La Riabilitazione Interdisciplinare

L'esercizio fisico e le patologie cardiorespiratorie: dalla valutazione funzionale alla prescrizione

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Functional Evaluation and Exercise Prescription In Cardiac Patients

Background and Key Questions

Background:

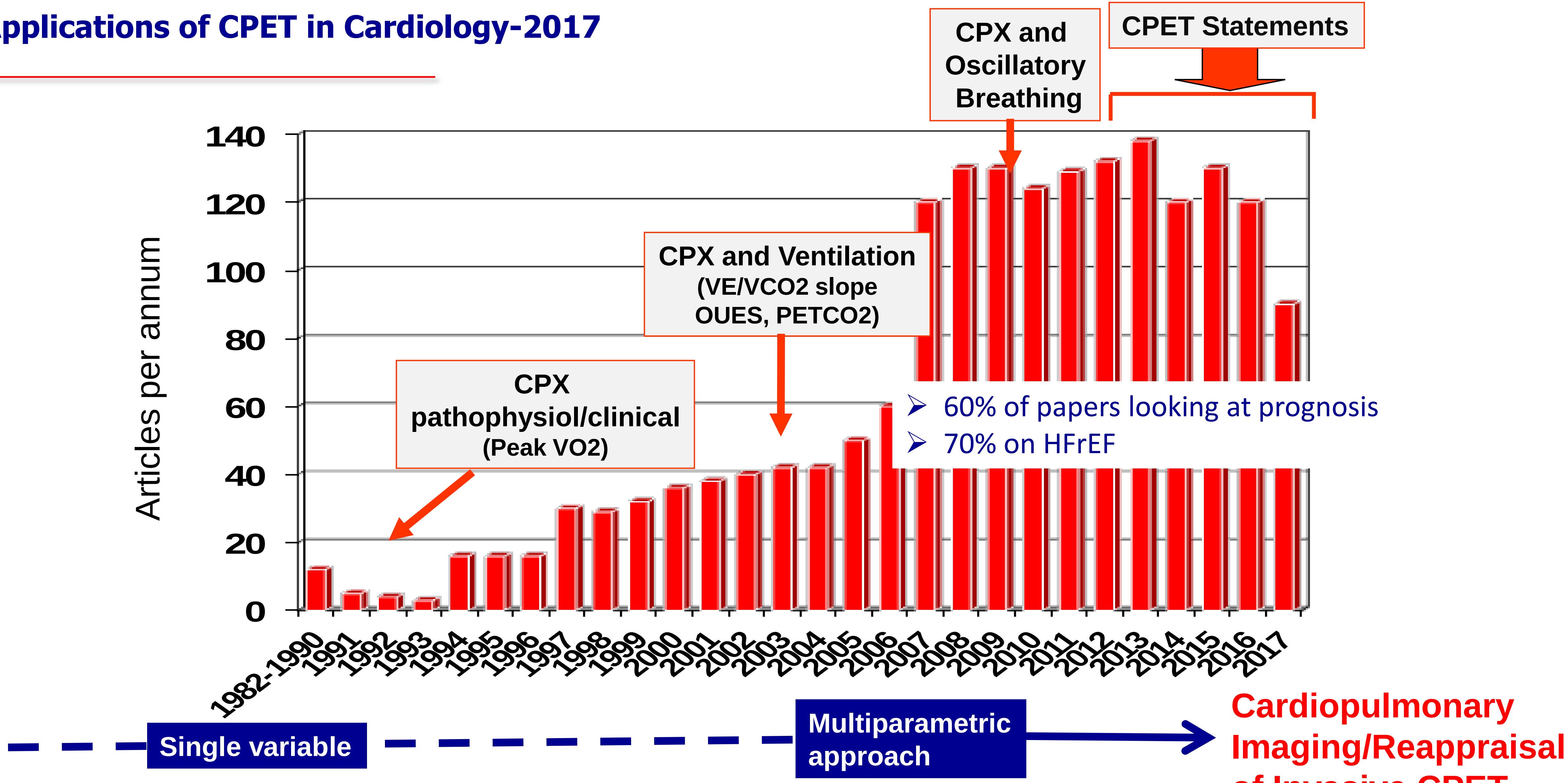
- Exercise is a Mainstay Physiological Stressor and VO_2 is a Key Measure of CV Health

Questions:

- O_2 Transport and Utilization Chain: What The Wrong Pathways in HF?
- Gas Exchange Analysis and Exercise Prescription

Functional Evaluation in Heart Failure

Applications of CPET in Cardiology-2017



Pubmed search analysis: CPET/CPX cardiac patients, heart disease, cardiopulmonary disease,exercise gas exchange

From 9 plots to Score Risk Tables…

European Heart Journal Advance Access published September 5, 2012

European Heart Journal
doi:10.1093/eurheartj/ehs221

POSITION STATEMENT

EACPR/AHA Joint Scientific Statement

Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations

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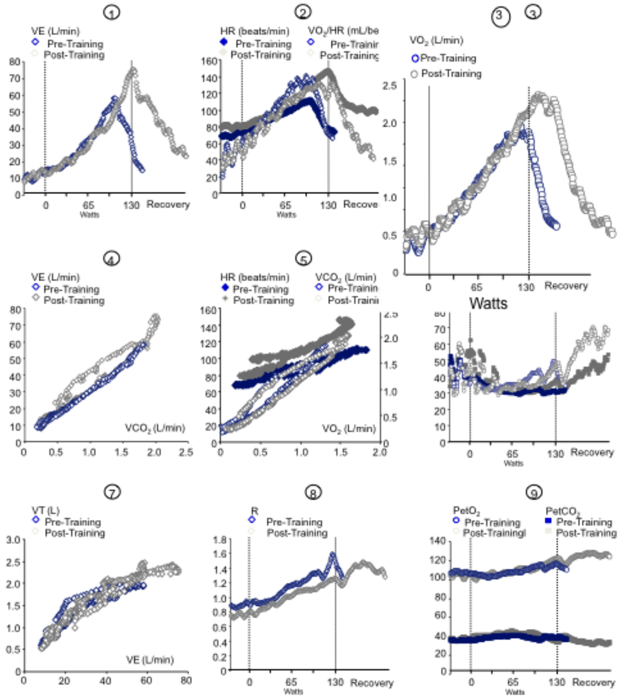
CHF
(ischemic cardiomyopathy)
male, 56 years

2 months aerobic training



Universal Report

Appendix I: Universal CPX reporting form (complete all boxes that apply for given ET indication)

Exercise modality: [ ] Treadmill [ ] Lower extremity ergometer

Protocol:		
Peak V_{O_2} (mL O_2•kg^{-1}•min^{-1}) V_{O_2} at VT (mL O_2•kg^{-1}•min^{-1})	Per cent-predicted peak V_{O_2} (%)[a] Peak RER	VE/V_{CO_2} slope EOV [ ] Yes [ ] No
$P_{ET}CO_2$ (mmHg) Resting: Increase during ET:	VE/V_{O_2} at peak ET	$\Delta Q/\Delta V_{O_2}$[b]
VE/MVV[c]:	PEF (L/min): Pre-ET	Post-ET
O_2 pulse trajectory[d] [ ] Continual rise throughout ET [ ] Early and sustained plateau [ ] Decline		
$\Delta V_{O_2}/\Delta W$ trajectory[d] [ ] Continual rise throughout ET [ ] Early and sustained plateau [ ] Decline		
Resting HR (b.p.m.) Peak HR (b.p.m.) Percent of age-predicted maximal HR[e] HRR at 1 min (beats)	Resting BP (mmHg) Peak BP (mmHg) Maximal workload [ ] Treadmill speed/grade: [ ] Cycler ergometer Watts:	Resting pulse oximetry (%) Peak pulse oximetry (%)
ECG criteria [ ] No arrhythmias/Ectopy/ST segment changes [ ] Arrhythmias/Ectopy/ST segment changes: not exercise limiting [ ] Arrhythmias/Ectopy/ST segment changes: exercise limiting		ECG description
Subjective symptoms (check box for primary termination criteria) RPE [ ] Angina [ ] Dyspnoea [ ]		
Additional notes		

CPX, cardiopulmonary exercise testing; ET, exercise testing; V_{O_2}, oxygen consumption; VT, ventilator threshold; RER, respiratory exchange ratio; VE/V_{CO_2}, minute ventilation/carbon dioxide production; EOV, exercise oscillatory ventilation; $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide production; VE/V_{O_2}, minute ventilation/oxygen consumption; VE/MVV, peak minute ventilation/maximal voluntary ventilation; $\Delta Q/\Delta V_{O_2}$, change in cardiac output/change in oxygen consumption; PEF, peak expiratory flow; O_2, oxygen; $\Delta V_{O_2}/\Delta W$, change in oxygen consumption/change in Watts; HR, heart rate; BP, blood pressure; HRR, heart rate recovery; ECG, electrocardiogram; RPE, rating of perceived exertion
[a]Use equations proposed by Wasserman.
[b]Requires additional equipment of assess Q response to exercise through non-invasive rebreathing technique.
[c]Directly measure MVV at baseline.
[d]Requires O_2 pulse and $\Delta V_{O_2}/\Delta W$ plot from initiation to end of ET. If these variables required for assessment, electronically braked cycle ergometer should be used for testing.
[e]Use equation: (peak HR/220-age) * 100.

Color-Coded Score Tables

Appendix 2: Prognostic and diagnostic stratification for patients with HF

Primary CPX variables

VE/V_{CO_2} slope	Peak V_{O_2}[a]	EOV	$P_{ET}CO_2$
Ventilatory class I VE/V_{CO_2} slope <30.0	Weber class A Peak V_{O_2} >20.0 mL O_2•kg^{-1}•min^{-1}	Not present	Resting $P_{ET}CO_2$ ≥33.0 mmHg 3–8 mmHg increase during ET
Ventilatory class II VE/V_{CO_2} slope 30.0–35.9	Weber class B Peak V_{O_2} = 16.0–20.0 mL O_2•kg^{-1}•min^{-1}		
Ventilatory class III VE/V_{CO_2} slope 36.0–44.9	Weber class C Peak V_{O_2} = 10.0–15.9 mL O_2•kg^{-1}•min^{-1}	Present	Resting $P_{ET}CO_2$ <33.0 mmHg <3 mmHg increase during exercise
Ventilatory class IV VE/V_{CO_2} slope ≥45.0	Weber class D Peak V_{O_2} <10.0 mL O_2•kg^{-1}•min^{-1}		

Standard ET variables

Haemodynamics	ECG	HRR
Rise in systolic BP during ET	No sustained arrhythmias, ectopic foci, and/or ST segment changes during ET and/or in recovery	>12 beats at 1 min recovery
Flat systolic BP response during exercise	Altered rhythm, ectopic foci, and or ST segment changes during ET and/or in recovery: did not lead to test termination	≤12 beats at 1 min recovery
Drop in systolic BP during ET	Altered rhythm, ectopic foci, and or ST segment changes during ET and/or in recovery: led to test termination	

Patient reason for test termination

Lower extremity muscle fatigue	Angina	Dyspnoea

Interpretation

- All variables in green: excellent prognosis in next 1–4 years (≥90% event free)
  - Maintain medical management and retest in 4 years.
- Greater number of CPX and standard ET variables in red/yellow/orange indicative of progressively worse prognosis.
  - All CPX variables in red: risk for major adverse event extremely high in next 1–4 years (>50%).
- Greater number of CPX and standard ET variables in red/yellow/orange indicative of increasing HF disease severity.
  - All CPX variables in red: expect significantly diminished cardiac output, elevated neurohormones, higher potential for secondary PH.
- Greater number of CPX and standard ET variables in red/yellow/orange warrants strong consideration of more aggressive medical management and surgical options.

