation-to-carbon-dioxide production slope and V_{O_2} at ventilatory threshold, also showed significant within-subject variation with minimal mean differences between tests.

In conclusion, pV_{O_2} showed substantial within-subject variability in patients with heart failure and should be taken into account in clinical applications. However, on repeated baseline cardiopulmonary exercise tests, there appears to be no familiarization effect for V_{O_2} in patients with HF. Therefore, in multicenter trials, there is no need to perform >1 baseline cardiopulmonary exercise test. © 2008 Elsevier Inc. All rights reserved. (Am J

Cardiol 2008;102:712-717)



Καρδιοαναπνευστική κόπωση και ασφάλεια του ασθενούς

Θάνατος σε 2-5 ασθενείς : 100.000 εξετάσεις

Reproducibility of CPET measurements in PAH.



Hansen JE et al. Chest 2004; 126 (3):816-24.

- Using specific guidelines, key CPET measurements can be **safely, reliably and reproducibly** assessed **even in PAH patients with severe exercise intolerance.**



Ιατρικό ιστορικό

- Θήλυ, γεννηθείσα το 1969, καπνίστρια.
- Δύσπνοια προσπάθειας (2004).
- Καρδιολογική εκτίμηση (echo RVSP=55mmHg).
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- **RHC: PAP= 76/36/49, PCWP= 8, PVR= 10 WU**
- Έναρξη Bosentan (7/2005)
- Παραπομπή στο Νοσοκομείο ΑΤΤΙΚΟΝ (2006)



Καρδιοαναπνευστική δοκιμασία κόπωσης σε ασθενείς με πνευμονική αρτηριακή υπέρταση

- Μείωση **peak VO₂** (μειωμένη ικανότητα του ασθενούς για μέγιστη άσκηση).
- Μείωση του **AT** (πρώιμη εμφάνιση αναερόβιου μεταβολισμού και φαίνεται να αποτελεί έναν ανεξάρτητο προγνωστικό παράγοντα για την εξέλιξη της πνευμονικής υπέρτασης).
- Μείωση του **O₂ pulse** (μείωση του όγκου παλμού και της καρδιακής παροχής).
- Αύξηση **VE/VCO₂ ≥35** (ανεπάρκεια του αναπνευστικού συστήματος ως προς την ανταλλαγή αερίων κατά τη διάρκεια της άσκησης).
- Αποκορεσμός της αιμοσφαιρίνης (**Δsat >4-5%**).

1^η εκτίμηση - 2005

(ένα χρόνο υπό Tracleer 125mg 1x2)

6MWT

- 570 meters

CPET

- Time: 9.00 min
- Load: 69% predicted
- **VO₂: 17.1 ml/kg/min (74% predicted),**
- **O₂ pulse: 95% predicted**
- BR: 28% (sat: 99%-95%)

- **VE/VCO₂: 57**

- Αίτιο διακοπής: κόπωση κάτω άκρων

2^η εκτίμηση-2007

(δύο χρόνια υπό Tracleer 125mg 1x2)

6MWT

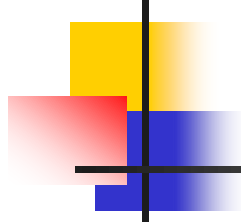
- 510 meters ↓

CPET

- Time: 7.30 min ↓
- Load: 61% predicted
- **VO₂: 15.3 ml/kg/min (63% predicted)** ↓
- **O₂ pulse: 82% predicted** ↓
- BR: 26% (sat: 98%-98%)
- **VE/VCO₂: 48**
- Αίτιο διακοπής: κόπωση κάτω άκρων

3^η εκτίμηση-2008

(τρία χρόνια υπό Tracleer 125mg 1x2)



Triplex καρδιάς

- RVSP: 82mmHg,

RHC

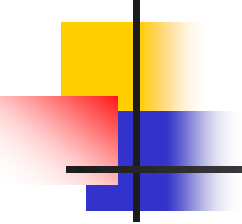
- mPAP 62

CPET

- **Time: 7.00 min** ↓
- Load: 57% predicted
- **VO₂: 16.2 ml/kg/min (68% predicted)** ↓
- **O₂ pulse: 78% predicted** ↓
- BR: 22% (sat: 97%-95%)

