

Τμήμα Επιστήμης Φυσικής  
Αγωγής & Αθλητισμού



**Πρόγραμμα Μεταπτυχιακών Σπουδών: Άσκηση και Υγεία**  
ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ - Τ.Ε.Φ.Α.Α., ΚΑΡΥΕΣ 42100, ΤΡΙΚΑΛΑ

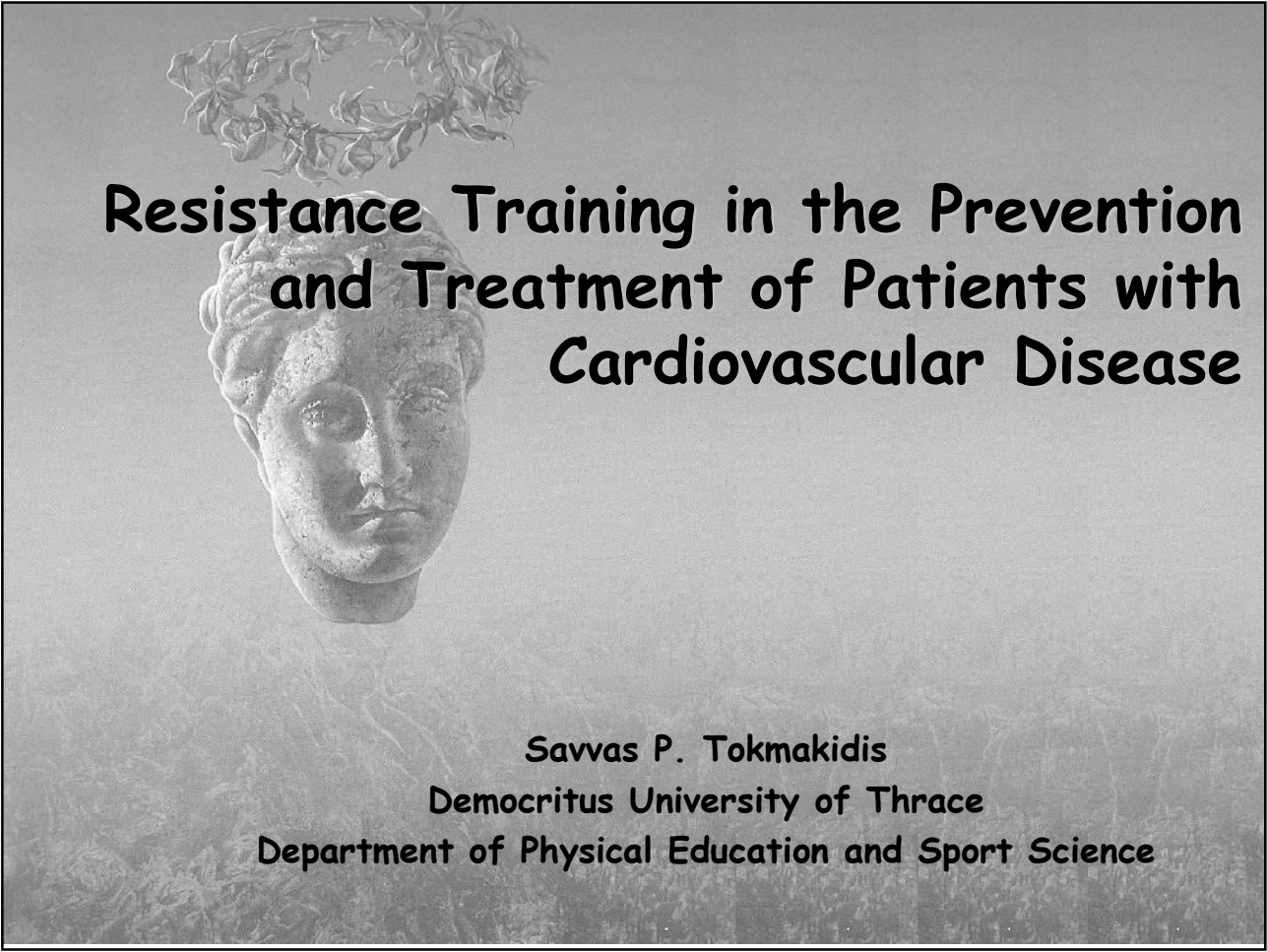
**Μάθημα: MB05**  
Άσκηση, Πρόληψη και Αποκατάσταση Καρδιοπαθειών

**Διάλεξη 12<sup>η</sup>**

## **Άσκηση με Αντιστάσεις για Πρόληψη και Θεραπεία Ασθενών με Καρδιαγγειακές Παθήσεις**

**Καθηγητής Σάββας Π. Τοκμακίδης**

Δημοκρίτειο Πανεπιστήμιο Θράκης - Τμήμα Επιστήμης Φυσικής Αγωγής και Αθλητισμού



**Resistance Training in the Prevention  
and Treatment of Patients with  
Cardiovascular Disease**

**Savvas P. Tokmakidis  
Democritus University of Thrace  
Department of Physical Education and Sport Science**

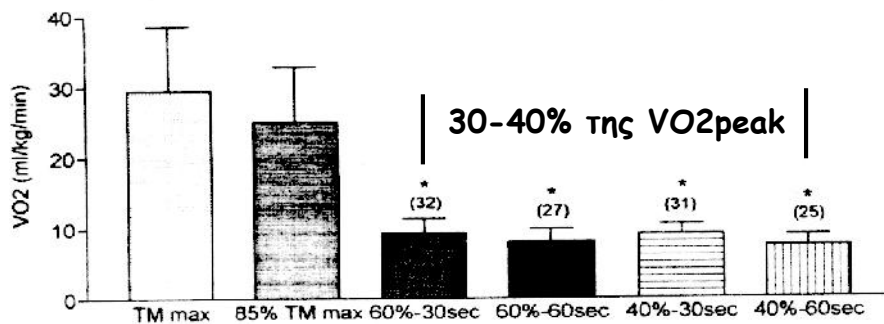
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## Historical background

- Until 1950 exercise focused on cardiovascular health
- After 1950 resistance protocols were introduced in the rehabilitation programs of veterans in order to improve muscle mass and strength
- 1980-2000 resistance training was widely used in the prevention and rehabilitation of many chronic diseases including cardiovascular disease
- >2000 first guidelines published from ACSM, AHA, ADA

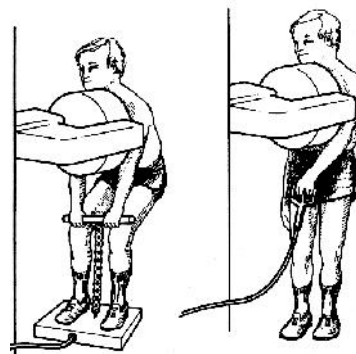
**Safety Aspects of Resistance  
Exercise in Patients with  
Cardiovascular Disease**

## Resistance Exercise, Oxygen Cost and Left Ventricular Function



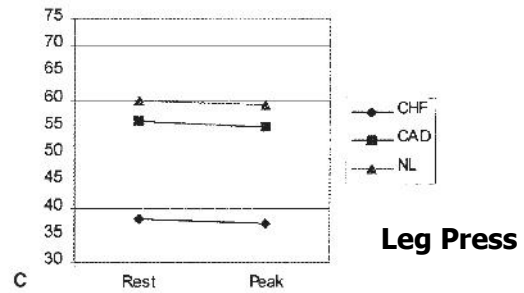
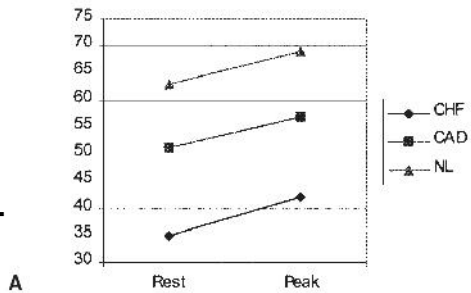
De Groot et al. (1998). *J Cardiopulm Rehabil*; 18: 145-152

Sagiv et al. (1985). *Am J Cardiol*; 58: 785-790

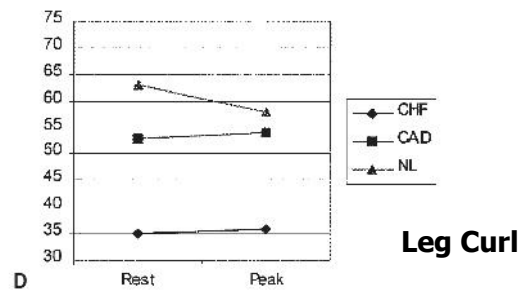
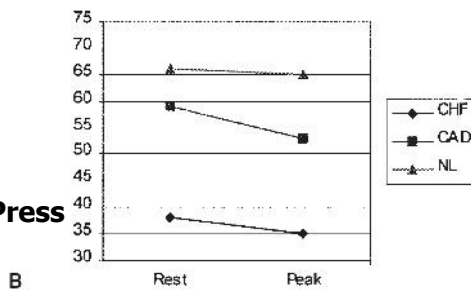


## Changes in Left Ventricular Ejection Fraction during Resistance Exercise in Cardiac Patients

**Bicycle  
90% VT**

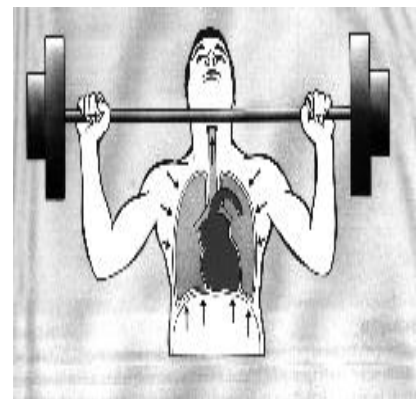
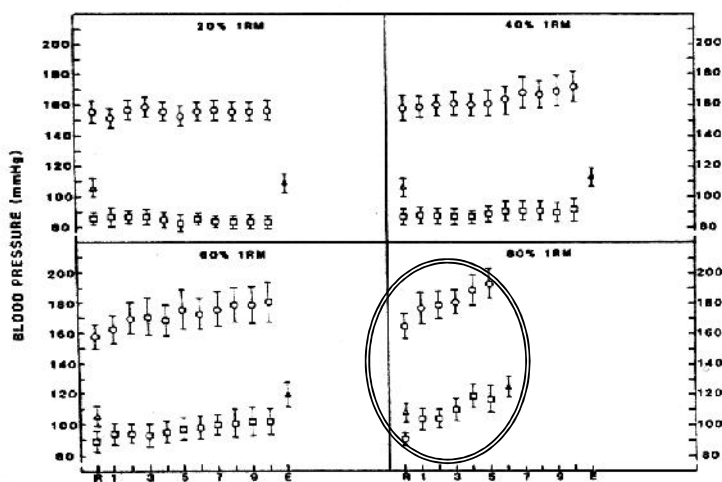