VE/V_{CO_2}, minute ventilation/carbon dioxide production; V_{O_2}, oxygen consumption; EOV, exercise oscillatory ventilation; $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide; BP, blood pressure; CPX, cardiopulmonary exercise test; ECG, electrocardiogram; ET, exercise test; HRR, heart rate recovery; RER, respiratory exchange ratio.
[a]Peak V_{O_2} valid if peak RER is at least 1.00 or test terminated secondary to abnormal haemodynamic or ECG exercise response.

…..the ultimate goal is to increase awareness of the value of CPET and to increase the number of healthcare professionals who are able to perform clinically meaningful interpretation.

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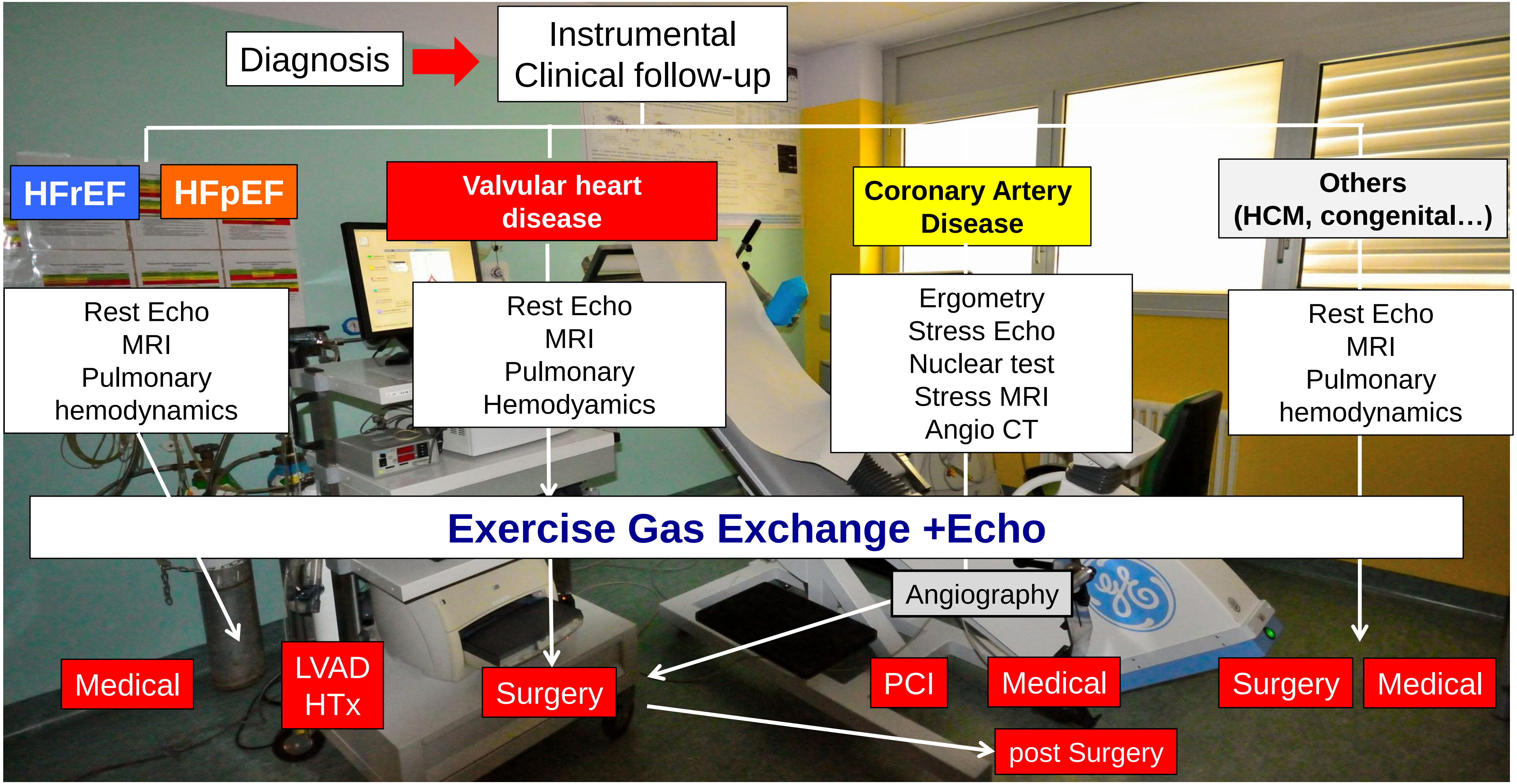
American Heart Association

Applications of NonInvasive Echo Combined Approach in the CPX Lab…



STATE-OF-THE-ART REVIEW

Cardiopulmonary Exercise Testing

What Is its Value?

Marco Guazzi, MD, PhD,[a] Francesco Bandera, MD, PhD,[a] Cemal Ozemek, PhD,[b] David Systrom, MD,[c,d]
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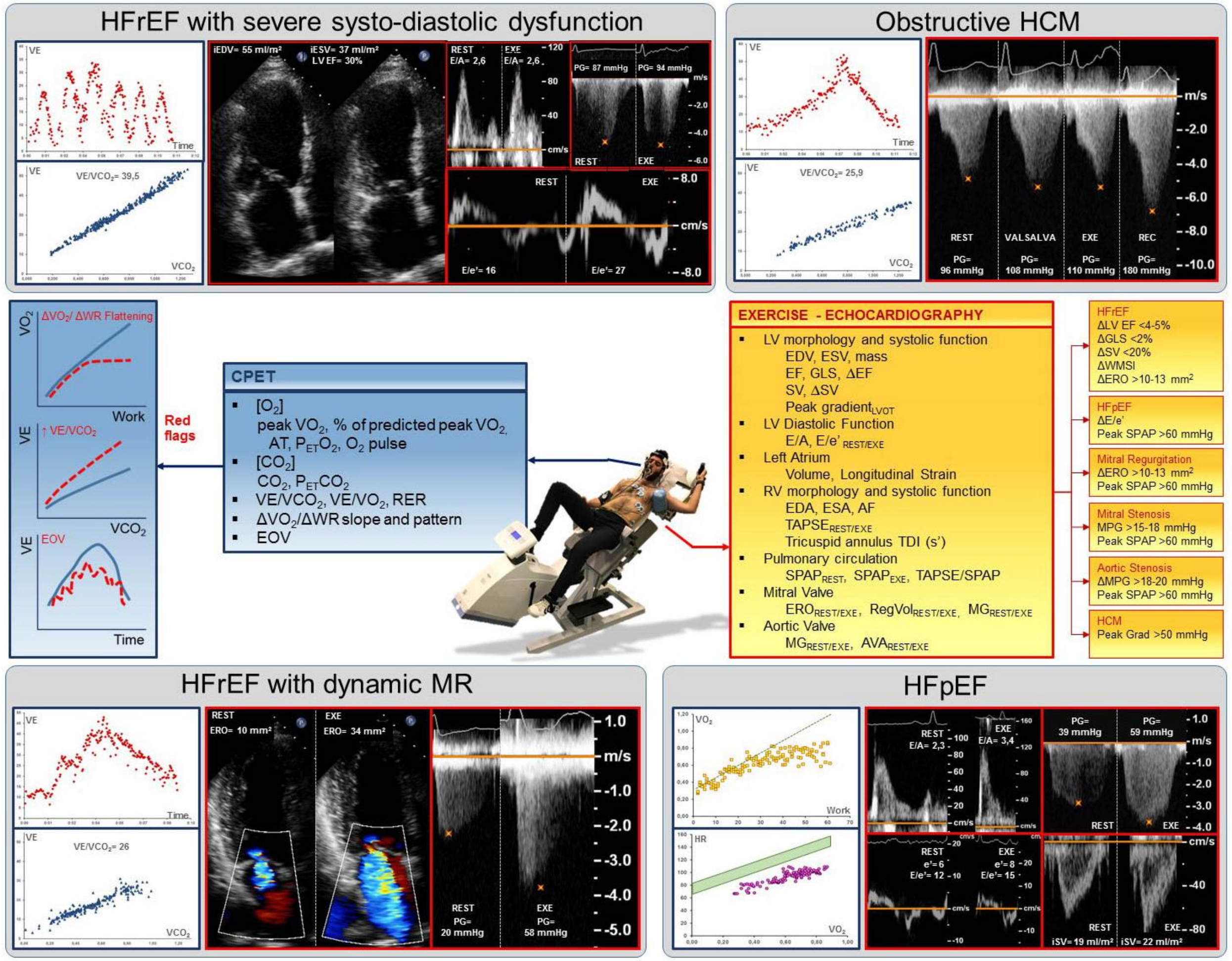
Cardiopulmonary Imaging

CPET imaging is a quite recent and valuable testing modality, which is receiving attention for its potential to combine exercise physiological data with noninvasive recordings of cardiac function by measures of systolic and diastolic function, including the evaluation of left atrium (LA) function (85). In addition, the

. In addition, the assessment of cardiac "functional reserve" by CPET imaging is greatly improved by the study of the pathophysiological response of the pulmonary circulation to exercise, whose clinical implications appear complementary to and synergistic with the information obtained with iCPET (86,87). A typical example of this

JACC VOL. 70, NO. 13, 2017
SEPTEMBER 26, 2017:1618-36



Determinants of Effort Intolerance in Patients With Heart Failure

Combined Echocardiography and Cardiopulmonary Stress Protocol

JACC: HEART FAILURE

PUBLISHED BY ELSEVIER INC.

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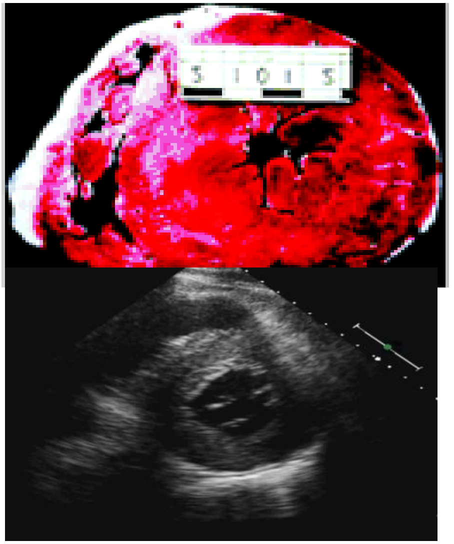
Amir Halkin, MD,* Meirav Ingbir, MD,* Nahum Nesher, MD,‡ Simon Biner, MD,* Gad Keren, MD,* Yan Topilsky, MD*