- **VE/VCO₂: 66**

- Αίτιο διακοπής: κόπωση κάτω άκρων



Ιατρικό ιστορικό

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- Δύσπνοια προσπάθειας (2004).
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- **Προσθήκη Sildenafil (2009)**

4^η εκτίμηση-2010

(τρία χρόνια bosentan-ένα χρόνος διπλός συνδυασμός)

Triplex καρδιάς

- RVSP: 66 mmHg,

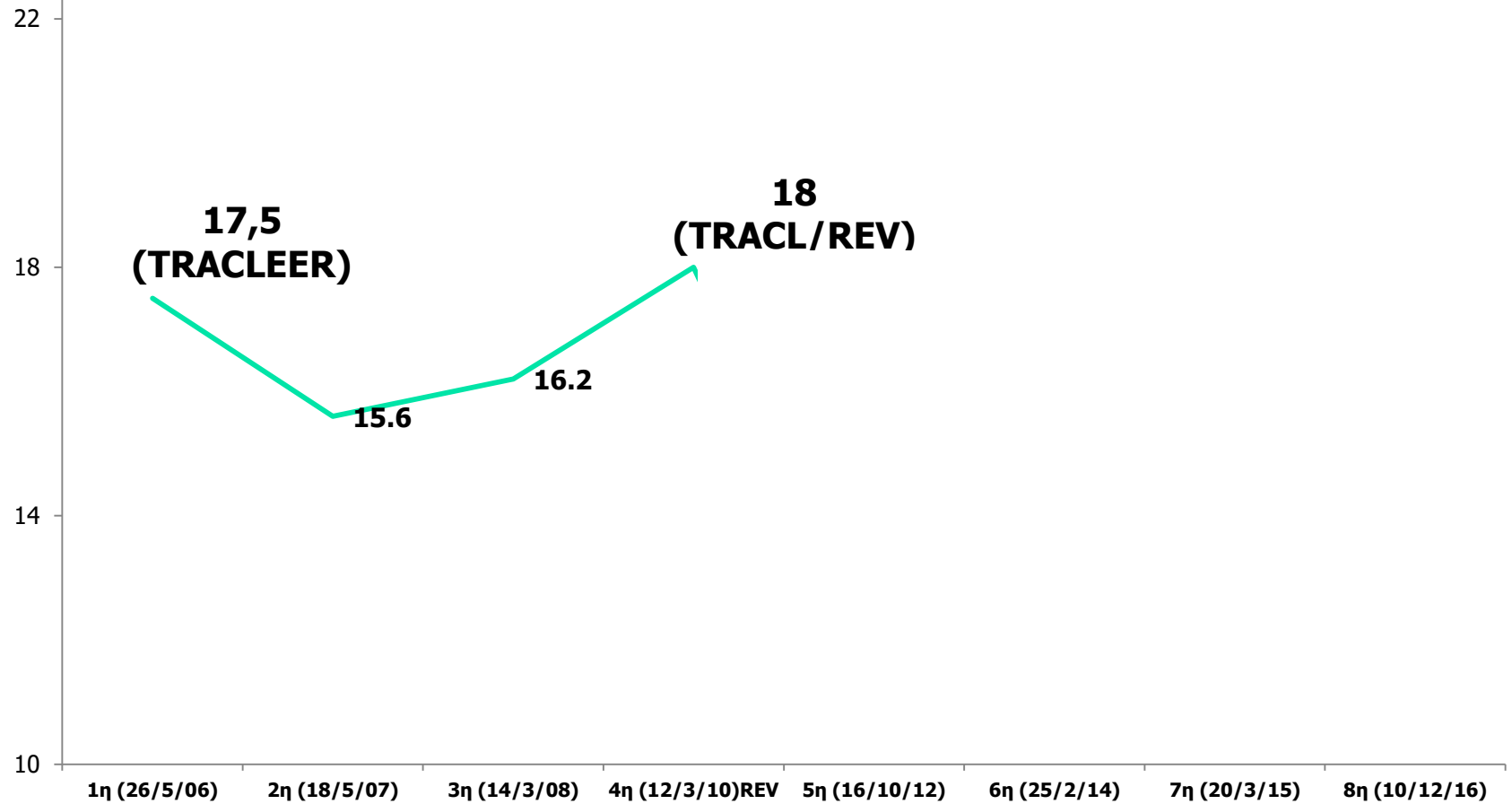
6MWT

- 528 meters

CPET

- Time: **9.45** min ↑
- Load: 59% predicted
- **VO₂: 18 ml/kg/min (75% predicted)** ↑
- **O₂ pulse: 90% predicted** ↑
- BR: 9% (sat: 96%-98%)
- **VE/VCO₂: 59** ↓
- Αίτιο διακοπής: κόπωση κάτω άκρων

Peak O₂ consumption (VO₂)



5^η εκτίμηση-2012

(τρία χρόνια bosentan- τρία χρόνια διπλός συνδυασμός)

CPET

- **Time: 7.25 min**
- Load: 67% predicted
- **VO₂: 11.8 ml/kg/min (52% predicted)** ↓↓
- **O₂ pulse: 64% predicted** ↓↓
- BR: 21% (sat: 96%-98%)

- **VE/VCO₂: 58**

- Αίτιο διακοπής: κόπωση κάτω άκρων

6^η εκτίμηση-2014

(τρία χρόνια bosentan- 4 ½ χρόνια διπλός συνδυασμός)