**Shoulder Press**



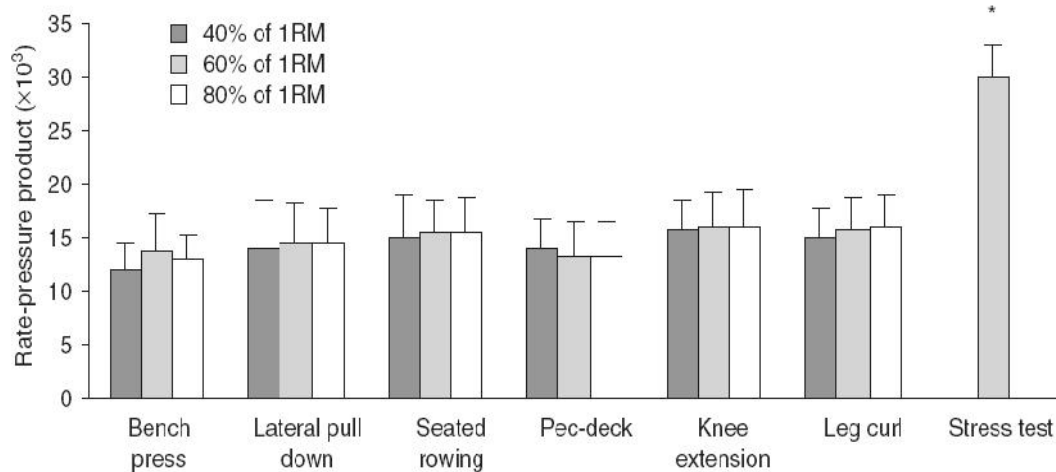
Karlsdottir et al. (2002). *J Cardiopulm Rehabil*; 22: 170-177

## Systolic and Diastolic Pressure Alterations during Resistance Exercise of Different Intensities



Haslam et al. (1988). *J Cardiopulm Rehabil*; 8: 213-215

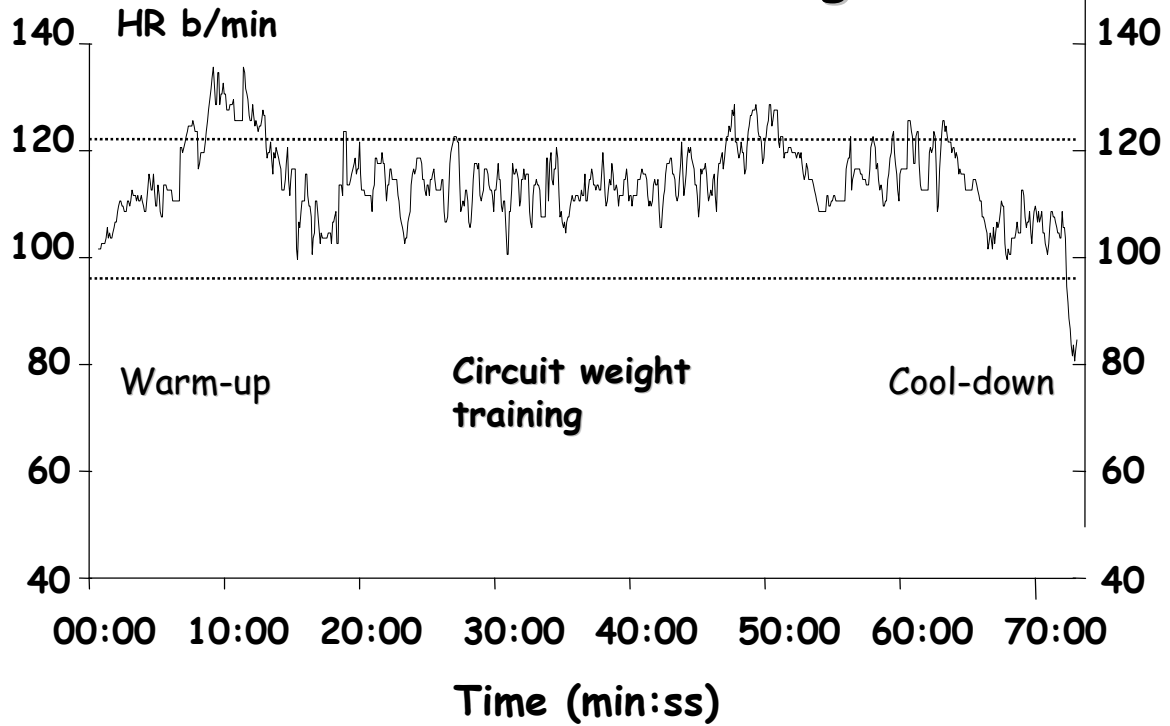
## Rate Pressure Product during Resistance Exercise in Patients with CAD



Volaklis & Tokmakidis (2005), *Sports Med* 35(12): 1085-1103



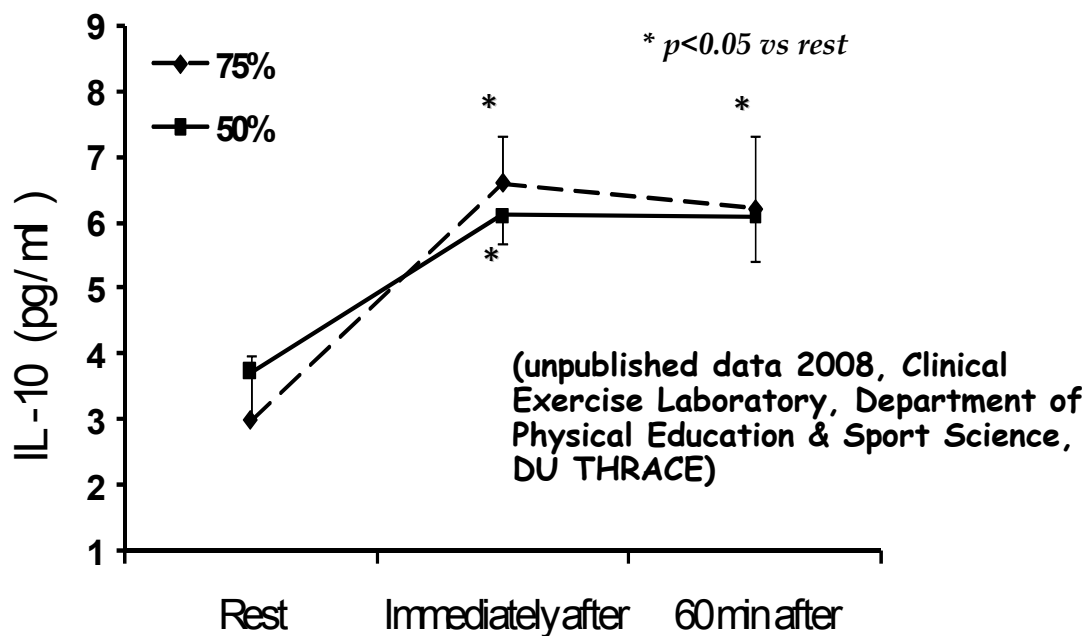
## Heart rate responses during resistance training



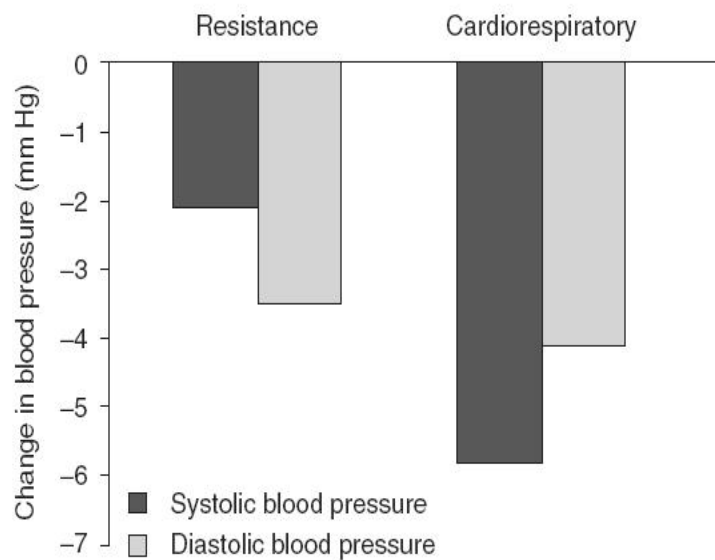
**Anti-inflammatory Responses  
after Resistance Protocols in  
Patients with CAD**

## Inflammatory Responses after Resistance Exercise

- TNF- $\alpha$ , INF- $\gamma$ , IL-6 : NS alterations
- IL-10 : Significant alterations

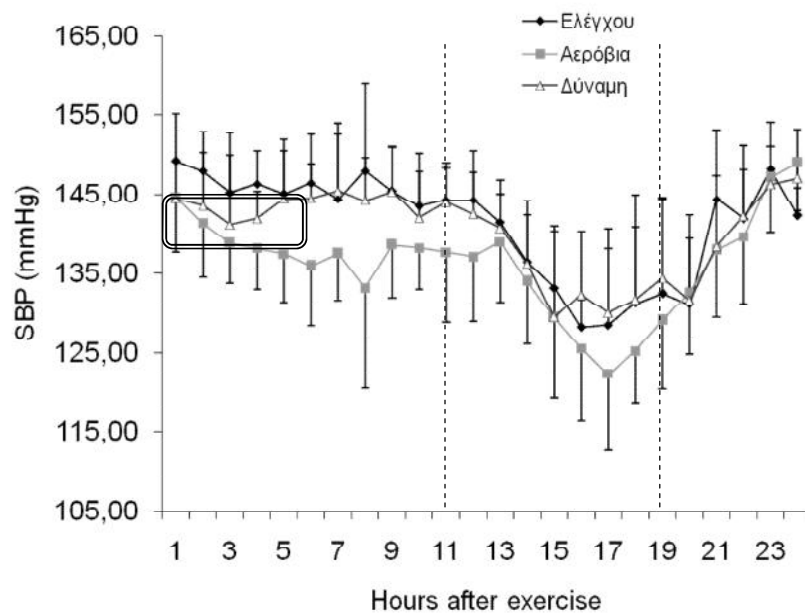


## Long-term Blood Pressure Adaptations after Resistance and Aerobic Training



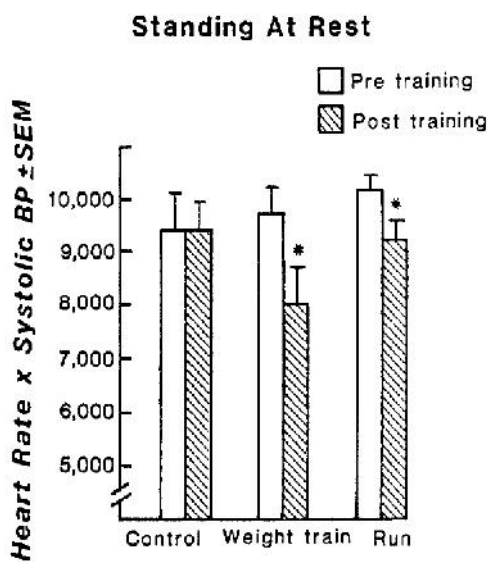
Wallace et al. (2003), *Sports Med* 33: 585-598

## 24-h Ambulatory Systolic Pressure Records after a Single Resistance & Aerobic Exercise Session in Patients with Stage I Hypertension

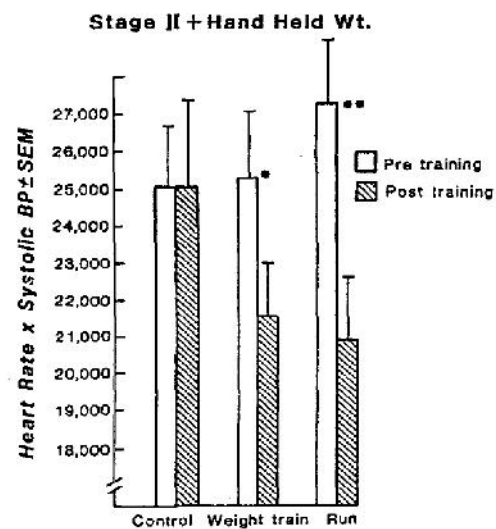


(unpublished data 2009, Clinical Exercise Laboratory, Department of Physical Education & Sport Science, DU THRACE)