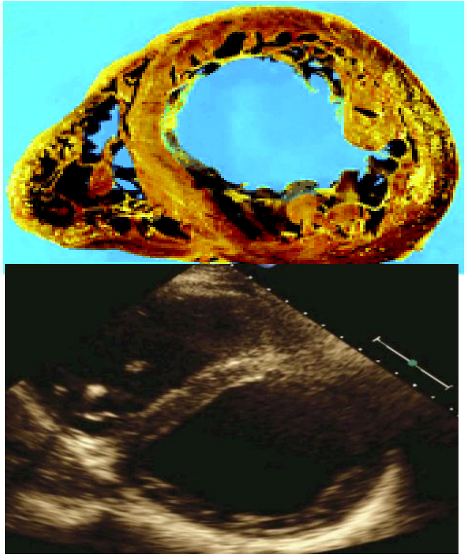
Measurement	Baseline	Unloaded Effort	Anaerobic Threshold	Maximal Effort	P Value for Each Group	Within Group	Between Groups	Time-Group Interaction
Stroke volume, ml								
Normal	77.3 ± 10.0	92.1 ± 15.0†	105 ± 16†	98.6 ± 13.0	<0.0001			
HFpEF	78.8 ± 17.0	91 ± 20*	94.5 ± 24.0	86.7 ± 19,0*	0.007	<0.0001	0.006	0.0001
HFrEF	67.1 ± 20.0	67.5 ± 18.0	74.7 ± 27.0	70.7 ± 31.0	0.12			
Cardiac output, l/min								
Normal	6.2 ± 1.1	8.0 ± 1.8†	12.6 ± 2.6†	14.5 ± 2.9*	<0.0001			
HFpEF	6.0 ± 1.5	7.7 ± 2.0†	9.4 ± 3.5*	9.6 ± 4.2	0.007	<0.0001	0.0001	<0.0001
HFrEF	4.9 ± 1.5	5.8 ± 1.3	7.0 ± 2.8	8.2 ± 4.4	0.10			
Vo_2, l/min								
Normal	0.36 ± 0.09	[illegible]	[illegible]	[illegible]	[illegible]			
HFpEF	0.37 ± 0.08	[illegible]	[illegible]	[illegible]	[illegible]	<0.0001	0.003	<0.0001
HFrEF	0.34 ± 0.09	[illegible]	[illegible]	[illegible]	<0.0001			
Mitral regurgitation, ml								
Normal	0.1 ± 0.3	1.2 ± 2.4	0.4 ± [illegible]	1.2 ± 2.8	0.50			
HFpEF	4.2 ± 4.1	8.6 ± 3.4*	3.8 ± [illegible]	3.7 ± 5.9	0.04	0.05	<0.0001	0.01
HFrEF	8.6 ± 13.5	24.0 ± 27.0*	21.3 ± 22.0	23.9 ± 22.8	0.05			
Avo_2diff, l/l								
Normal	0.06 ± 0.01	0.07 ± 0.11†	0.10 ± 0.02†	0.13 ± 0.03†	<0.0001			
HFpEF	0.06 ± 0.02	0.07 ± 0.02	0.10 ± 0.03†	0.13 ± 0.05†	<0.0001	<0.0001	0.06	0.80
HFrEF	0.08 ± 0.03	0.09 ± 0.02*	0.12 ± 0.02*	0.14 ± 0.01*	0.02			

Values are mean ± SD, or n (%). *p< 0.01, †p <0.001
AVo_2Diff = arterial-venous oxygen content difference; EDV = end-diastolic volume; other abbreviations as in Table 1

AVO2 diff estimation by CO estim and VO2

Determinants of the O_2 Transport and Utilization Chain Framed on the Fick Principle





Heart Failure

Signs and Symptoms

HFpEF

HFrEF

Exercise Intolerance
Dyspnea and Fatigue

Organ limiting steps in O_2 uptake
[convection (delivery), release, diffusion and use]

$$VO_2 = C.O. \times C\,(a\text{-}v)\,O_2$$

Pulmonary	Cardiac	Hematological	Vascular	Mitochondrial
Ventilation Alveolar gas diffusion	SV HR	Hb concentration Mediators of release	Vasoregulation Capillary network	Krebbs cycle- ATP generation
impaired O_2 diffusion (alveolar)	Impaired O_2 delivery	Impaired O_2 delivery and release	Delayed/insufficient O_2 diffusion	Impaired O_2 utilization (extraction)

Low Pcap O_2 (Pulmonary, Cardiac, Hematological)

High PvO_2 (Vascular, Mitochondrial)

Guazzi, M. et al. J Am Coll Cardiol. 2017;70(13):161

Fick Principle: Determinants

Delivery or convection

Extraction

$$\dot{V}O_2 = C.O. \times c\,(a\text{-}v)\,O_2$$

2.5 times

1.2 times

2.5 times

$$C.O. = HR \times SV$$

Mixed Venous

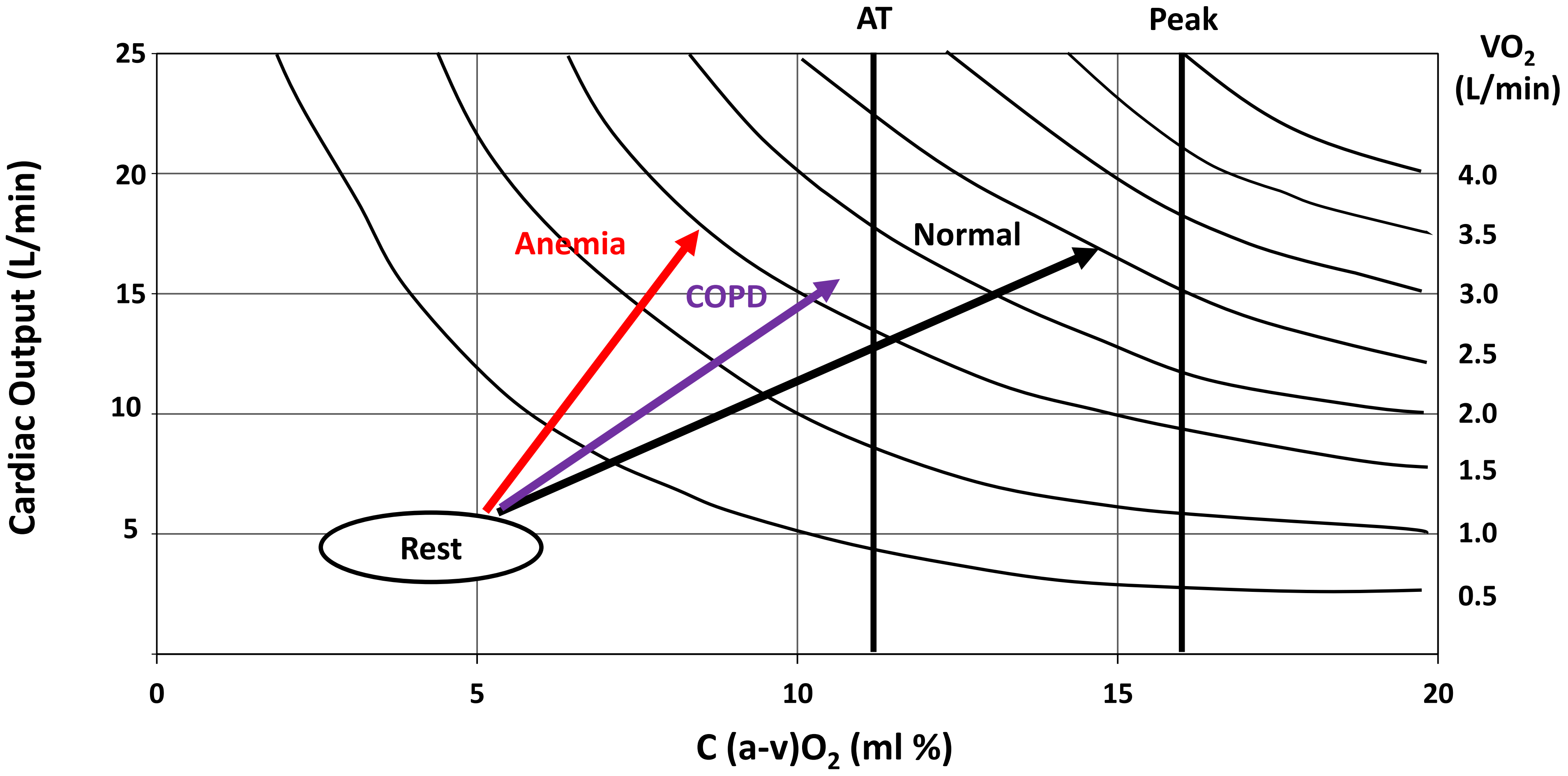
$$C = 1.34 \times Sat\,O_2 \times [Hb]$$