Triplex καρδιάς:

- RVSP: 103mmHg, ↑↑

6MWT

- 528 meters

CPET

- Time: 6.30 min
- Load: 60% predicted
- **VO₂: 12.7 ml/kg/min (56% pred),** ↓↓
- **O₂ pulse: 74% predicted** ↓↓
- BR: 30% (sat: 94%-93%)
- RER: 1.38
- **VE/VCO₂: 46**
- Αίτιο διακοπής: κόπωση κάτω άκρων

7^η εκτίμηση-2015

(τρία χρόνια bosentan- 5 ½ χρόνια διπλός συνδυασμός)



Triplex καρδιάς:

- **RVSP: 95**mmHg,
TVR:4,6m/sec, **TAPSE: 23**

6MWT

- 550 meters

RHC:

- PA 93/44/**60**, PCWP: 10,
PVR: **13**, CI: **2.0**

CPET

- Time: 7.00 min
- Load: 67% predicted
- **VO₂: 13.7 ml/kg/min (61% pred)** ↓ ↓ ↓
- **O₂ pulse: 78% predicted** ↓ ↓
- BR: 5% (sat: 94%-93%)

- VE/VCO₂: 51

- Αίτιο διακοπής: κόπωση κάτω άκρων



Ιατρικό ιστορικό

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- Δύσπνοια προσπάθειας (2004).
- Καρδιολογική εκτίμηση (echo RVSP=55mmHg).
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- Παραπομπή στο Νοσοκομείο ΑΤΤΙΚΟΝ (2006)
- Προσθήκη Sildenafil (2009)
- Προσθήκη Treprostenil (2015)

8^η εκτίμηση (12/2016)