## Μεταβολή του διπλού γινόμενου με την προπόνηση με βάρη



**Figure 1.** Resting rate pressure product  $\pm$ SEM before and after 16 weeks among the 3 groups. \* $p \leq 0.05$



**Figure 4.** Rate pressure product  $\pm$ SEM during mixed exercise (treadmill walking at 2.5 mph at 12% grade) while carrying a 9.07-kg weight before and after 16 weeks among the 3 groups. \* $p < 0.05$ ; \*\* $p < 0.01$

**Τρέξιμο:** 20 – 45 min στο 85% HRmax, 3 φορές την εβδομάδα, 16 εβδομάδες

**Βάρη:** 8 ασκήσεις, 3 x 3-8 επαναλήψεις, 2 min διάλειμμα, 3 φορές την εβδομάδα, 16 εβδομάδες

**Υγιείς άνδρες ηλικίας  $37 \pm 4$  χρόνων**

## Συχνότητα Εμφράγματος σε Υπερτασικά και Νορμοτασικά Άτομα ανάλογα με τη Φυσική Δραστηριότητα

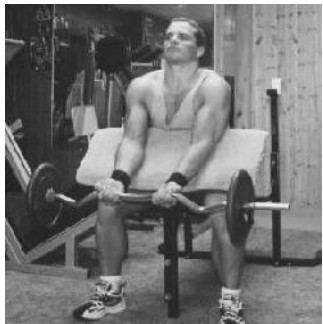


Shaper et al. (1994). J Hum Hypertens; 8: 3-10

# **Isometric versus Dynamic Resistance Exercise Protocols**

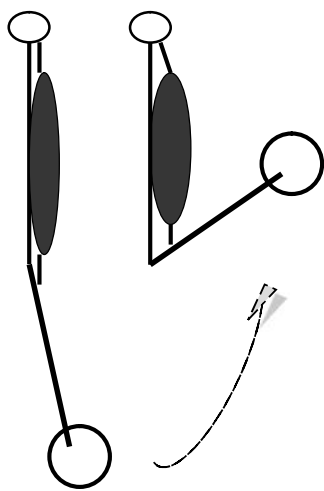


## **Resistance exercise or weight lifting** (combination of dynamic and static contraction)

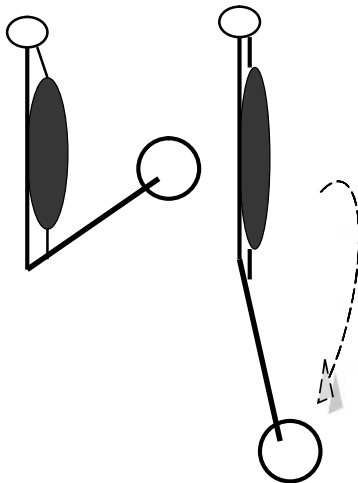


- **Start lifting: static (isometric) contraction**
- **Raise the weight: dynamic, concentric (shortening)**
- **Lower the weight: dynamic, eccentric (lengthening)**
- **Relaxation phase: varies between successive lifts**

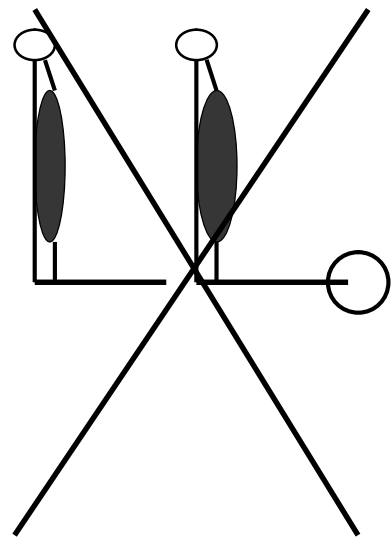
## Types of Muscle Activation during Resistance Exercise



**Concentric**



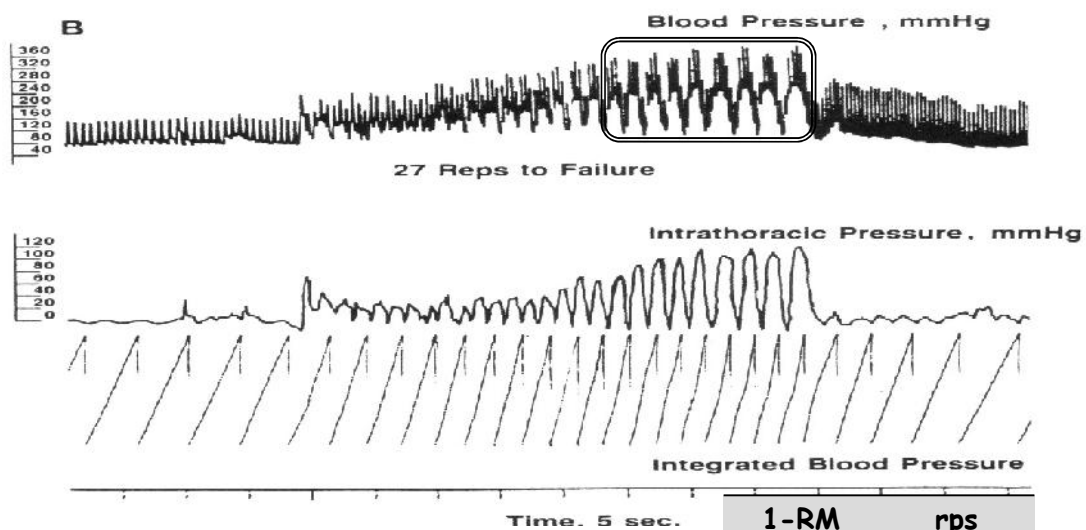
**Eccentric**



**Isometric**

**Dynamic Exercise**

**Static Exercise**



## Intra-thoracic and Intra-arterial Pressure during Leg Press Resistance Exercise

MacDougall et al. 1992

1-RM	rps
100	1
95	2 - 3
90	4 - 5
85	6 - 8
80	8 - 10
75	10 - 12
70	12 - 14
65	14 - 16
60	17 - 20

**Muscular Strength as a  
Predictor of Mortality  
Epidemiological Data**

**Several studies during the last decade demonstrated that muscular strength is inversely and independently associated with death from cardiovascular disease, even after adjusting for cardiorespiratory fitness**

**Ruiz et al. (2008). Br Med J; 337: 92-95**

**Sasaki et al. (2007). Am J Med; 120: 337-342**

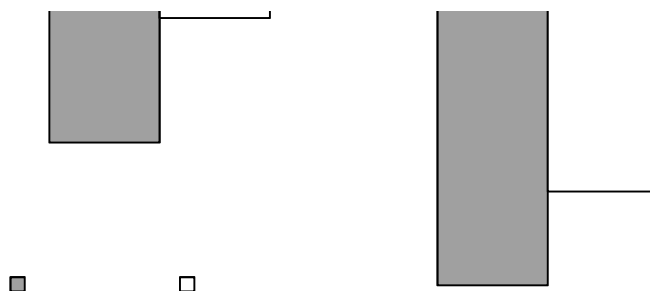
**Gale et al. (2007). Int J Epidemiol; 36: 228-235**

**Metter et al. (2002). Med Sci Sports Exerc; 36: B359-365**

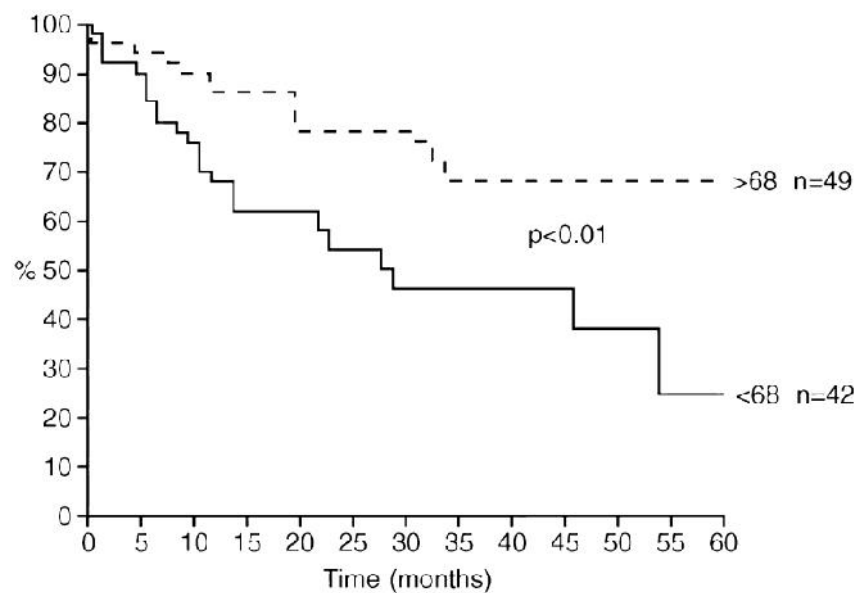
**Tanasescu et al. (2002). JAMA; 288: 1994-2000**