Ventilation
Gas diffusion
Perfusion

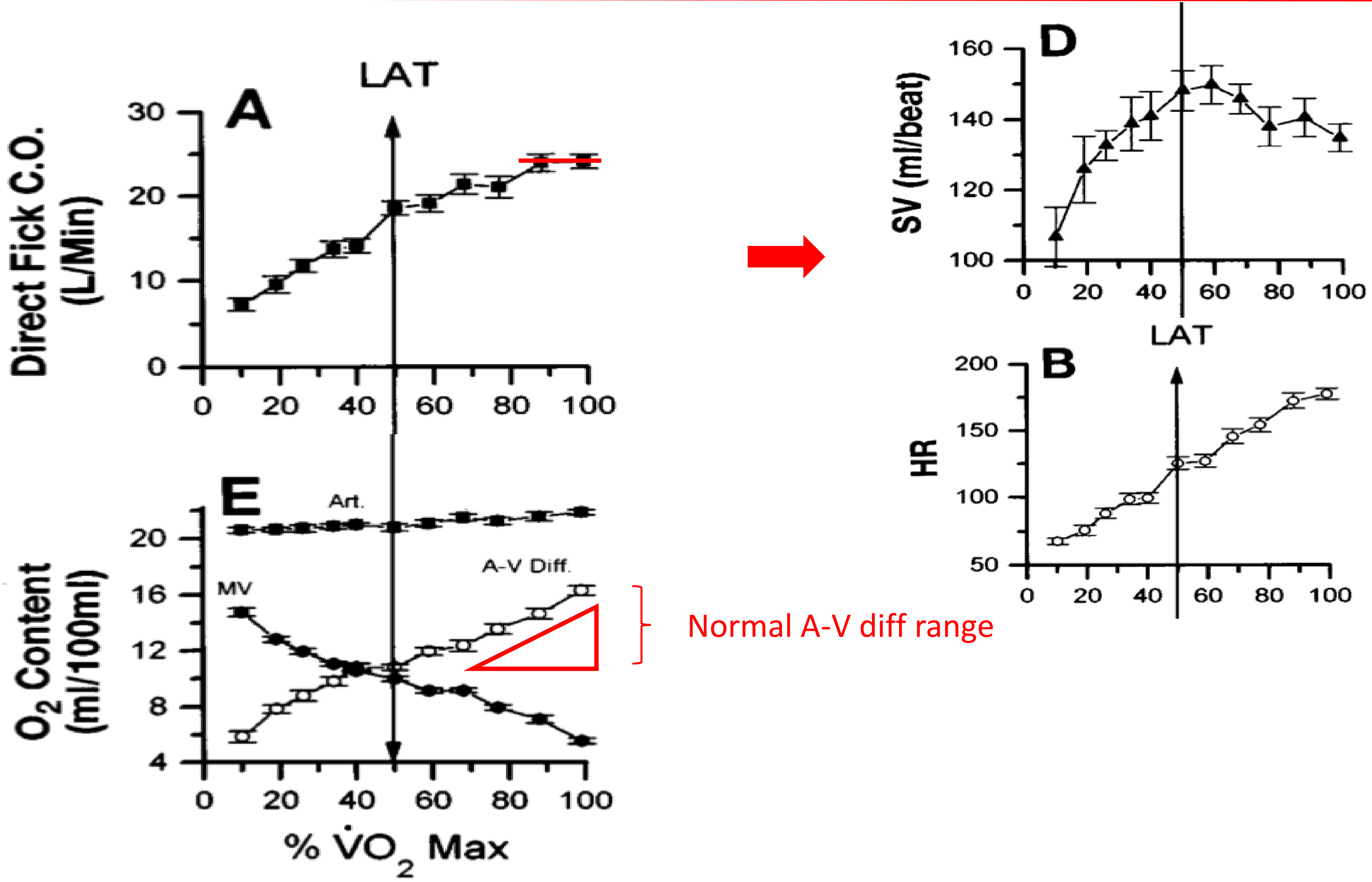
HYPOXIA

ANEMIA

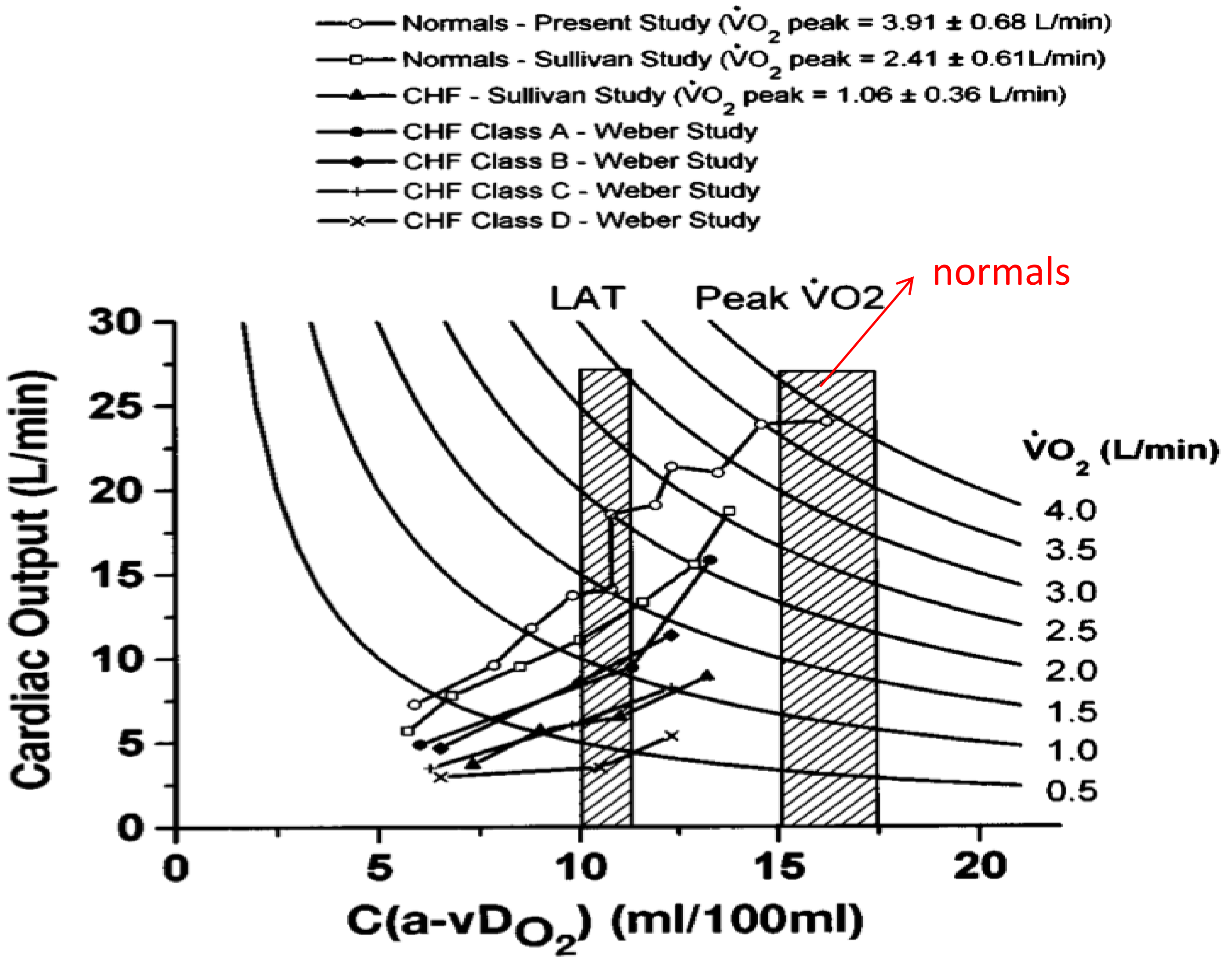
$$C.O. \times C(a-\bar{v})O_2 = \dot{V}O_2$$



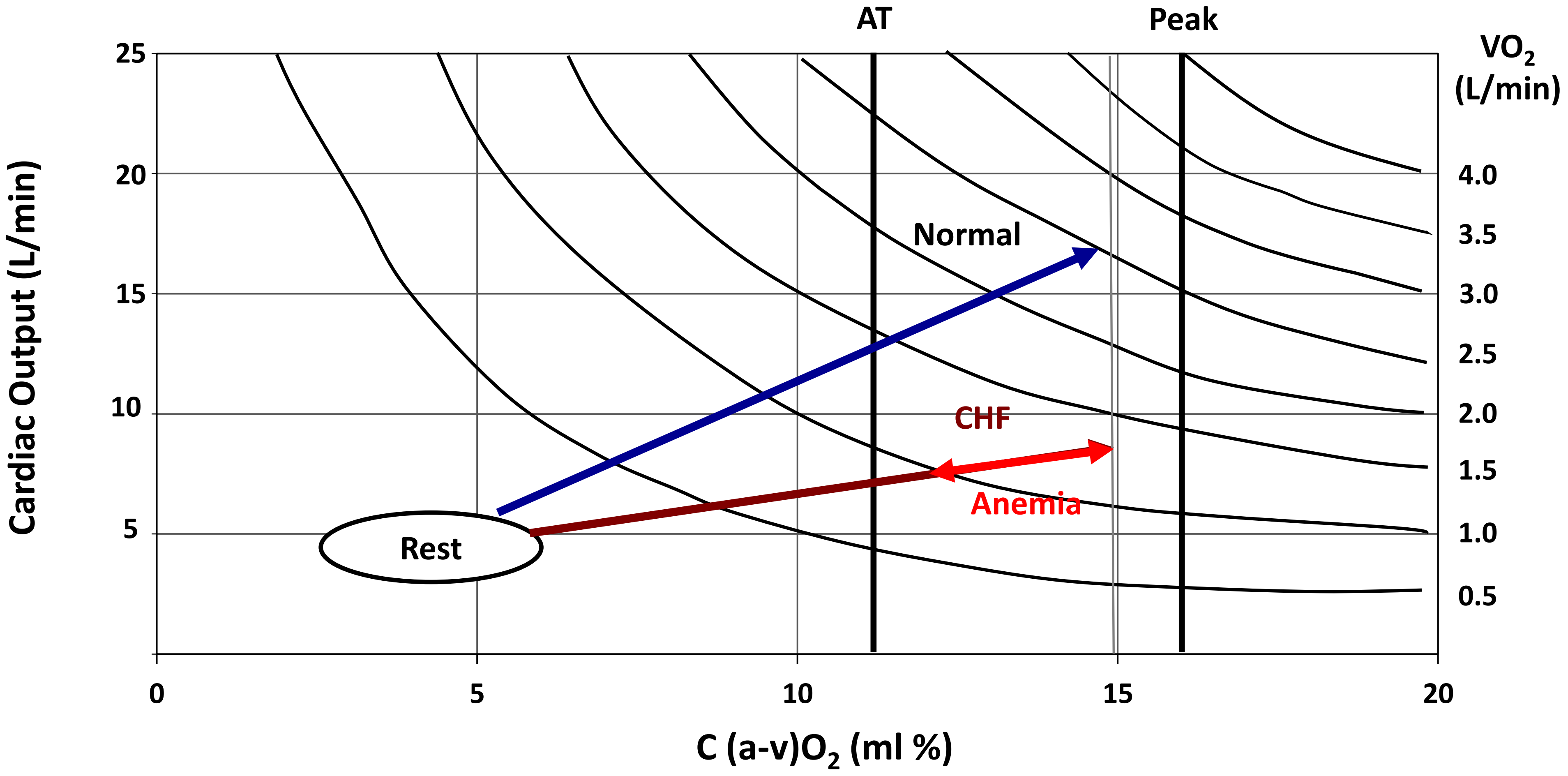
Cardiac Output and O_2 Extraction at Maximum Exe. in Normal Individuals *Stringer et al J Appl Physiol 1997;*83:631-43.



Cardiac Output and O_2 Extraction at Peak Exe. in HFrEF



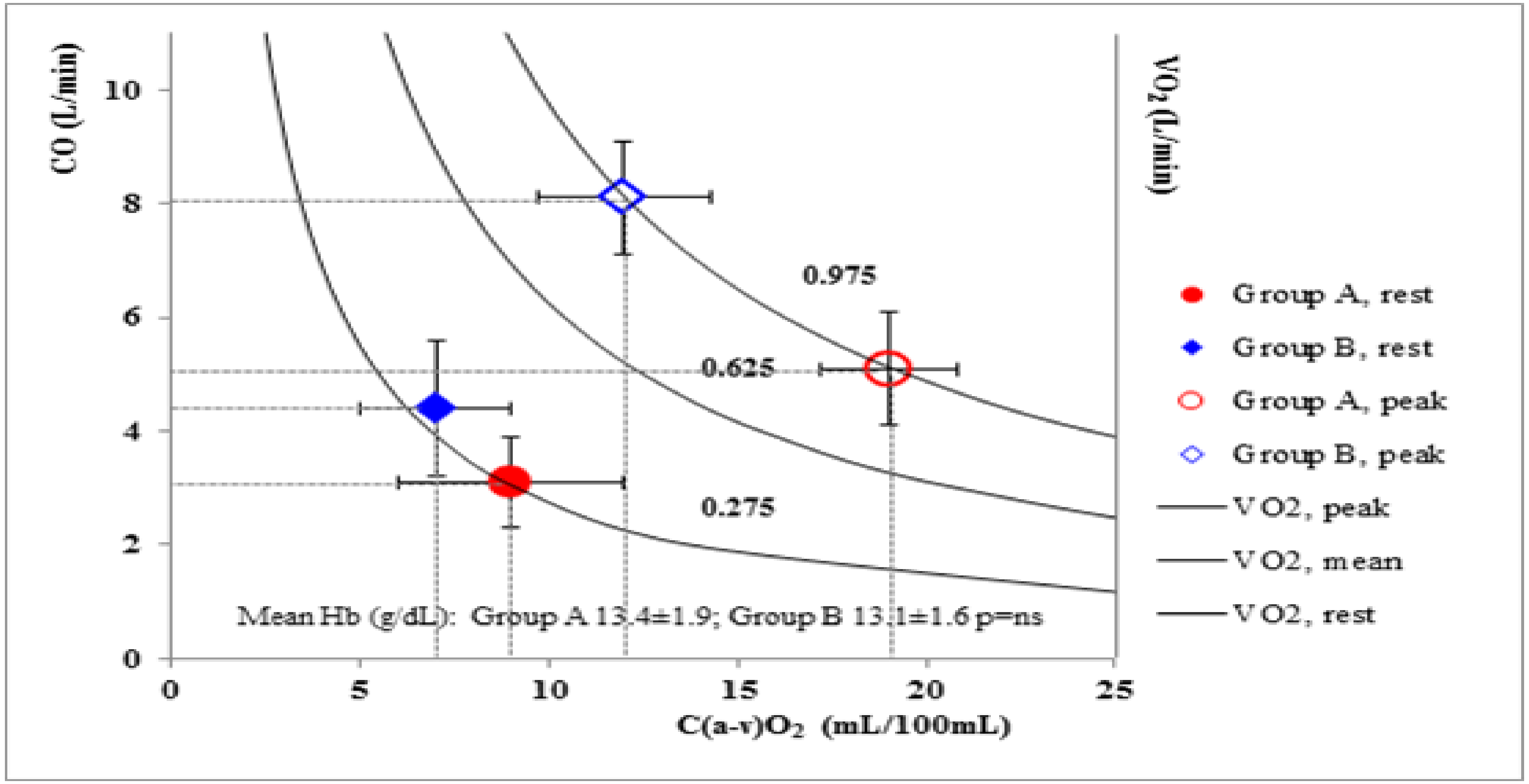
$C.O. \times C(a-\bar{v})O_2 = \dot{V}O_2$