τρία χρόνια bosentan- 5 ½ χρόνια διπλός συνδυασμός-
1 ½ χρόνο τριπλός συνδυασμός

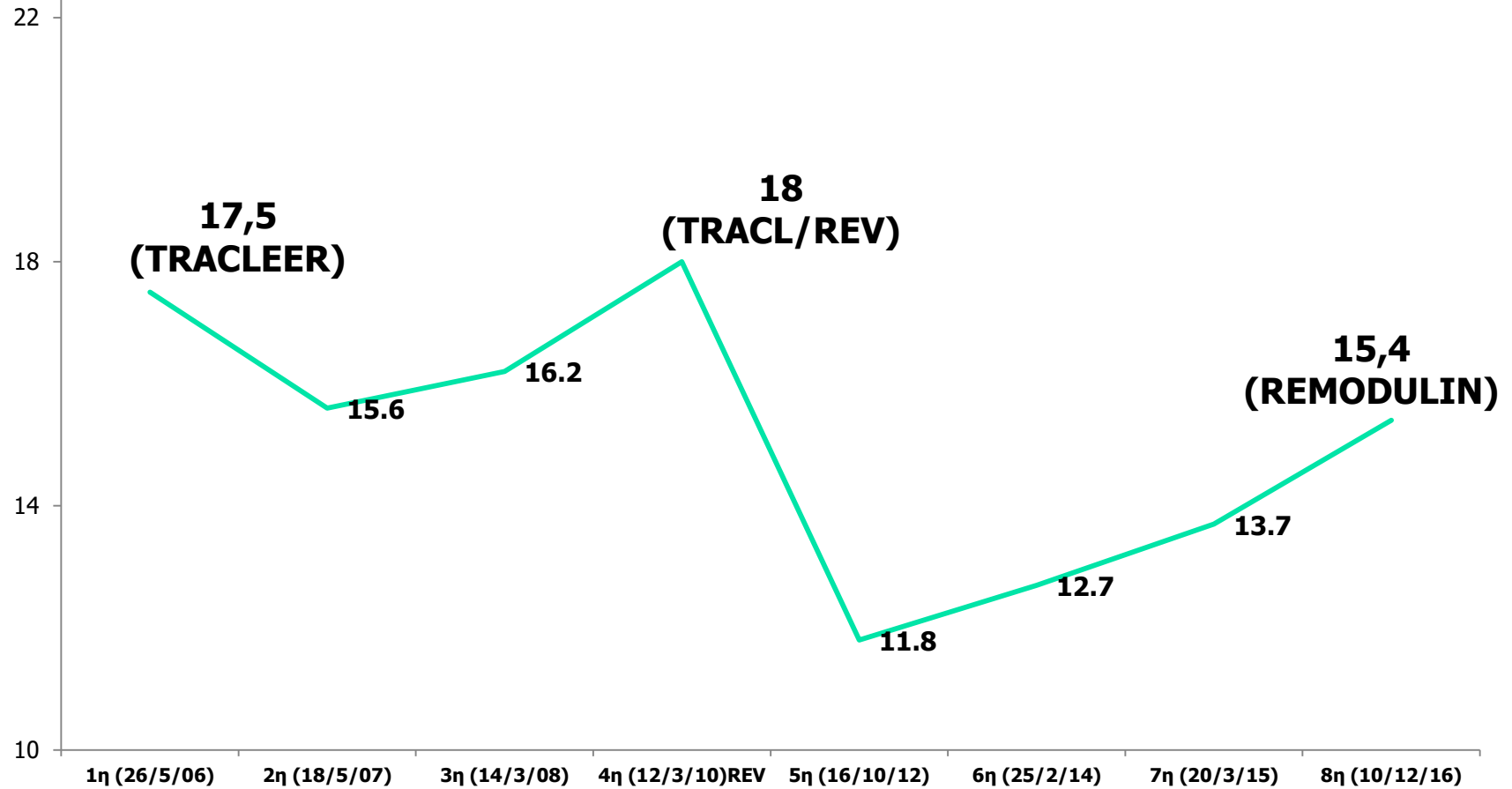
6MWT

- 581 meters ↑

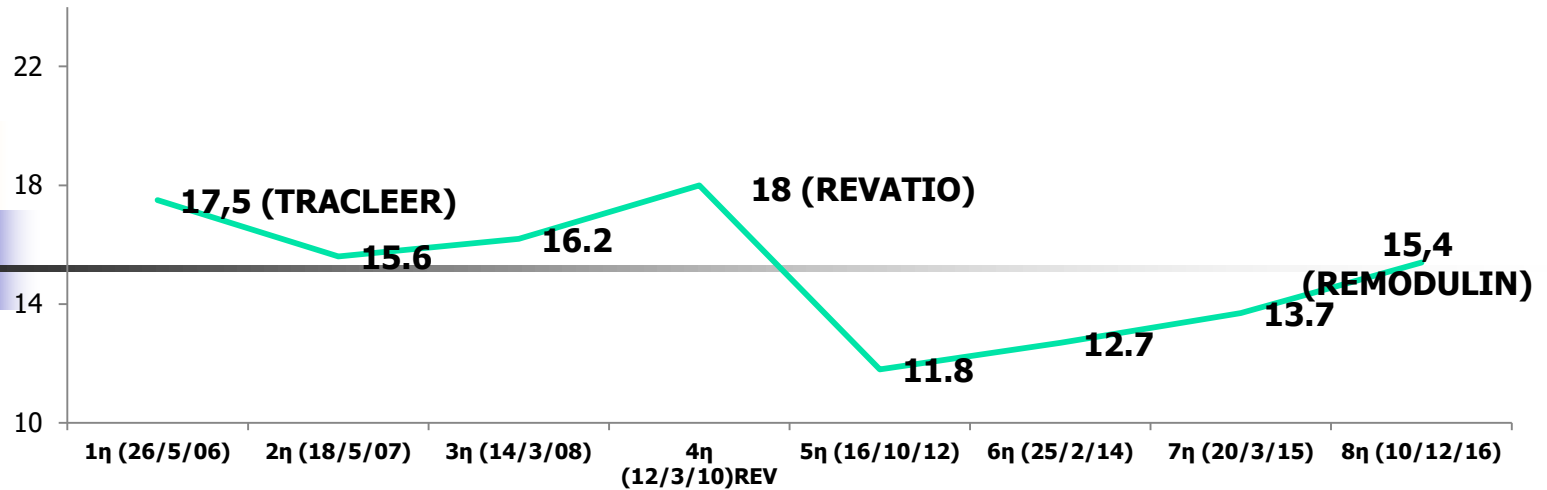
CPET

- Time: 7.00 min
- Load: 73% pred