## Relative Risk of Coronary Heart Disease Associated with Resistance Training

n=8205, 25-69 yrs, 1977-1995  
Tanasescu et al. (2002); *JAMA* 288: 1994-2000



## Association between Muscular Strength and Survival in Patients with Heart Failure

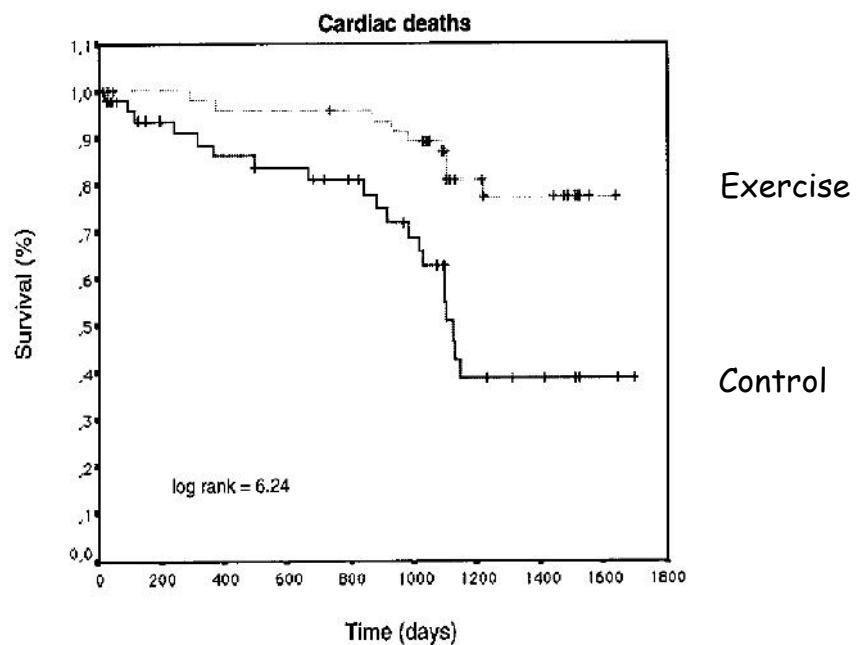


Huelschman et al. Eur J Heart Fail 2004; 6: 101-107

**Άσκηση με Βάρη σε  
Ασθενείς με Καρδιακή  
Ανεπάρκεια**

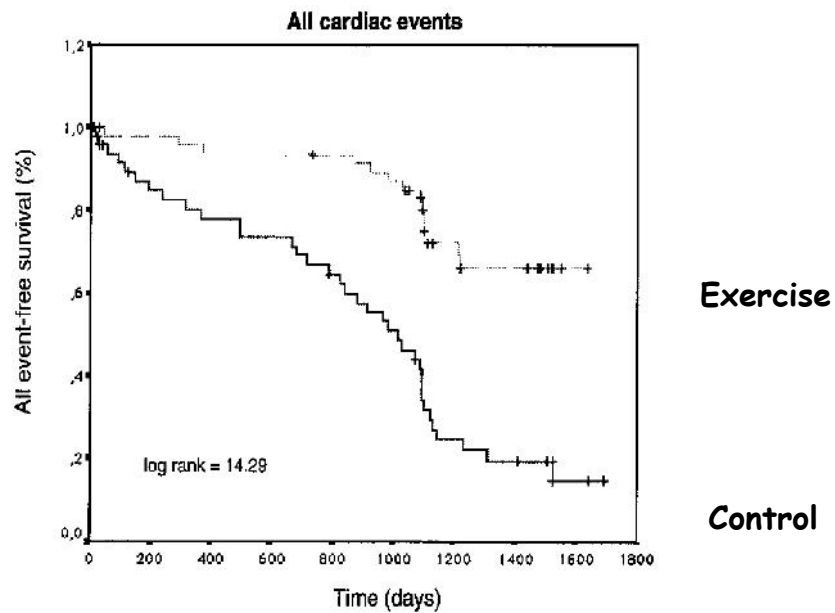


## Μείωση Θανάτων μετά από άσκηση σε ασθενείς με καρδιακή ανεπάρκεια



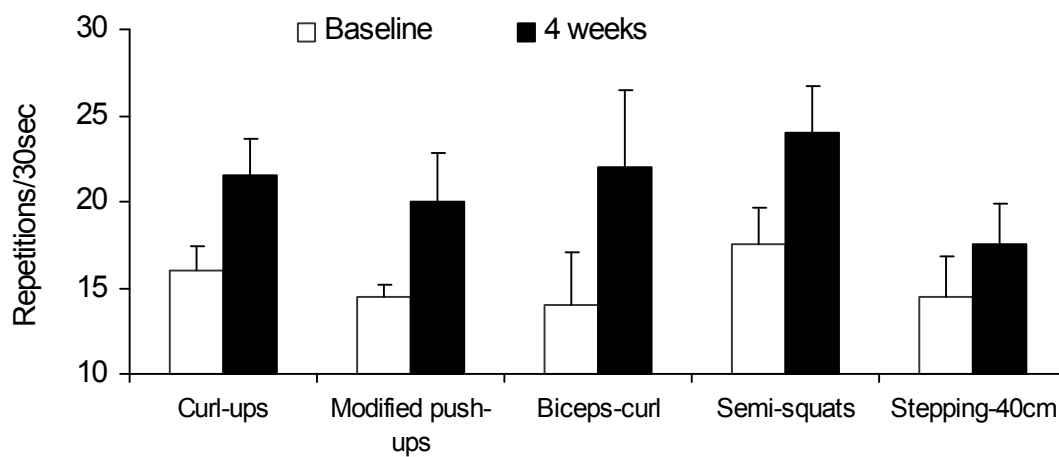
Belardinelli et al. (1999), *Circulation* 342: 454-460

## Μείωση καρδιαγγειακών επεισοδίων μετά από άσκηση σε ασθενείς με καρδιακή ανεπάρκεια

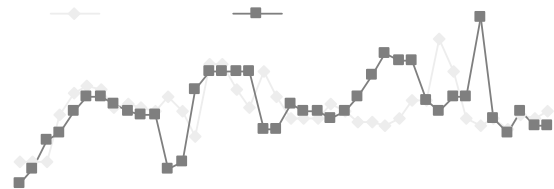
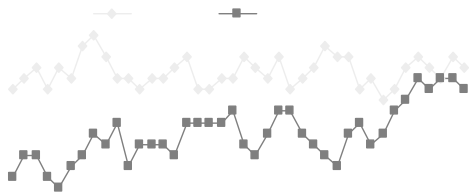


Belardinelli et al. (1999), *Circulation* 342: 454-460

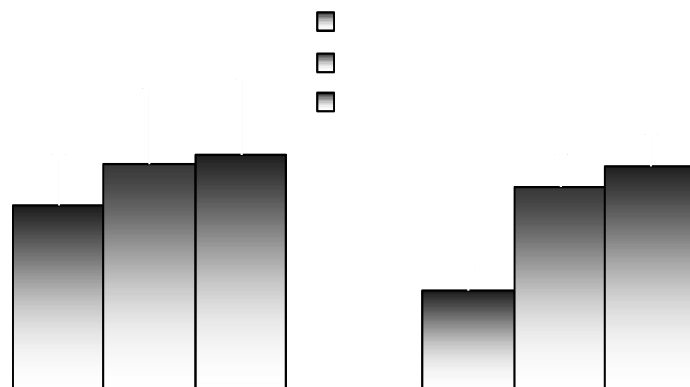
## Improvement of muscular strength in patients with heart failure



## Heart rate responses in patients with heart failure

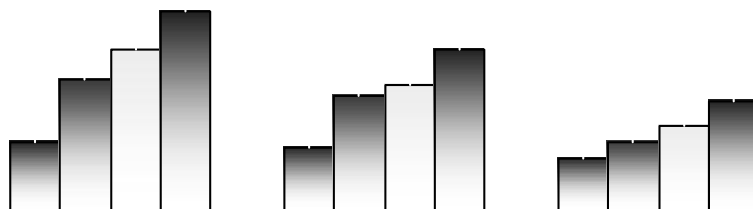
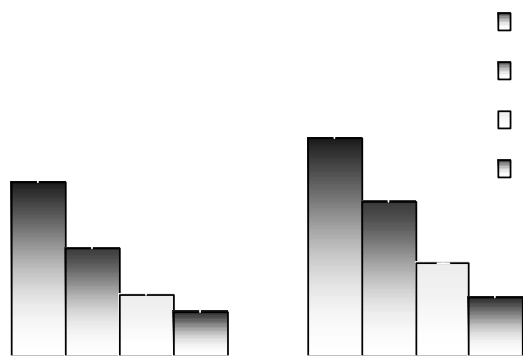


## Muscular Strength Improvements after 14 weeks of a Combined Program in patients with HF



(unpublished data 2004, Clinical Exercise Laboratory, Department of Physical Education & Sport Science, DU THRACE)

# Βελτίωση μουϊκής αντοχής



## Comparison of the Effects of Aerobic to Resistance Training on Health and Fitness Variables

Braith et al. (2006),  
Circulation 113: 2642-2650

Variable	Aerobic Exercise	Resistance Exercise
Bone mineral density	↑	↑ ↑ ↑
Body composition		
Fat mass	↓ ↓	↓
Muscle mass	↔	↑ ↑
Strength	↔	↑ ↑ ↑
Glucose metabolism		
Insulin response to glucose challenge	↓ ↓	↓ ↓
Basal insulin levels	↓	↓
Insulin sensitivity	↑ ↑	↑ ↑
Serum lipids		
High-density lipoprotein	↑ ↔	↑ ↔
Low-density lipoprotein	↓ ↔	↓ ↔
Resting heart rate	↓ ↓	↔
Blood pressure at rest		
Systolic	↓ ↓	↓
Diastolic	↓ ↓	↓
Physical endurance	↑ ↑ ↑	↑ ↑
Basal metabolism	↑	↑ ↑

# **Resistance Exercise in the Treatment of Cardiovascular Disease**

## **Guidelines for Training**



## **AHA Scientific Statement**

### **Resistance Exercise in Individuals With and Without Cardiovascular Disease: 2007 Update**

#### **A Scientific Statement From the American Heart Association Council on Clinical Cardiology and Council on Nutrition, Physical Activity, and Metabolism**

Mark A. Williams, PhD, Co-Chair; William L. Haskell, PhD, FAHA, Co-Chair; Philip A. Ades, MD;  
Ezra A. Amsterdam, MD; Vera Bittner, MD; Barry A. Franklin, PhD; Meg Gulanick, RN, PhD;  
Susan T. Laing, MD; Kerry J. Stewart, EdD

*Abstract*—Prescribed and supervised resistance training (RT) enhances muscular strength and endurance, functional capacity and independence, and quality of life while reducing disability in persons with and without cardiovascular disease. These benefits have made RT an accepted component of programs for health and fitness. The American Heart Association recommendations describing the rationale for participation in and considerations for prescribing RT were published in 2000. This update provides current information regarding the (1) health benefits of RT, (2) impact of RT on the cardiovascular system structure and function, (3) role of RT in modifying cardiovascular disease risk factors, (4) benefits in selected populations, (5) process of medical evaluation for participation in RT, and (6) prescriptive methods. The purpose of this update is to provide clinicians with recommendations to facilitate the use of this valuable modality. (*Circulation*. 2007;116:572-584.)

## **Absolute and Relative Contraindications to Resistance Training in Cardiac Patients**

**Williams et al. (2007),  
Circulation 116: 572-584**

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### **Absolute**

- Unstable CHD
- Decompensated HF
- Uncontrolled arrhythmias
- Severe pulmonary hypertension (mean pulmonary arterial pressure >55 mm Hg)
- Severe and symptomatic aortic stenosis
- Acute myocarditis, endocarditis, or pericarditis
- Uncontrolled hypertension (>180/110 mm Hg)
- Aortic dissection
- Marfan syndrome
- High-intensity RT (80% to 100% of 1-RM) in patients with active proliferative retinopathy or moderate or worse nonproliferative diabetic retinopathy

### **Relative (should consult a physician before participation)**

- Major risk factors for CHD
- Diabetes at any age
- Uncontrolled hypertension (>160/>100 mm Hg)
- Low functional capacity (<4 METs)
- Musculoskeletal limitations
- Individuals who have implanted pacemakers or defibrillators

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## **Requirements for Participation in Resistance Exercise Programs**

- **Ejection fraction > 45%**
- **Functional capacity > 7 METs**
- **Appropriate HR and BP responses during cardiopulmonary stress testing**
- **No angina during exercise**
- **Absence of arrhythmias**
- **Participation in aerobic training for 8 weeks**

**ACSM 1998**

## **Termination Criteria for Resistance Exercise in Patients with CAD**

- **Moderate to severe angina**
- **Drop of heart rate  $> 10$  b/min**
- **Drop of blood pressure  $>10$  mmHg from baseline BP**
- **Hypertensive response (SP  $>220$ , DP  $>110$  mmHg)**
- **Increasing nervous system symptoms**
- **Signs of poor perfusion**

**ACSM 1998**

## Cardiac Rehabilitation Resistance Training Guidelines by Diagnosis

Diagnosis	Guidelines from the American Association of Cardiovascular and Pulmonary Rehabilitation	Guidelines from the American College of Sports Medicine
Myocardial infarction	1- to 3-lb hand weights on cardiac rehabilitation program entry; <u>traditional resistance training at 5 weeks</u> if 4 weeks of supervised endurance training have been completed	<u>Traditional resistance training at 3 months</u> ; 1- to 3-lb hand weights 2 weeks after myocardial infarction
Percutaneous coronary intervention	1- to 3-lb hand weights on cardiac rehabilitation program entry; <u>traditional resistance training at 3 weeks</u> if 2 weeks of supervised endurance training have been completed	<u>2 weeks of aerobic exercise prior to traditional resistance training</u>