Partitioning C (a-v) O_2 Contribution to VO_2 Increase in Severe HFrEF

To define the $C(a\text{-}v)O_2$ phenotypes (high vs low) by estimating extraction from the CO/VO_2ratio

- ❑ 104 HFrEF patients (mean age 64±11 y, male %, ischemic etiology 68%, mean LVEF 34±9%)
- ❑ Population divided by CO/VO_2 median value
- ❑ Group A (<0.49) vs Group B (>0.49)



In preparation

Functional and Echocardiographic Characteristics According to the Extent of C (a-v) O_2 Extent

Variables	Group A (n=52)		Group B (n=52)		p value	
	Rest	Peak	Rest	Peak	Rest	Peak
CPET						
VO_2, L/min	0.26±0.1	0.96±0.3	0.29±0.1	0.99±0.3	.03	ns
Peak VO_2, ml O_2*Kg^{-1}*min^{-1}		11.8±4		12.6±3.1		ns
C(a-v)O_2, mL/100mL	9±3	19±5	7±1	12±3	.000	.000
VE/VCO_2, slope		36±11		31±7		.01
ECHO						
LVEDVi, ml/m^2	101±33		91±23		.09	
MR ERO, mm^2	22±10	33±13	16±9	25±12	.02	.003
E/e’	28±15		22±11		.02	
CO, l/min	3.1±0.8	5.1±1.8	4.4±1.2	8.1±2.3	.000	.000

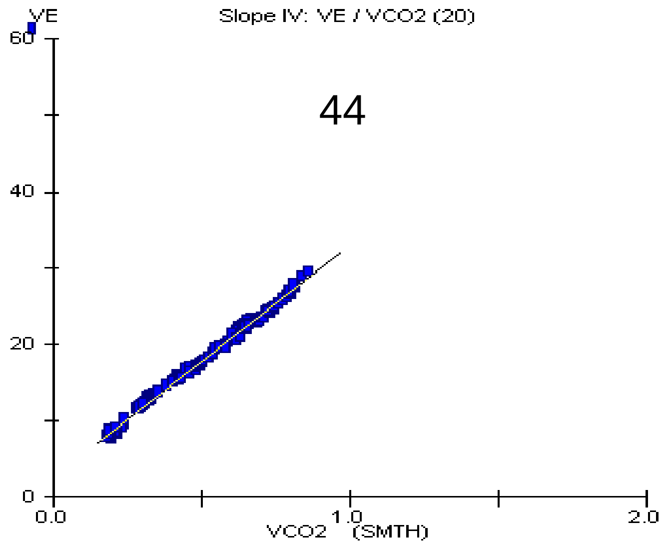
“Good Extractor”

(peak exercise CO/VO_2<0.49)

CO, L/min:
Rest 2.9; Peak 3.72

VO_2: L/min
Rest 0.27; Peak 0.65

$C(a\text{-}v)O_2$ mL/100 mL Rest 9; Peak 17



Impaired ventilatory efficiency

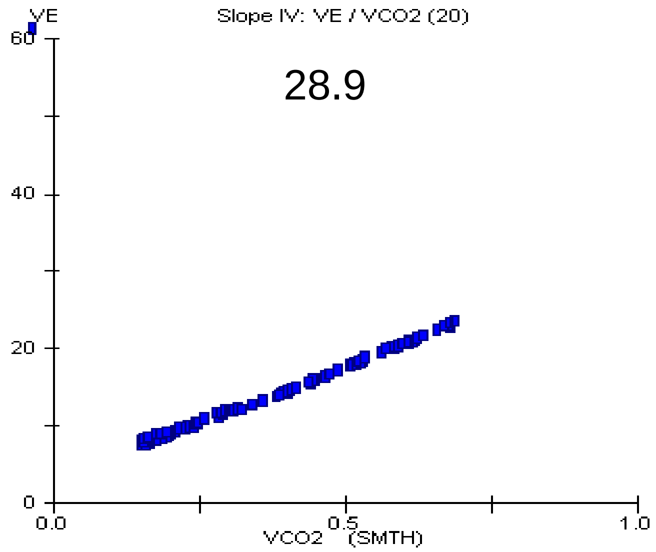
“Bad Extractor”

(peak exercise CO/VO_2 ≥0.49)

CO, L/min:
Rest 3.3; Peak 5.2

VO_2: L/min
Rest 0.19 ; Peak 0.61

$C(a\text{-}v)O_2$ mL/100 mL Rest 6; Peak 12

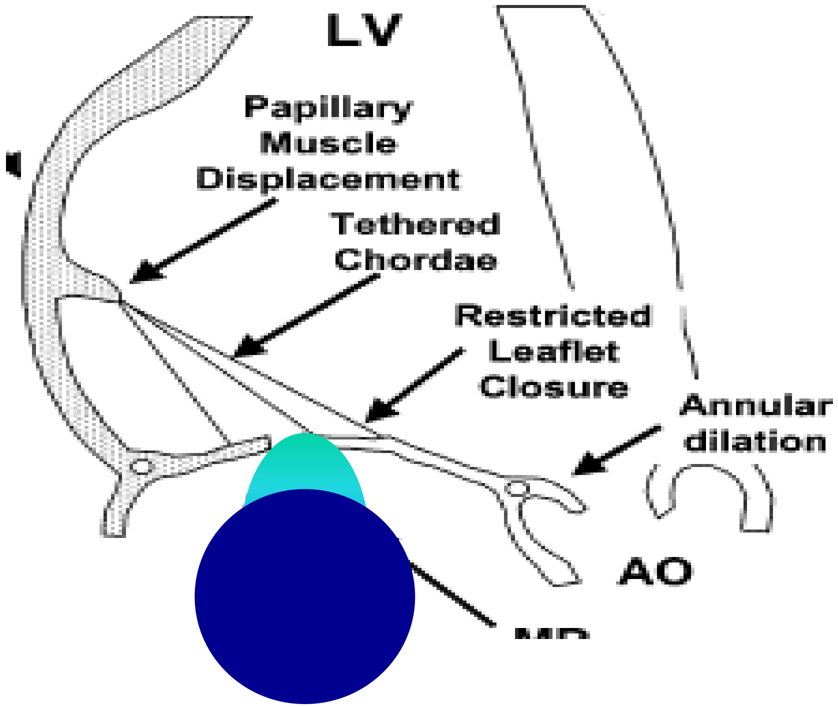


Preserved ventilatory efficiency

Effects of Exe. Central Blood Flow Distribution on Fick Principle in HFrEF

To define the role of mitral regurgitation on $C(a\text{-}v)O_{2,}$ CO and related functional phenotype

- ❑110 HFrEF patients (mean age 65±11 y, male %, ischemic etiology 64%, mean LVEF 32±8%) divided by severe MR
- ❑33 Controls



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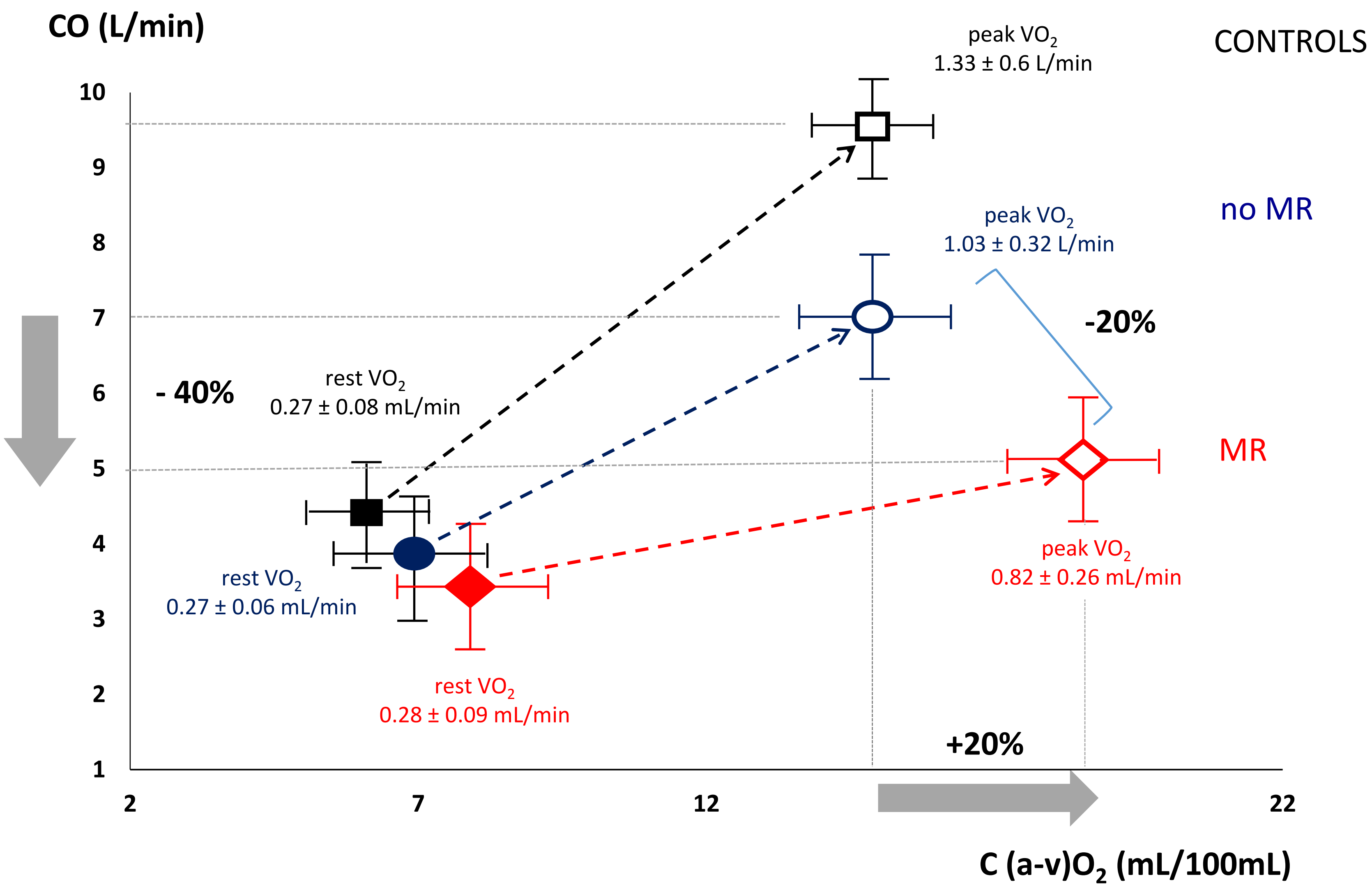
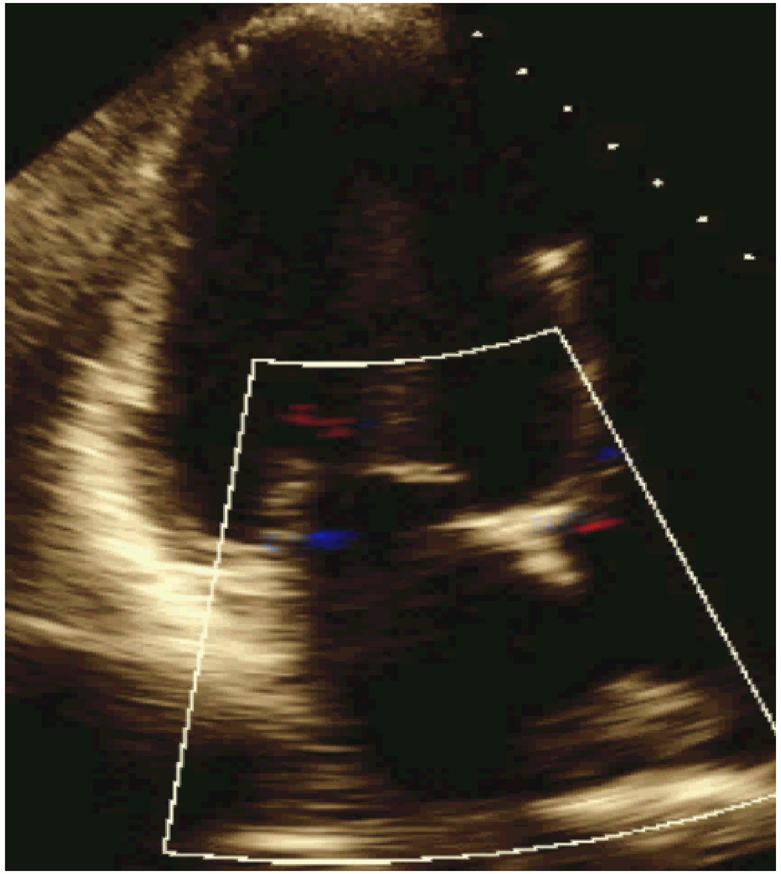