- **VO₂: 15.4 ml/kg/min (65% predicted)** ↑
- **O₂ pulse: 78% predicted**
- BR: 5% (sat: 97%-93%)
- **VE/VCO₂: 68**
- Αίτιο διακοπής: κόπωση κάτω άκρων

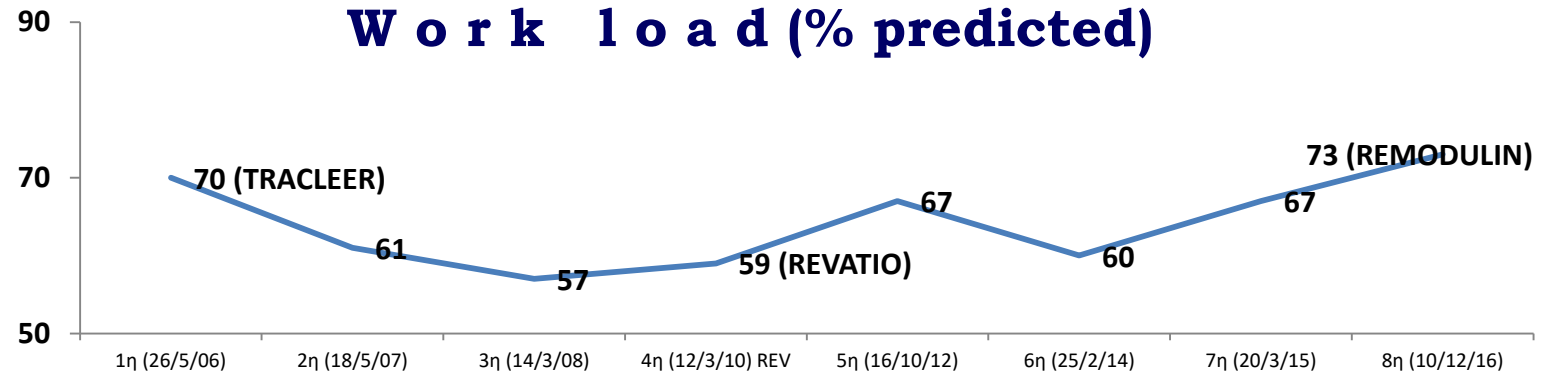
Peak O₂ consumption (VO₂)