**ACSM 2000, AACPR 2004**

**Forces Required to Perform 32 Activities of Daily Living in CAD patients**

**Adams et al. (2006),  
Am J Cardiology 97:  
281-286**

Activity*	Force lbs
Lifting 1-lb dumbbell	2
Lifting 3-lb dumbbell	4
Lifting 5-lb dumbbell	6
Lifting 10-lb dumbbell	12.5
Pushing open door to cardiac rehabilitation	15.5
Pulling open door to leave cardiac rehabilitation	22
Pushing open cardiac rehabilitation bathroom door	12.5
Pulling open door to leave cardiac rehabilitation bathroom	11
Pushing door to exit cardiac rehabilitation building	13
Pulling door to enter cardiac rehabilitation building	13.5
Opening door to enter Baylor University Medical Center	15
Pushing door to exit Baylor University Medical Center	22.5
Pulling open door at doctor's office	14.5
Pushing doctor's office door to leave	15.5
Pushing door to enter hospital room	6.5
Pushing IV pole with full drip bag across carpet	6.5
Hold elevator door from closing	14.5
Opening refrigerator	9
Opening refrigerator freezer	10.5
Pulling 1 gallon of milk from refrigerator	10.5
Lifting 1 gallon of milk	10.5
Closing microwave door	6.5
Pulling open oven door	6.5
Pulling out full dishwasher rack	5
Lifting full laundry hamper	21.5
Pushing vacuum cleaner	7.5
Pulling vacuum cleaner	8.5
Flushing industrial toilet	13.5
Lifting purse	7.5
Pulling full file drawer	10
Lifting copy machine lid	6
Lifting full coffee pot	6.5
Pushing with aid of right arm to rise off bench	27.5
Pulling chair across linoleum floor	5
Opening car door	12.5
Lifting a Dallas phone book	4.5

## Summary of Exercise Programming Recommendations for Stroke Survivors

Mode of Exercise	Major Goals	Intensity/Frequency/Duration
<b>Aerobic</b>		
<ul style="list-style-type: none"> <li>• Large-muscle activities (eg, walking, treadmill, stationary cycle, combined arm-leg ergometry, arm ergometry, seated stepper)</li> </ul>	<ul style="list-style-type: none"> <li>• Increase independence in ADLs</li> <li>• Increase walking speed/efficiency</li> <li>• Improve tolerance for prolonged physical activity</li> <li>• Reduce risk of cardiovascular disease</li> </ul>	<ul style="list-style-type: none"> <li>• 40%–70% peak oxygen uptake; 40%–70% heart rate reserve; 50%–80% maximal heart rate; RPE 11–14 (6–20 scale)</li> <li>• 3–7 d/wk</li> <li>• 20–60 min/session (or multiple 10-min sessions)</li> </ul>
<b>Strength</b>		
<ul style="list-style-type: none"> <li>• Circuit training</li> <li>• Weight machines</li> <li>• Free weights</li> <li>• Isometric exercise</li> </ul>	<ul style="list-style-type: none"> <li>• Increase independence in ADLs</li> </ul>	<ul style="list-style-type: none"> <li>• 1–3 sets of 10–15 repetitions of 8–10 exercises involving the major muscle groups</li> <li>• 2–3 d/wk</li> </ul>
<b>Flexibility</b>		
<ul style="list-style-type: none"> <li>• Stretching</li> </ul>	<ul style="list-style-type: none"> <li>• Increase ROM of involved extremities</li> <li>• Prevent contractures</li> </ul>	<ul style="list-style-type: none"> <li>• 2–3 d/wk (before or after aerobic or strength training)</li> <li>• Hold each stretch for 10–30 seconds</li> </ul>
<b>Neuromuscular</b>		
<ul style="list-style-type: none"> <li>• Coordination and balance activities</li> </ul>	<ul style="list-style-type: none"> <li>• Improve level of safety during ADLs</li> </ul>	<ul style="list-style-type: none"> <li>• 2–3 d/wk (consider performing on same day as strength activities)</li> </ul>

Gordon et al. *Circulation* 2004; 109: 2031-2041

# Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



American  
Heart  
Association®

## AHA Scientific Statement

### **Exercise Standards for Testing and Training A Scientific Statement From the American Heart Association**

Gerald F. Fletcher, MD, FAHA, Chair; Philip A. Ades, MD, Co-Chair;  
Paul Kligfield, MD, FAHA, Co-Chair; Ross Arena, PhD, PT, FAHA; Gary J. Balady, MD, FAHA;  
Vera A. Bittner, MD, MSPH, FAHA; Lola A. Coke, PhD, ACNS, FAHA; Jerome L. Fleg, MD;  
Daniel E. Forman, MD, FAHA; Thomas C. Gerber, MD, PhD, FAHA;  
Martha Gulati, MD, MS, FAHA; Kushal Madan, PhD, PT; Jonathan Rhodes, MD;  
Paul D. Thompson, MD; Mark A. Williams, PhD; on behalf of the American Heart Association  
Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology,  
Council on Nutrition, Physical Activity and Metabolism, Council on Cardiovascular and Stroke  
Nursing, and Council on Epidemiology and Prevention

***Circulation. 2013;128:873-934; originally published online July 22, 2013;***



**Table 7. General Guidelines for Endurance and Resistance Training**



**American  
Heart  
Association®**

***Circulation.  
2013;128:873-934;***

Endurance training

Frequency	≥5 d/wk
Intensity	55%–90% maximum predicted HR* or 40%–80% Vo <sub>2</sub> max or HR reserve RPE 12–16
Modality	Walking, treadmill, cycling, etc
Duration	30–60 min

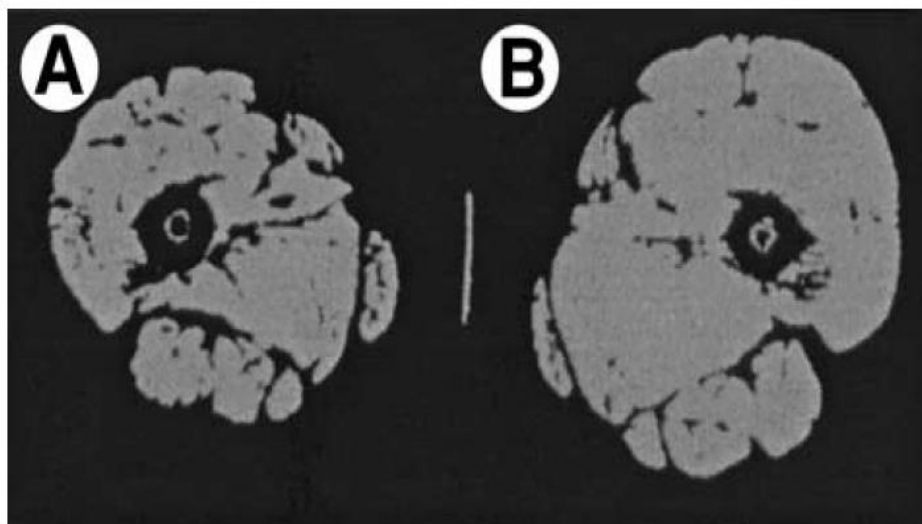
Resistance training

Frequency	2–3 d/wk
Intensity	50%–80% of 1-RM or RPE 12–16 1–3 sets of 8–15 repetitions per exercise
Modality	Lower extremity: leg extensions, leg curls, leg press. Upper extremity: bench press, lateral pulldowns, biceps curl, triceps extension
Duration	30–45 min

# **Resistance Training in the Treatment of Cardiovascular Disease**

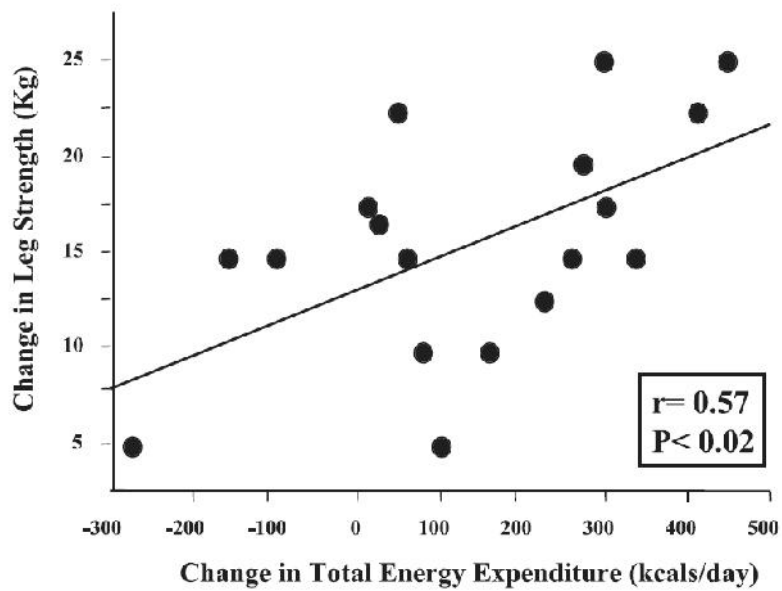
## **Chronic Adaptations**

## Cross Sectional Area after 40 Sessions of Resistance Training in a Patient with Heart Failure



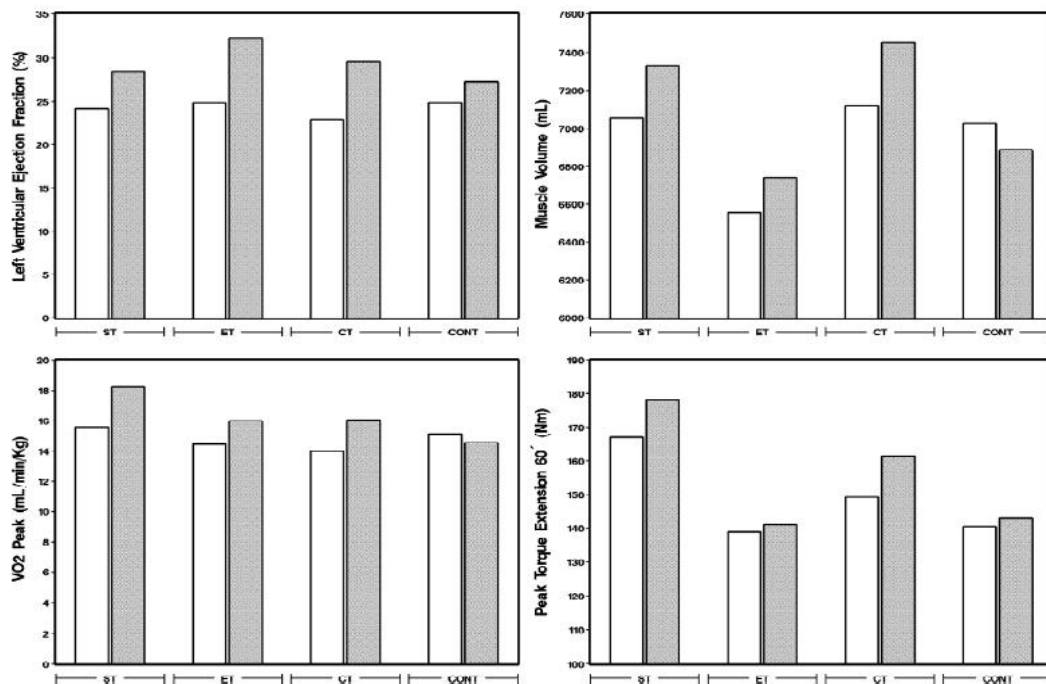
Feiereisen et al. (2004). *Eur J Cardiovasc Prev Rehabil* 11: 35-39

Association between Muscular Strength and  
RMR after Exercise in patients with CAD  
δύναμη και μεταβολισμός άσκησης σε γυναίκες ασθενείς  
διαβήτη τύπου 2