CO (L/min)
CONTROLS
no MR
MR
peak VO2
1.33 ± 0.6 L/min
peak VO2
1.03 ± 0.32 L/min
-20%
- 40%
rest VO2
0.27 ± 0.08 mL/min
rest VO2
0.27 ± 0.06 mL/min
rest VO2
0.28 ± 0.09 mL/min
peak VO2
0.82 ± 0.26 mL/min
+20%
10
9
8
7
6
5
4
3
2
1
2
7
12
22
C (a-v)O2 (mL/100mL)

Functional and Echocardiographic Characteristics According to MR

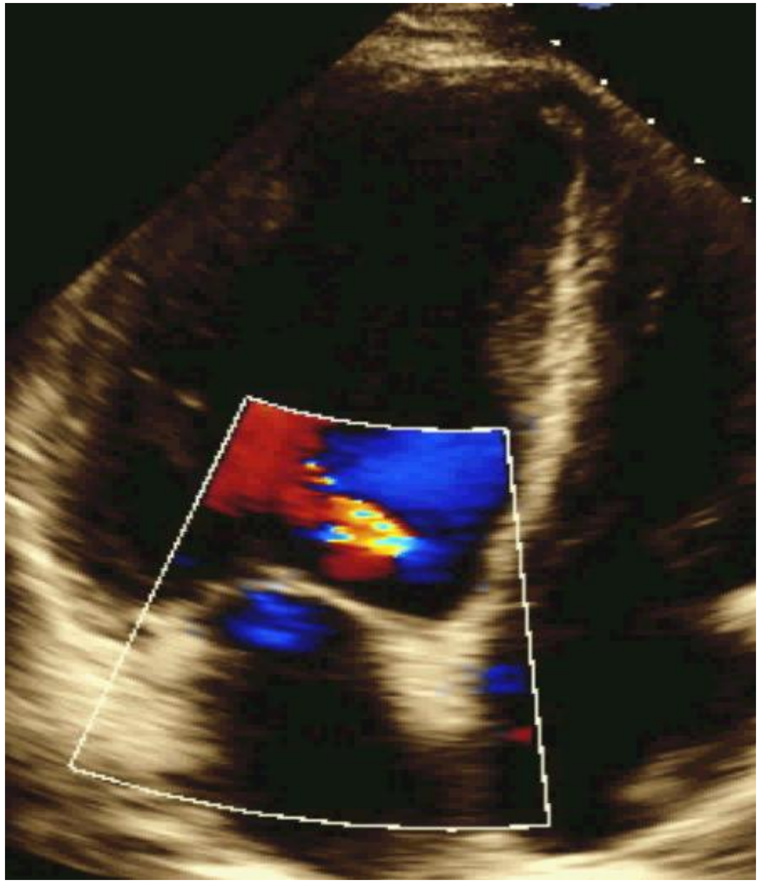
Variables	Group A (n=24)		Group B (n=80)		p value	
	Rest	**Peak**	**Rest**	**Peak**	**Rest**	**Peak**
CPET						
Peak VO_2, ml O_2*Kg^{-1}*min^{-1}		11.0±4		13.3±3		.01
C(a-v)O_2, mL/100mL	8±3	19±4	7.5±1	14±4	.000	.000
VE/VCO_2, slope		37±10		31±6		.01
ECHO						
LVEDVi, ml/m^2	111±30		89±22		.07	
E/e’	28±15		22±11		.02	
CO, l/min	3.5±0.8	5.1±1.8	3.8±1.2	7.0±2.3	.000	.000

Good Extractor



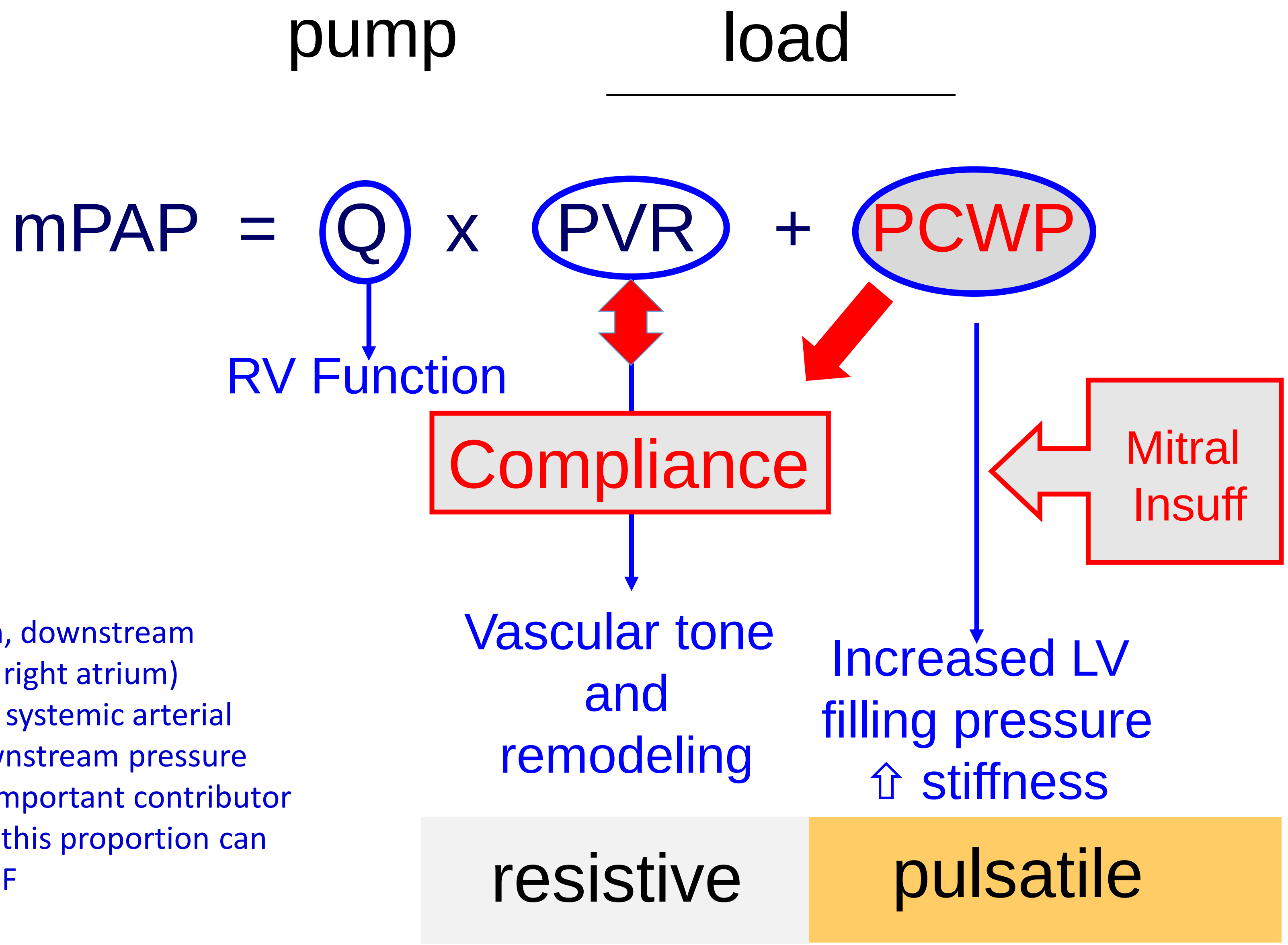
Severe mitral insufficiency (ERO=37 mm^2)
and LV dilatation (LVEDVi= 117 ml/m^2)

Bad Extractor



Mild mitral insufficiency (ERO=11 mm^2)
and LV dilatation (LVEDVi= 86 ml/m^2)

Determinants of mPAP in HFrEF

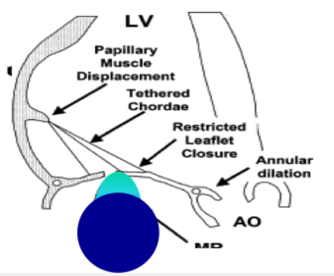


In the systemic circulation, downstream hydraulic pressure (in the right atrium) contributes little (<5%) to systemic arterial pressure. In the lung, downstream pressure (ie, LAP) is a much more important contributor to mean PAP (≈50%), and this proportion can become even greater in HF

Mitral Regurgitation Induces PH and RV Dysfunction

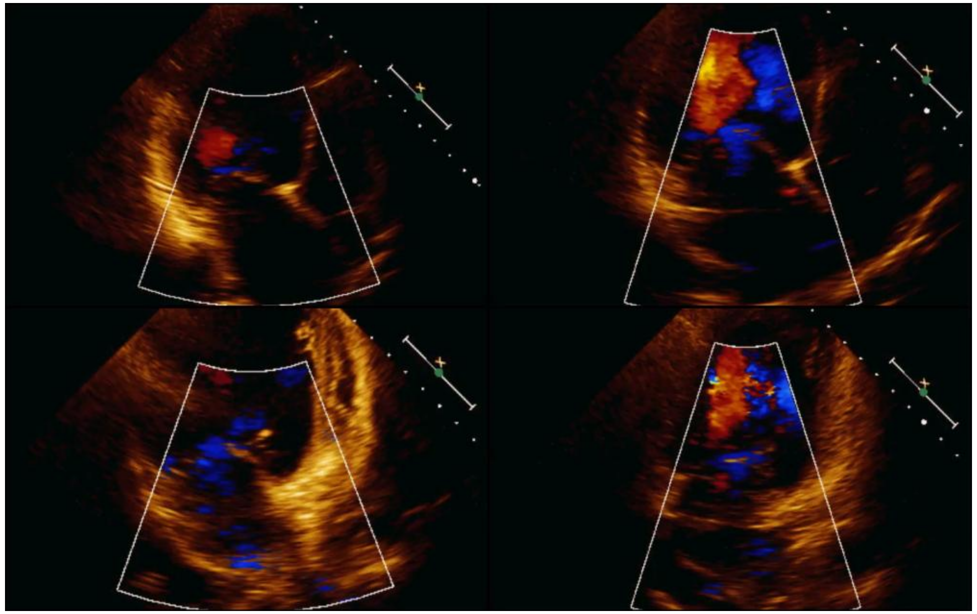
1. MR (primary or secondary) in both HFrEF and HFpEF is prognostically relevant [1,2] especially when detected during exercise [3,4]
2. Exercise-induced MR triggers PH and portends a severe outcome significance especially when RV dysfunction/failure coexists[5-7]