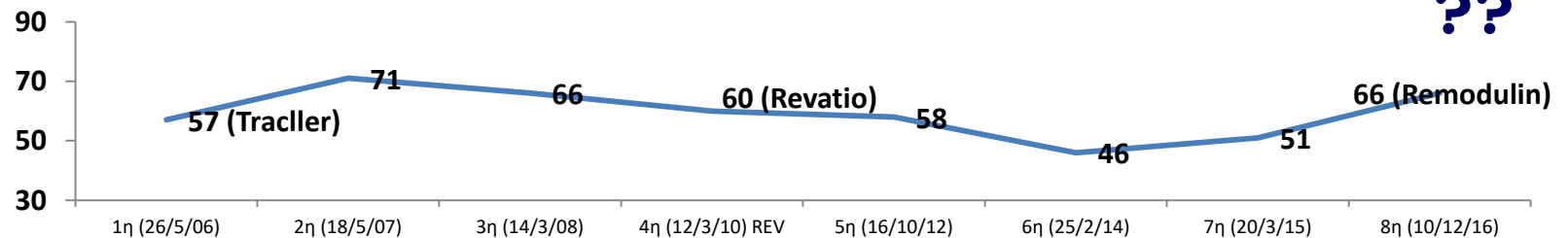
Peak O₂ consumption (ml/min/kg)



Work load (% predicted)