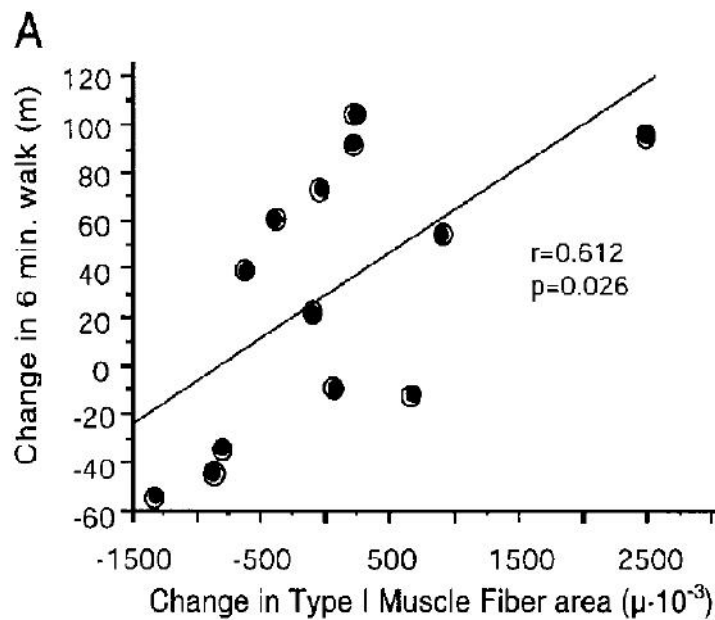
Ades et al. *J Appl Physiol* 2005, 98:2028-2035

## Physiological Adaptations after Three Different Training Modalities in Patients with HF



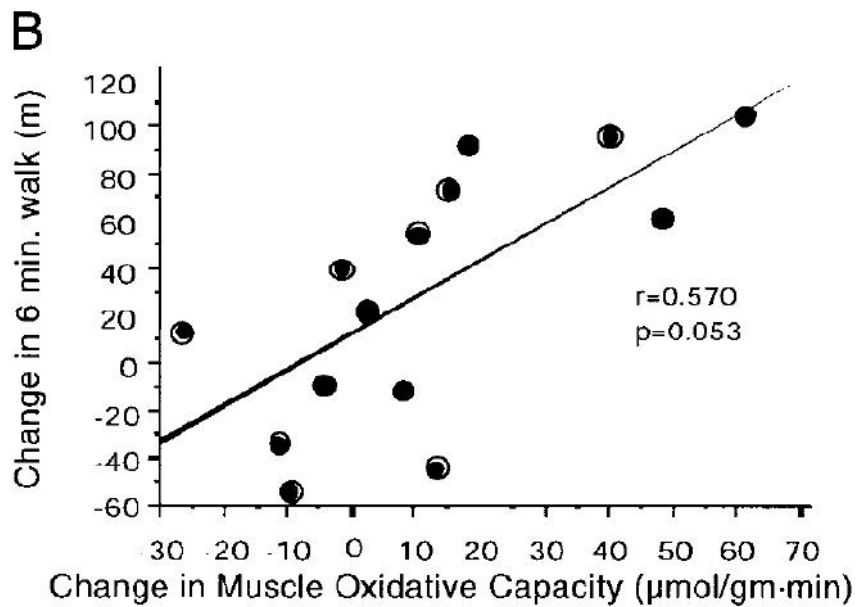
Feiereisen et al. (2007). *Med Sci Sports Exerc*; 11: 1910-1917

## Change in Type I Muscle Fiber Area after Resistance Training in Patients with Heart Failure



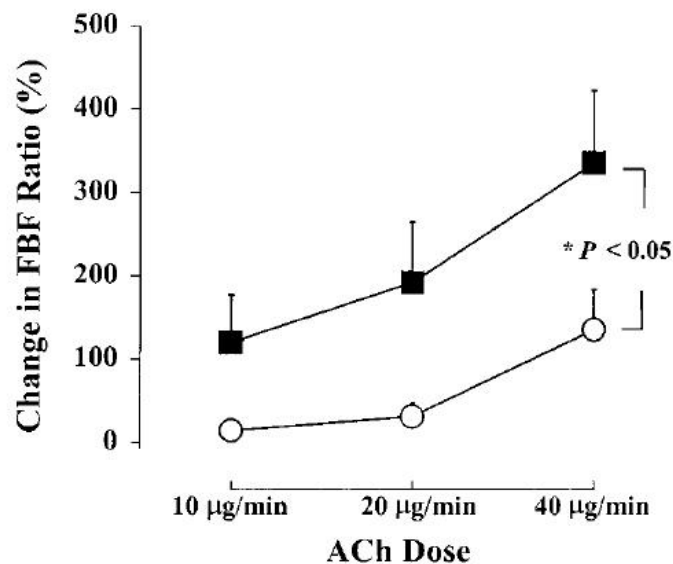
Pu et al. (2001), J Appl Physiol 342: 454-460

## Change in Muscle Oxidative Capacity after Resistance Training in Patients with Heart Failure



Pu et al. (2001), J Appl Physiol 342: 454-460

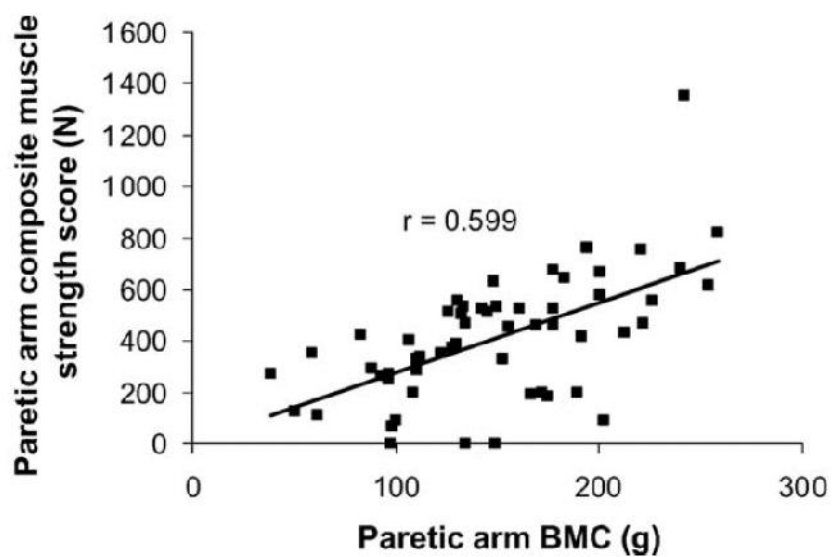
## Forearm Blood Flow Response after 8 Weeks of Circuit Weight Training in Patients with HF



Maiorana et al. (2000), Am J Physiol Heart Circ Physiol 279: H19999-H2005



## Association between Muscular Strength and BMC after Exercise in Patients with Stroke



Marco et al. (2005). Bone 37: 103-111

# Χαρακτηριστικά Άσκησης με Βάρη

**Circuit weight training**  
(κυκλική προπόνηση με αντιστάσεις)



## **Χαρακτηριστικά Άσκησης με Βάρη σε Ασθενείς με Χρόνιες Παθήσεις**

### **Προϋποθέσεις ασφαλούς συμμετοχής**

- **Κλάσμα εξώθησης > 45%**
- **Λειτουργική ικανότητα > 7 METs**
- **Απουσία υποτασικής ή υπερτασικής απάντησης στην κόπωση**
- **Έλλειψη στηθαγχικών συμπτωμάτων κατά την άσκηση**
- **Απουσία κοιλιακών αρρυθμιών**
- **Συμμετοχή σε αερόβια άσκηση για 8 εβδομάδες**

**ACSM 1998, AHA 2007**

## **Άσκηση με Βάρη σε Ασθενείς με Στεφανιαία Νόσο**

- **Επίσημες συστάσεις από την Αμερικανική  
Καρδιολογική Εταιρεία για εφαρμογή της  
άσκησης με βάρη στα προγράμματα  
άσκησης καρδιοπαθών**

**Fletcher et al. *Circulation* 1995; 91: 580-615**

**Pollock et al. *Circulation* 2000; 101: 828-833**

**Williams et al. *Circulation* 2007; 116: 572-584**

# **Training program**

## **(Exercise prescription)**

### **AEROBIC EXERCISE** **(2 days per week)**

- 60-80% of HRmax
- 5 min warm-up
- 45 min treadmill or aerobic activities
- 5 min cool-down  
*(stretching exercises)*

### **RESISTANCE EXERCISE** **(2 days per week)**

- 40-60% of 1 RM
- 8 exercises
- 12 repetitions, 3 sets
- Circuit weight training
- 5 min cool-down  
*(stretching exercises)*