1: Tumminello G et al 2: Guazzi M et al Circulation 2012; 3: Lancellotti P et al. *Circulation* 2003;108:1713-1717; 4: Lancellotti *P Eur Heart J* 2005;26:1528-1532; 5: Kusunose K *Circ Cardiovasc Imaging*. 2013;6:167-76. 7: Bandera F et al *Eur J Cardiov Imag* 2016



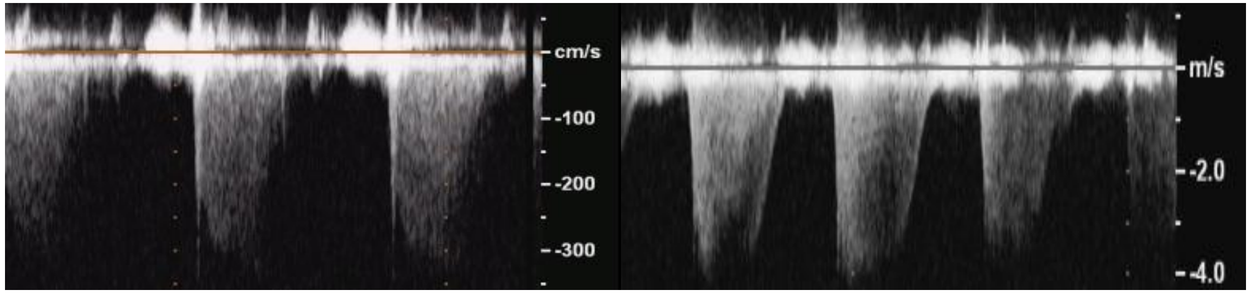
Rest

20 watt



40 watt

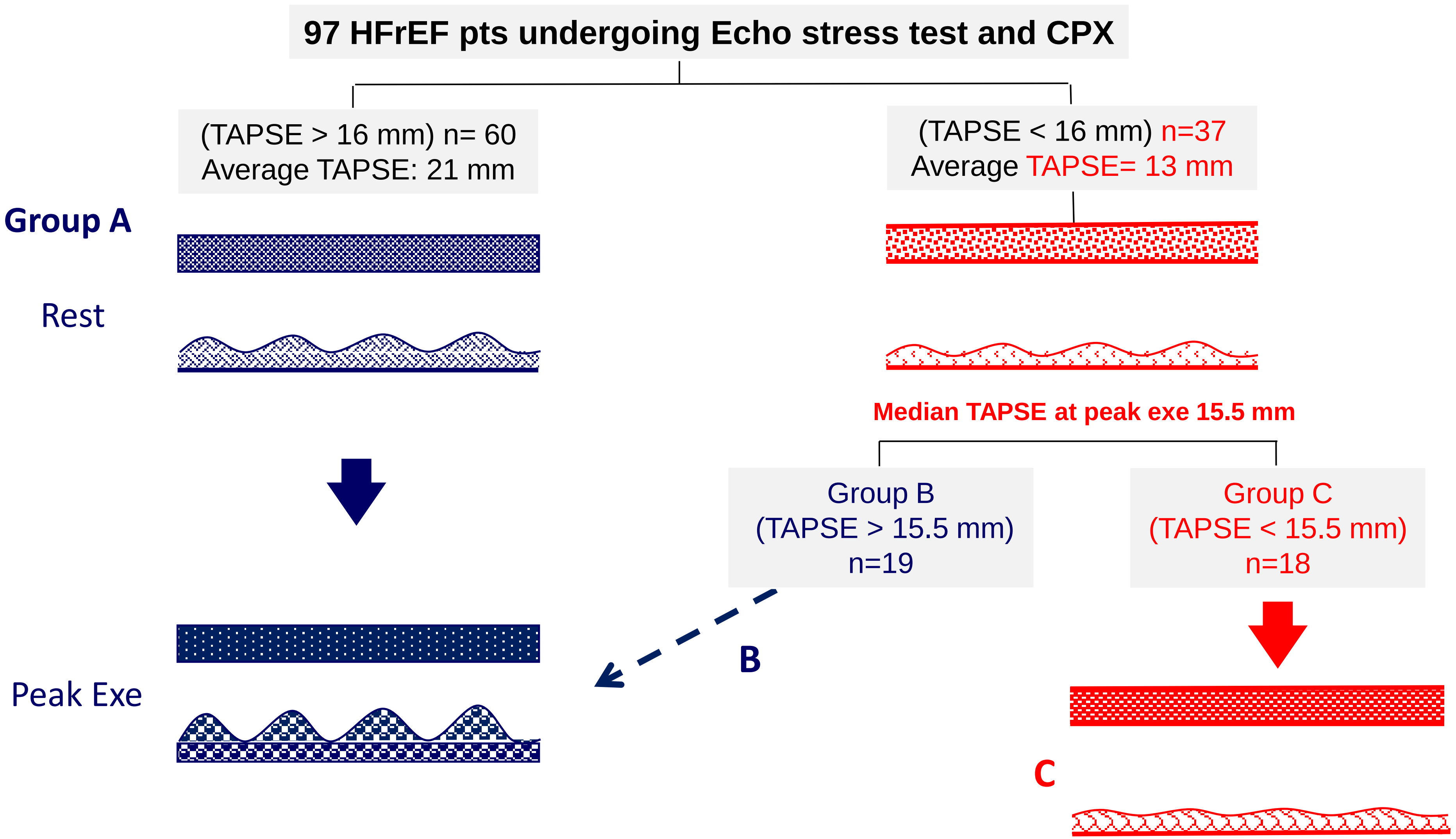
peak



PASP: 50 mmHg

PASP: 85 mmHg

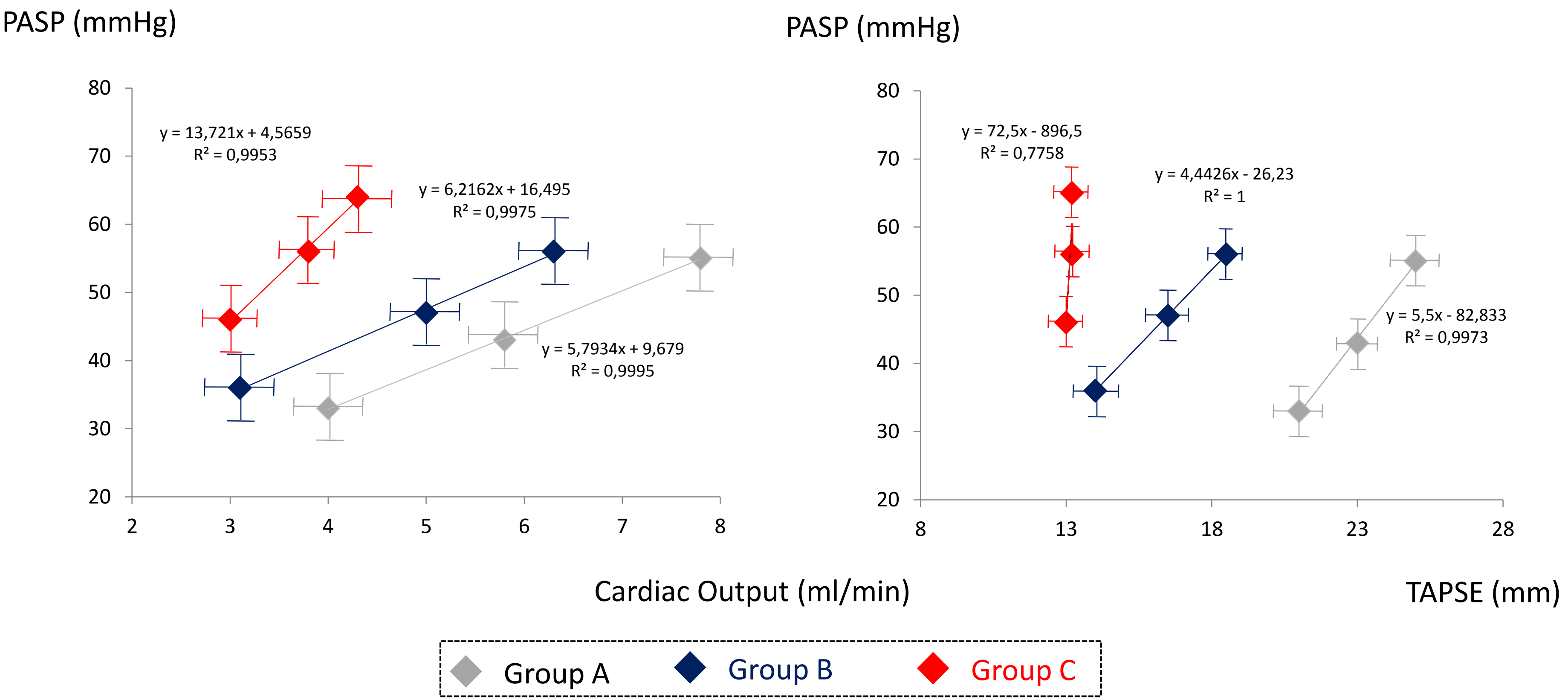
Right Ventricular Contractile Reserve and Pulmonary Circulation Uncoupling During Exercise Challenge in Heart Failure: Pathophysiology and Clinical Phenotypes *JACC HF 2016; 4(8):625-35*



Right Ventricular Contractile Reserve and Pulmonary Circulation Uncoupling During Exercise Challenge in Heart Failure: Pathophysiology and Clinical Phenotypes

- 97 HFrEF pts undergoing Echo stress test and CPX, divided according to TAPSE > 16 mm Group A or < 16 mmHg at rest with recovery (Group B) or not during exercise (Group C)

Results- RV to PC Coupling



tapraid4/zh4-ahea/zh4-ahea/zh402113/zh40917d13z | xppws | S=5 | 9/9/13 | 9:11 | MS: H-00157-2013 | Ini: 11/jl/dlh
Am J Physiol Heart Circ Physiol 305: H000–H000, 2013.
First published August 30, 2013; doi:10.1152/ajpheart.00157.2013.