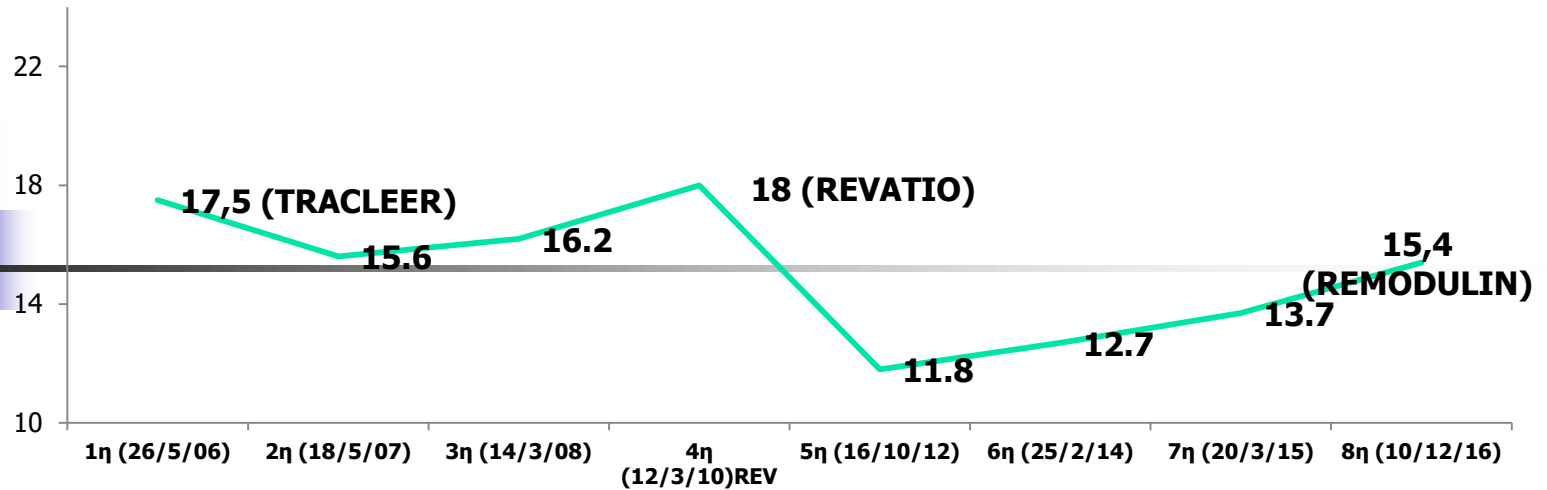


VE/VCO₂ slope

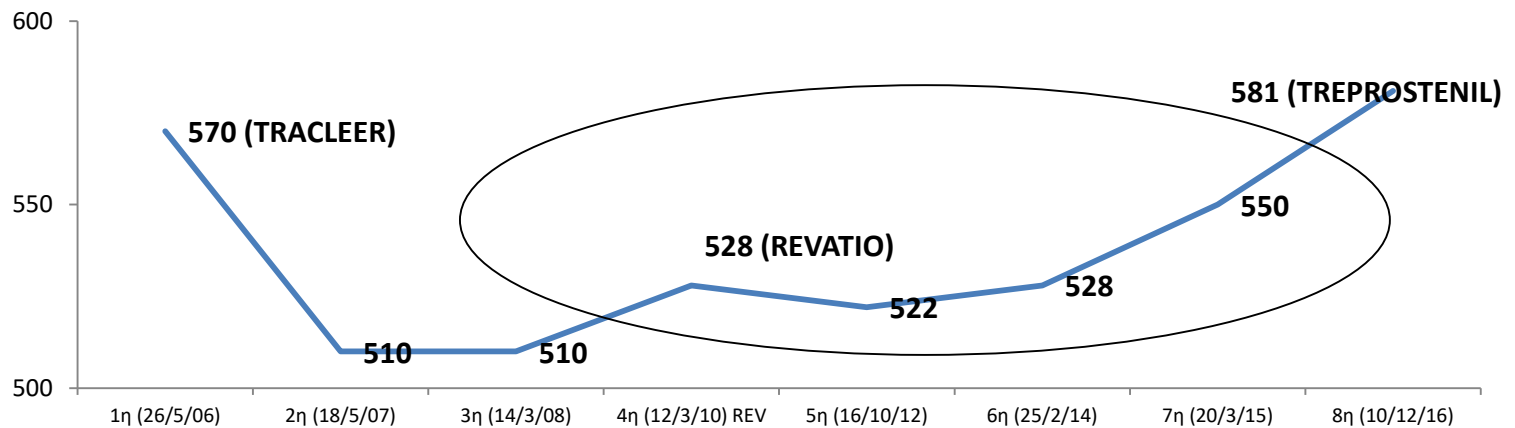


??

Peak O₂ consumption (ml/min/kg)