# **Exercise training programs in patients with coronary artery disease**

## **Results after a combined strength and aerobic exercise training program**

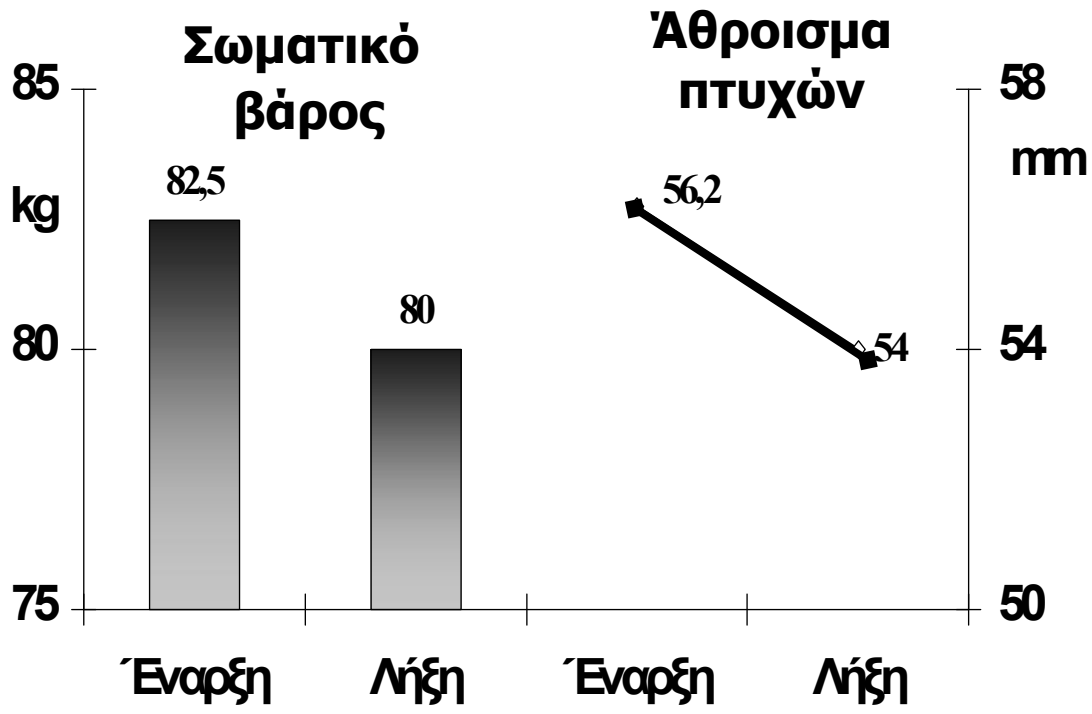
**(Duration: 8 months)**

**2 days per week**



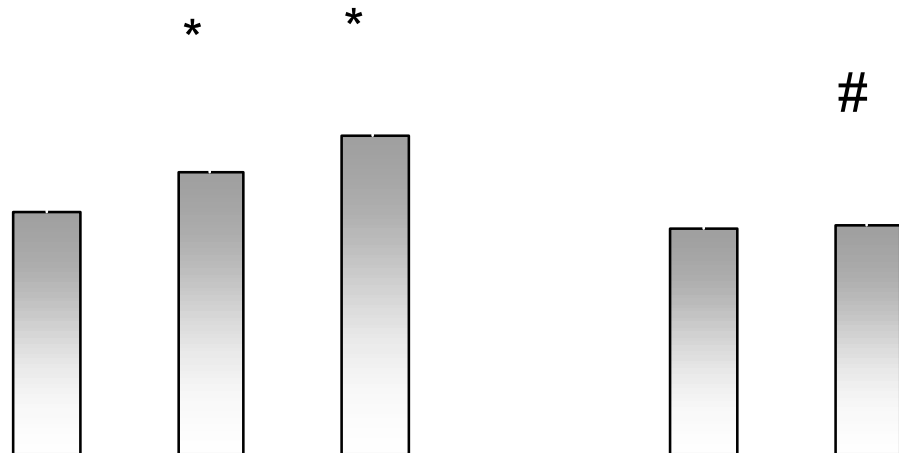
**2 days per week**





# Χρόνος Άσκησης

min

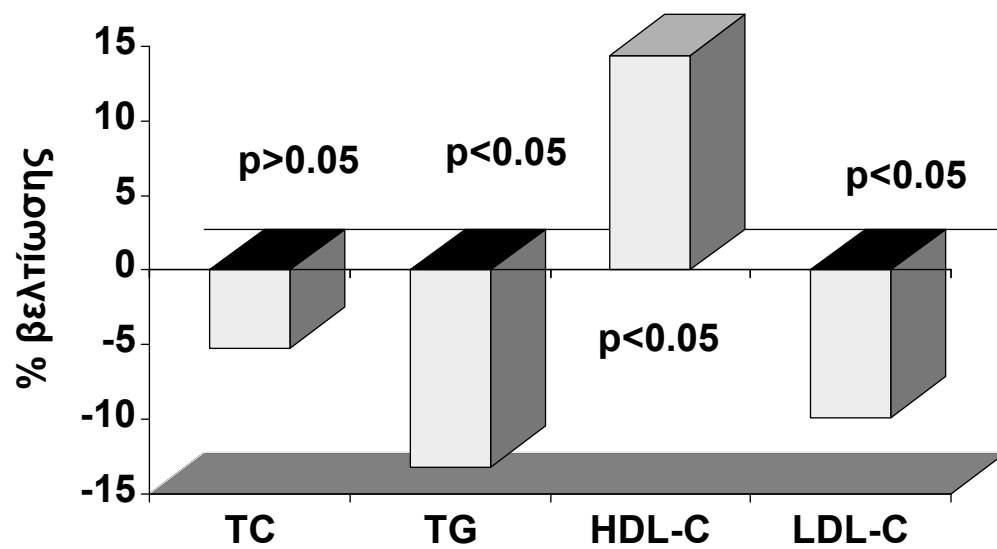


ΟΜΑΔΑ ΑΣΚΗΣΗΣ

ΟΜΑΔΑ ΕΛΕΓΧΟΥ

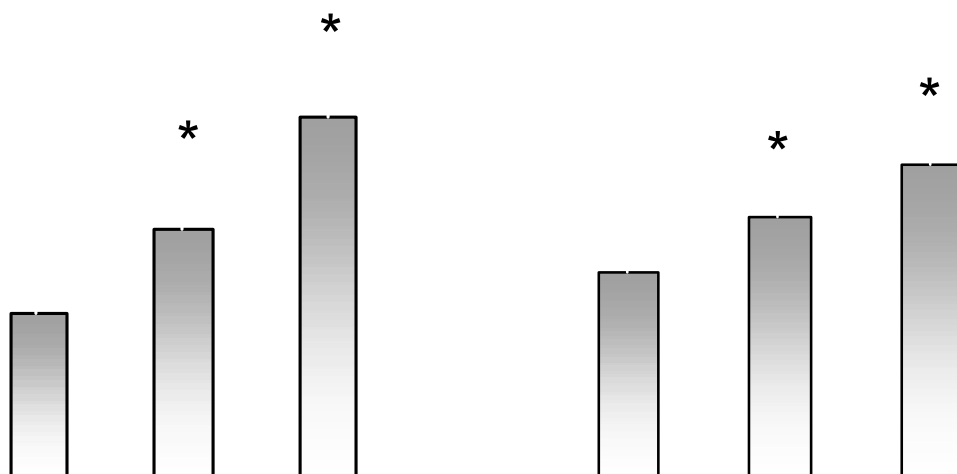


## Αιματολογικές παράμετροι

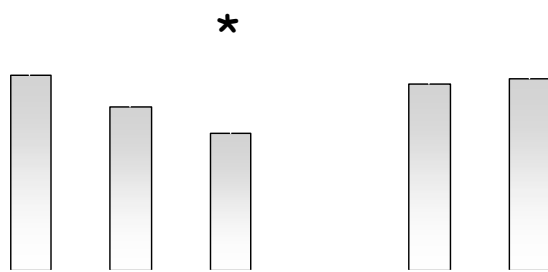


### Δύναμη άνω άκρων

### Δύναμη κάτω άκρων

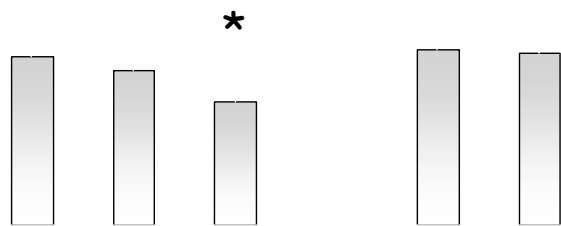


## Ολική χοληστερόλη (σε mg%)

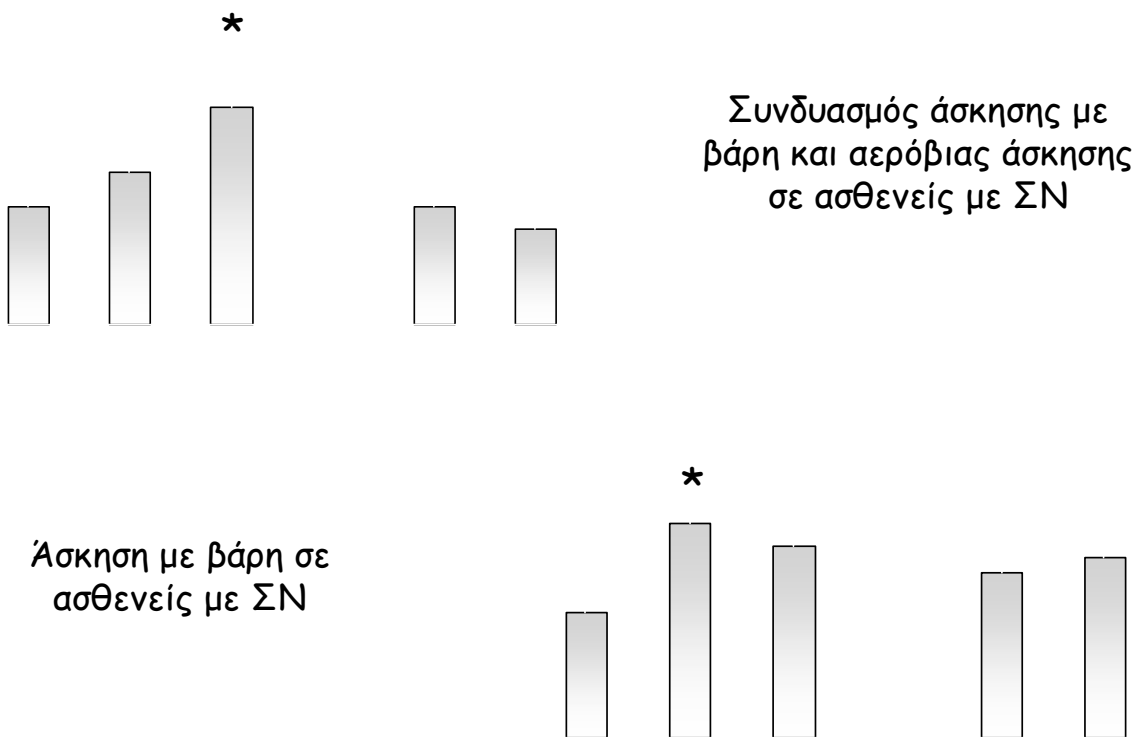


Συνδυασμός άσκησης με βάρη και αερόβιας άσκησης σε ασθενείς με ΣΝ

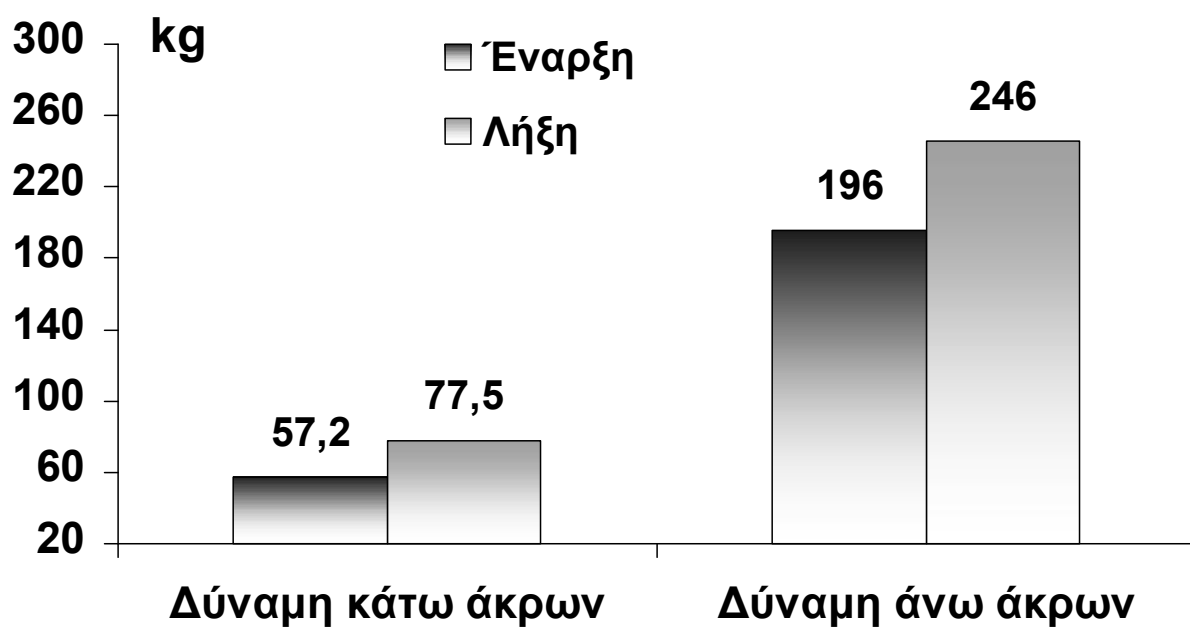
Άσκηση με βάρη σε ασθενείς με ΣΝ



## HDL-χοληστερόλη (σε mg%)



## Βελτίωση της μυϊκής δύναμης



**Resistance Exercise Protocols**  
**Different intensity - Similar volume**  
**Acute inflammatory responses**

**Submaximal Intensity - Muscular Hypertrophy**

**3 sets x 8 repetitions x 75% 1 RM, 90 sec rest**

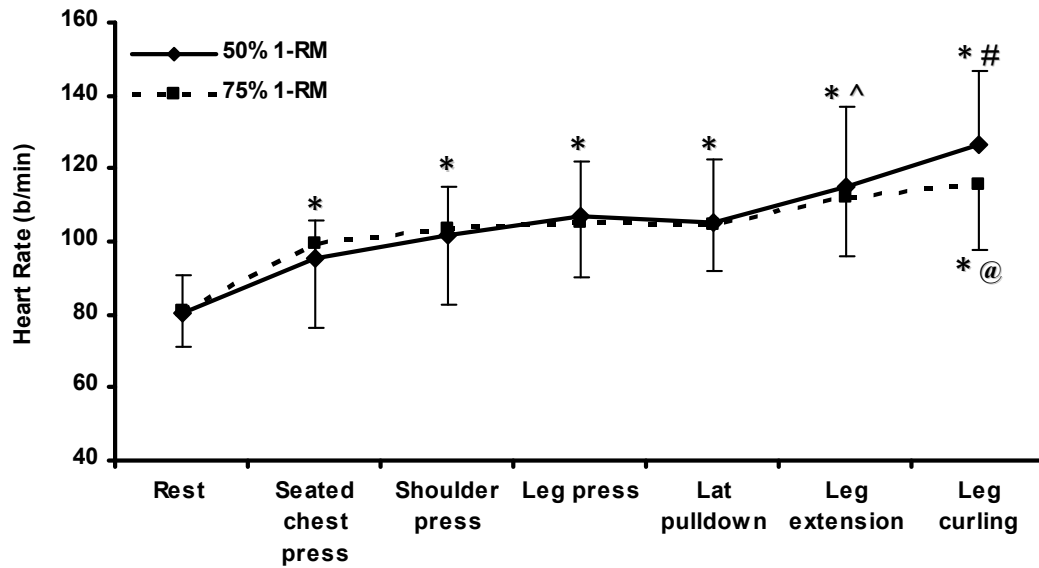
**Moderate Intensity - Muscular Endurance**