6 Minute Walking Test



Συσχετίσεις μεταξύ CPET και 6MWT στην Ιδιοπαθή Πνευμονική Υπέρταση

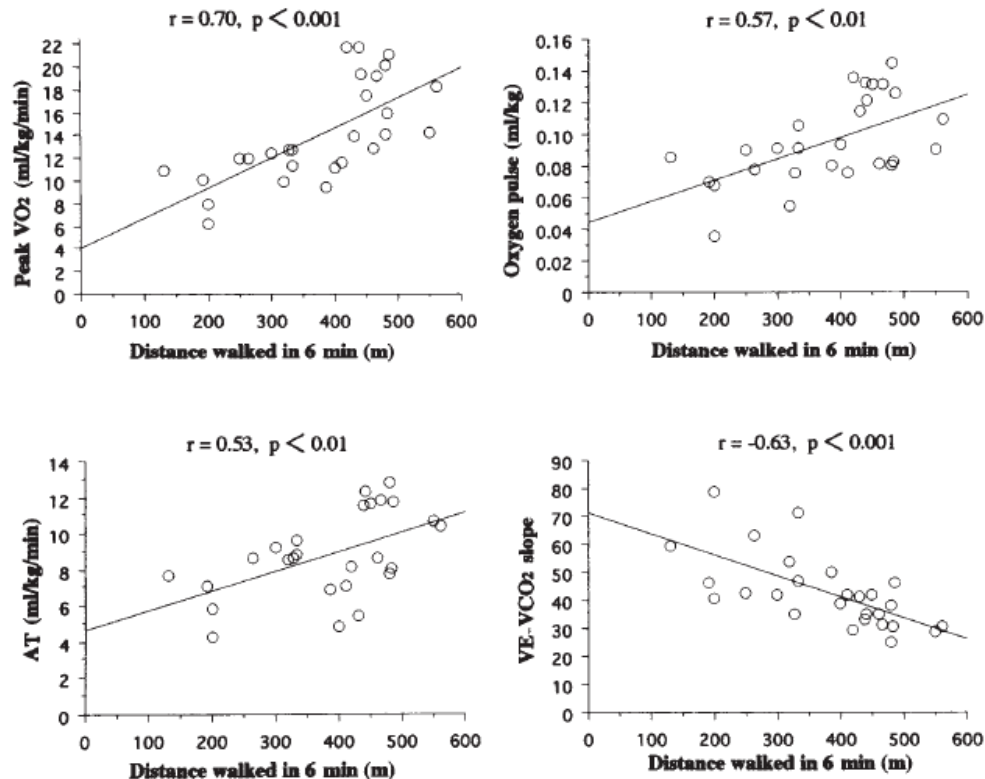
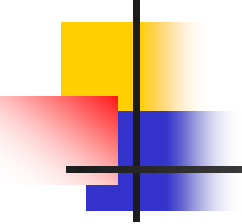


Figure 3. Relations between distance walked during six-minute walk test and exercise capacity determined by cardiopulmonary exercise testing in patients with PPH. Peak $\dot{V}O_2$ = peak exercise oxygen consumption; AT = anaerobic threshold; VE- $\dot{V}CO_2$ slope = regression slope relating minute ventilation to carbon dioxide output.



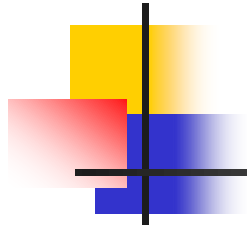
The role of CPET in the assessment of PAH.



- Regarding follow-up assessments **CPET can quantify** cardiopulmonary exercise capacity in **a more differentiated way than** global exercise tests like the **6MWT**.
- Different pathophysiological mechanisms accounting for PAH can be separately evaluated by CPET.

Clinical Recommendations for Cardiopulmonary Exercise
Testing Data Assessment in Specific Patient Populations

(*Circulation*. 2012;126:2261-2274.)



The combination of

- ✓ *standard exercise testing* (progressive exercise, serial electrocardiograms, hemodynamics, oxygen saturation, and subjective symptoms) and *measurement of ventilatory gas exchange amounts to a superior method to*
- ✓ accurately quantify cardiorespiratory fitness,
- ✓ delineate the physiologic system(s) underlying exercise responses, which can be applied as a means to identify the exercise-limiting pathophysiologic mechanism(s) and
- ✓ formulate function-based prognostic stratification.

Θέματα προς συζήτηση

- ✓ Η συνεχής παραμονή TAPSE >20 και η εντός φυσιολογικών ορίων συστολική λειτουργία της δεξιάς κοιλίας επί μία 10ετία παρά την προοδευτική επιβάρυνση των πνευμονικών αντιστάσεων.
- ✓ Η αναγκαιότητα πρώιμης έναρξης συνδυαστικής αγωγής.
- ✓ Η όψιμη επιτυχία της προσπάθειας να πεισθεί η ασθενής ως προς την αναγκαιότητα τριπλής αγωγής (υποδόρια, ενδοφλέβια).
- ✓ Η παρουσία υψηλού VE/VCO₂ 1 ½ έτος μετά την έναρξη τριπλής αγωγής και παρά την καλή πορεία της ασθενούς τι μπορεί να προδικάζει?