**2 sets x 18 repetitions x 50% 1 RM, 90 sec rest**

**Exercises**

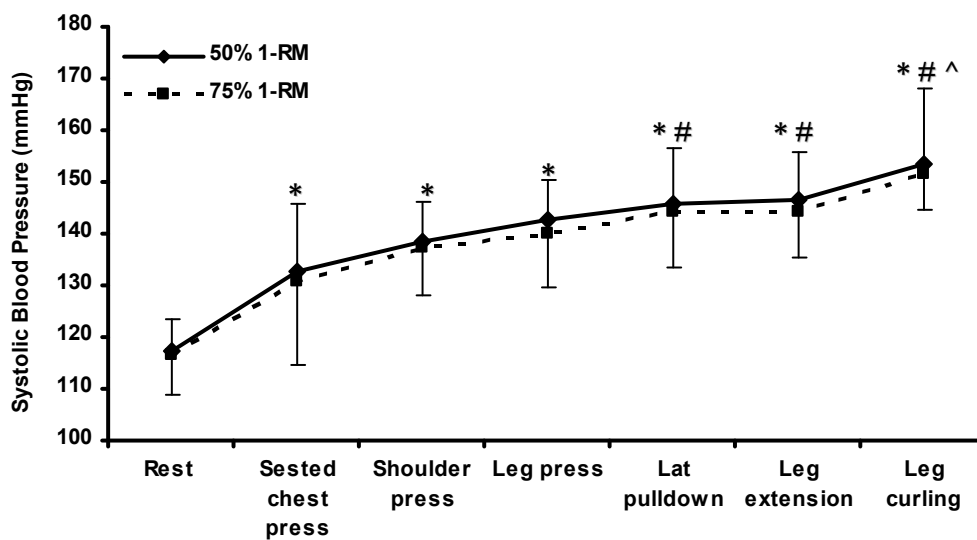
**Seated chest press, Shoulder press,  
Leg press, Lateral pulldown,  
Leg extension, Leg flexion**

# Heart rate



\*  $p < 0.05$  from rest, @  $p < 0.05$  from the first exercise,  
^  $p < 0.05$  from 1<sup>st</sup> and 2<sup>nd</sup> exercise, #  $p < 0.05$  from the first four exercises

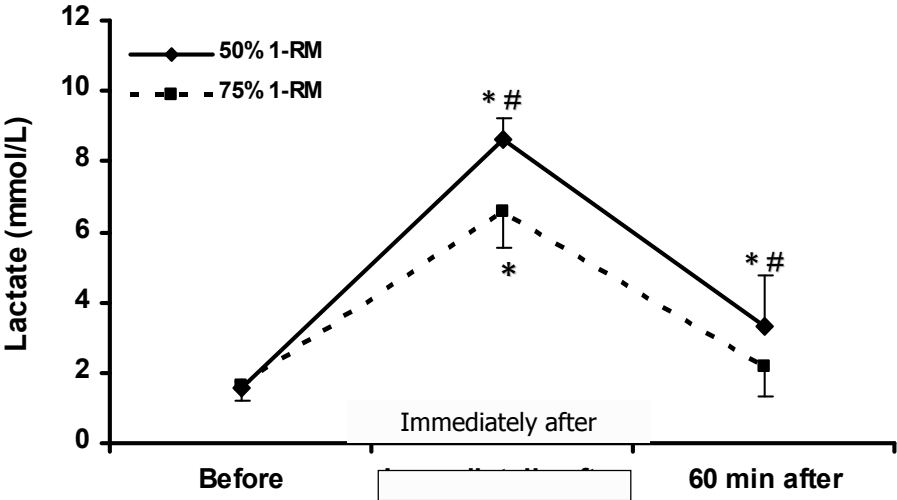
## Systolic Blood Pressure



\*  $p < 0.05$  from rest, #  $p < 0.05$  from the 1<sup>st</sup> exercise, ^  $p < 0.05$  from the 2<sup>nd</sup> exercise



# Blood Lactate

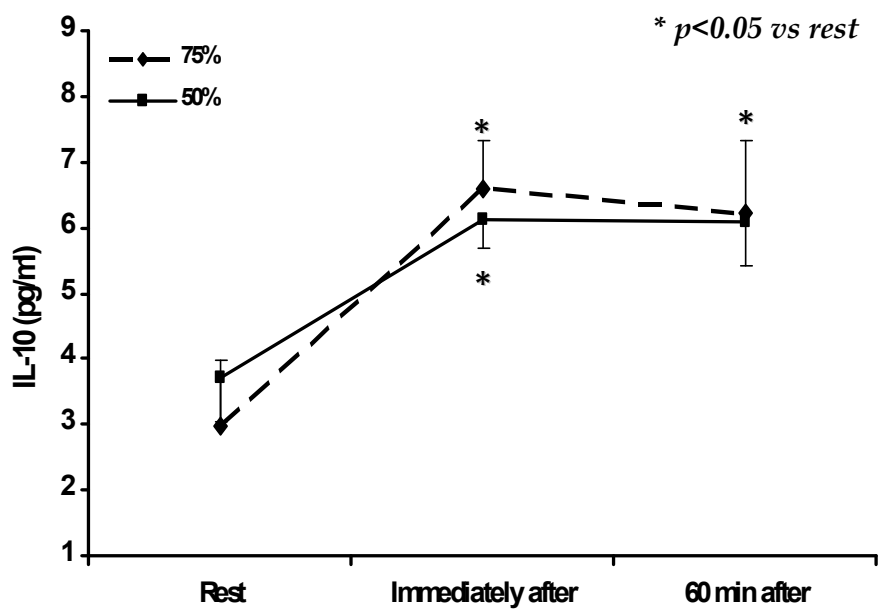


•  $p < 0.05$  from before exercise value  
• #  $p < 0.05$  from corresponding value with 75% 1-RM

### Inflammatory responses after resistance exercise

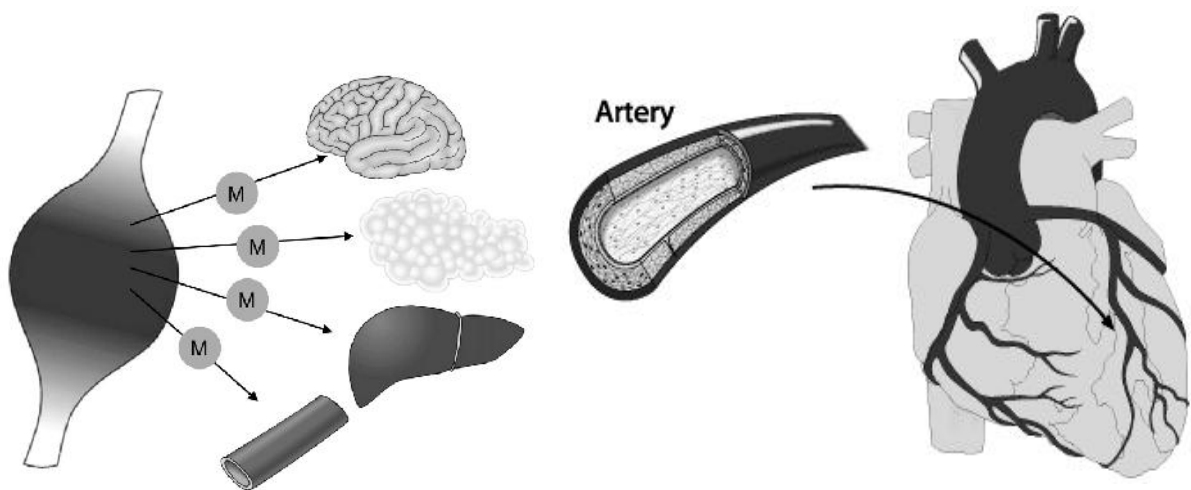
- TNF- $\alpha$  : NS alterations
- INF- $\gamma$  : NS alterations
- IL-6 : NS alterations
- IL-10 : Significant alterations

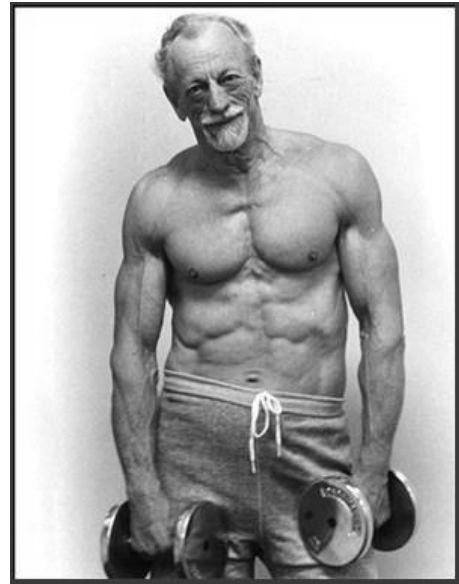
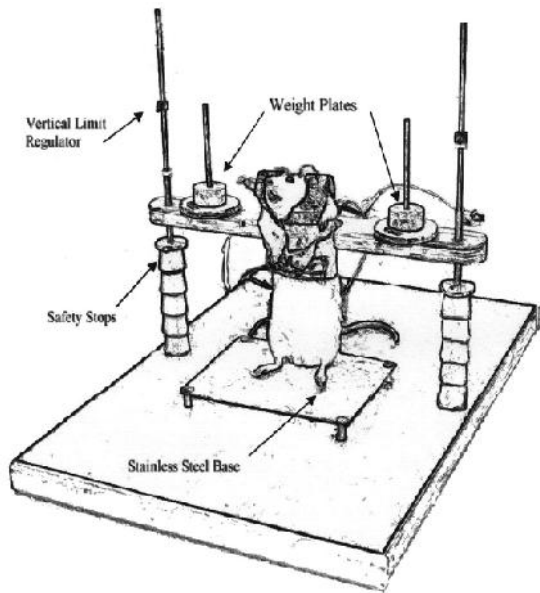
Thus, no inflammation occurs during resistance training at different intensities.



# Muscle as an Endocrine Organ

Pedersen et al. 2008; *Physiol Rev* 88: 1379-1406





**Thank you**