Tricuspid annular plane systolic excursion and pulmonary arterial systolic pressure relationship in heart failure: an index of right ventricular contractile function and prognosis

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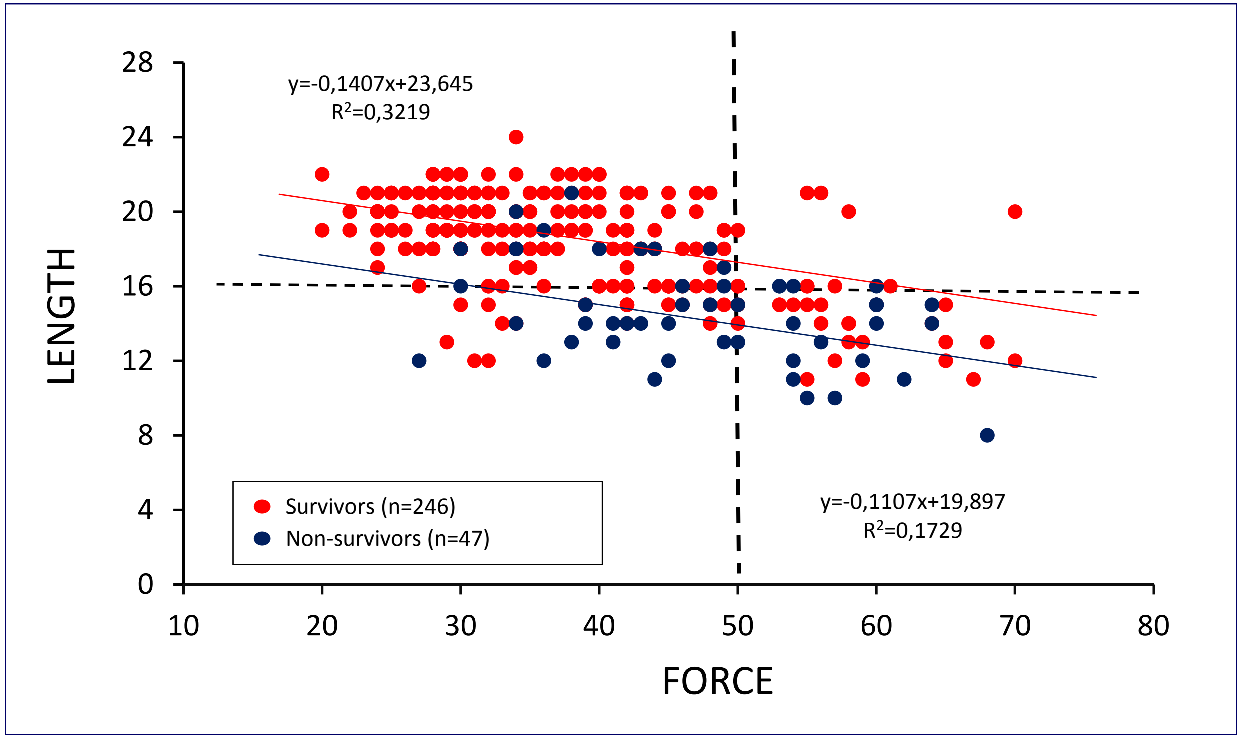
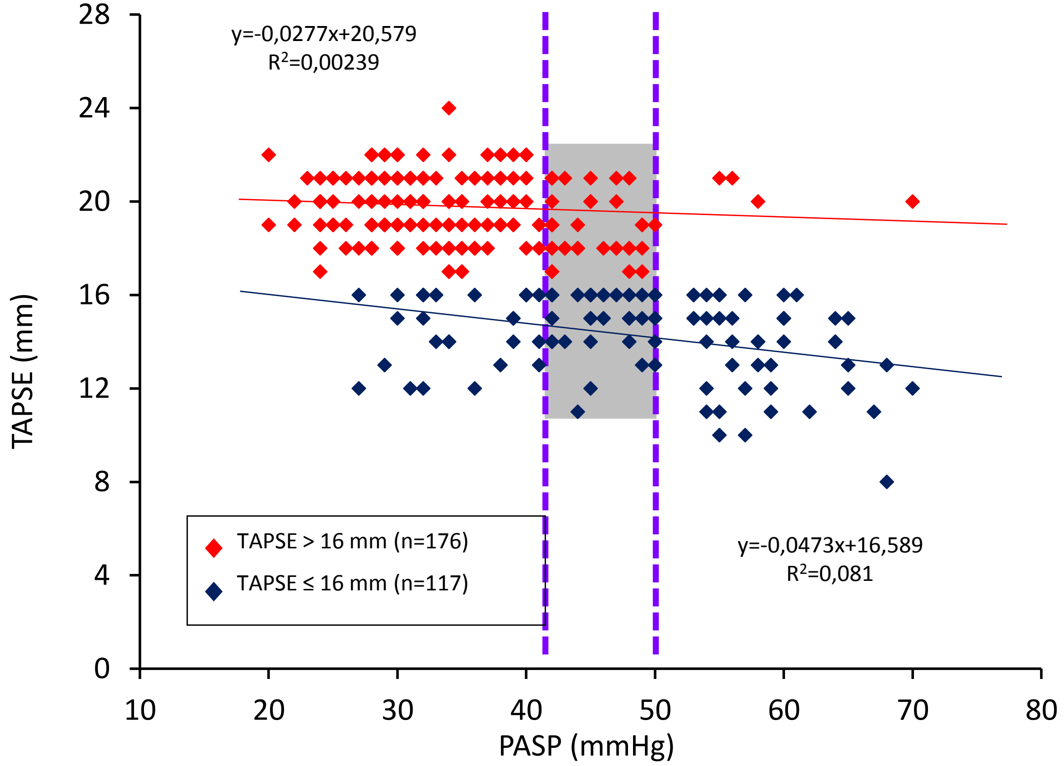
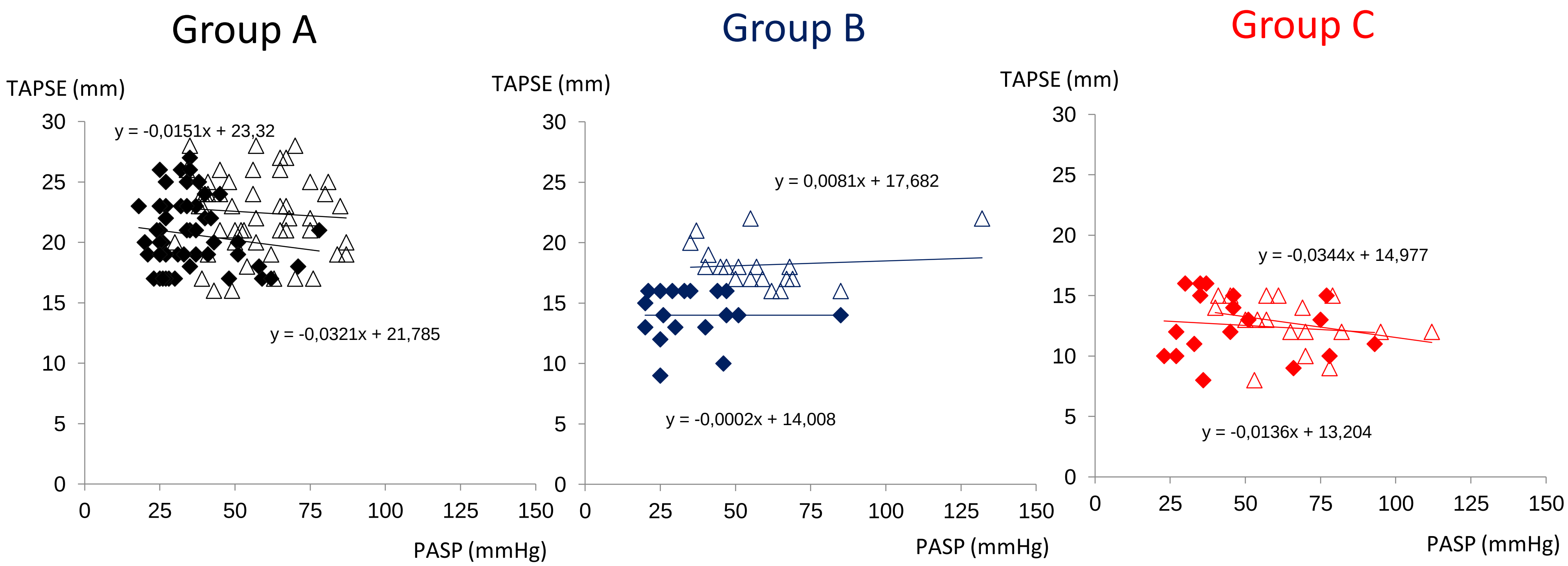
- 293 HF patients (247 HFrEF; 46 HFpEF)
- Echocardiographic evaluation of RV function, PH, LV function and biomarkers





Right Ventricular Contractile Reserve and Pulmonary Circulation Uncoupling During Exercise Challenge in Heart Failure: Pathophysiology and Clinical Phenotypes

Results- RV Contractile Reserve (TAPSE vs PASP relationship at rest and peak exe)



Full simbols: Rest   Empty symbols: Peak exercise

Right Ventricular Contractile Reserve and Pulmonary Circulation Uncoupling During Exercise Challenge in Heart Failure: Pathophysiology and Clinical Phenotype

Clinical Characteristics

	Group A (n=60)	Group B (n=19)	Group C (n=18)	P
Age, y	62±10	65±8	64±13	0.73
BMI	26±4	26±4	27±4	0.22
Female gender, %	16	28	35	0.27
BNP, pg/dl	1879 ±1804	2978 ±1812	2463 ±1251	0.03*

*:Group B and C vs Group A

LV Cardiac Data

	Group A (n=60)		Group B (n=19)		Group C (n=18)		P	
	Rest	Peak	Rest	Peak	Rest	Peak	Rest	Peak
LV ejection fraction, %	33±8	37±10	34±9	37±14	32±11	35±10	ns	ns
LV end diastolic vol. indexed, ml/m^2	90±23		95±28		113±47		ns	
LV mass indexed, g/m^2	126±30		121±22		154±37		.0017	
Left atrial volume indexed, ml/m^2	47±18		52±24		80±35		.0005	
E/e’	22±11		25±16		38±13		.001	
Cardiac output, l*min^{-1}	4.0±1.2	7.2±2.6	3.3±0.8	6.5±1.8	2.9±1.0	4.4±1.9	.0004	.0002
Severe MR, %	16		21		56			

Right Ventricular Contractile Reserve and Pulmonary Circulation Uncoupling During Exercise Challenge in Heart Failure: Pathophysiology and Clinical Phenotypes

CPET Data

	HF (n= 97)	Group A (n=60)	Group B (n=19)	Group C (n=18)	P Value
Maximal work, W	65 ± 25	69 ± 26	68 ± 21	46 ± 18‡	0.0029
Peak VO_2, ml/kg/min	13.0 ± 3.7	13.5 ± 3.5	14.1 ± 4.2	10.2 ± 2.3‡	0.008†
Predicted peak VO_2, %	53 ± 15	55 ± 14	55 ± 14	43 ± 13‡	0.0082†
Peak RER	1.17 ± 0.12	1.17 ± 0.14	1.17 ± 0.14	1.19 ± 0.12	0.88
Peak O_2 pulse, ml/beat	9.0 ± 2.7	9.3 ± 2.8	10.0 ± 2.7	7.4 ± 2.0‡	0.0068
VE/VCO_2 slope	34 ± 10	31 ± 7	35 ± 10	42 ± 12‡	0.0001†
End-tidal CO_2, mmHg	33 ± 6	35 ± 5	33 ± 6	28 ± 4‡	0.0001
Exercise Oscillatory Ventilation	44	40	42	61	0.28*
Circulatory power, mmHg · ml O_2 · kg^{-1} · min^{-1}	1,886 ± 672	2,144 ± 627	1,734 ± 508	1,182 ± 366	0.0001†
Ventilatory power, mmHg	4.8 ± 1.5	5.3 ± 1.3	4.7 ± 1.6	3.5 ± 1.2‡	<0.0001

*Values are mean ± SD or %. *Chi-square test. †Kruskal-Wallis test. ‡p < 0.025, group B versus group C.*
BP= blood pressure; EOV= exercise oscillatory ventilation; HF= heart failure; RER= respiratory exchange ratio; VCO2= carbon dioxide output; VE= minute ventilation; VO2 = oxygen uptake.

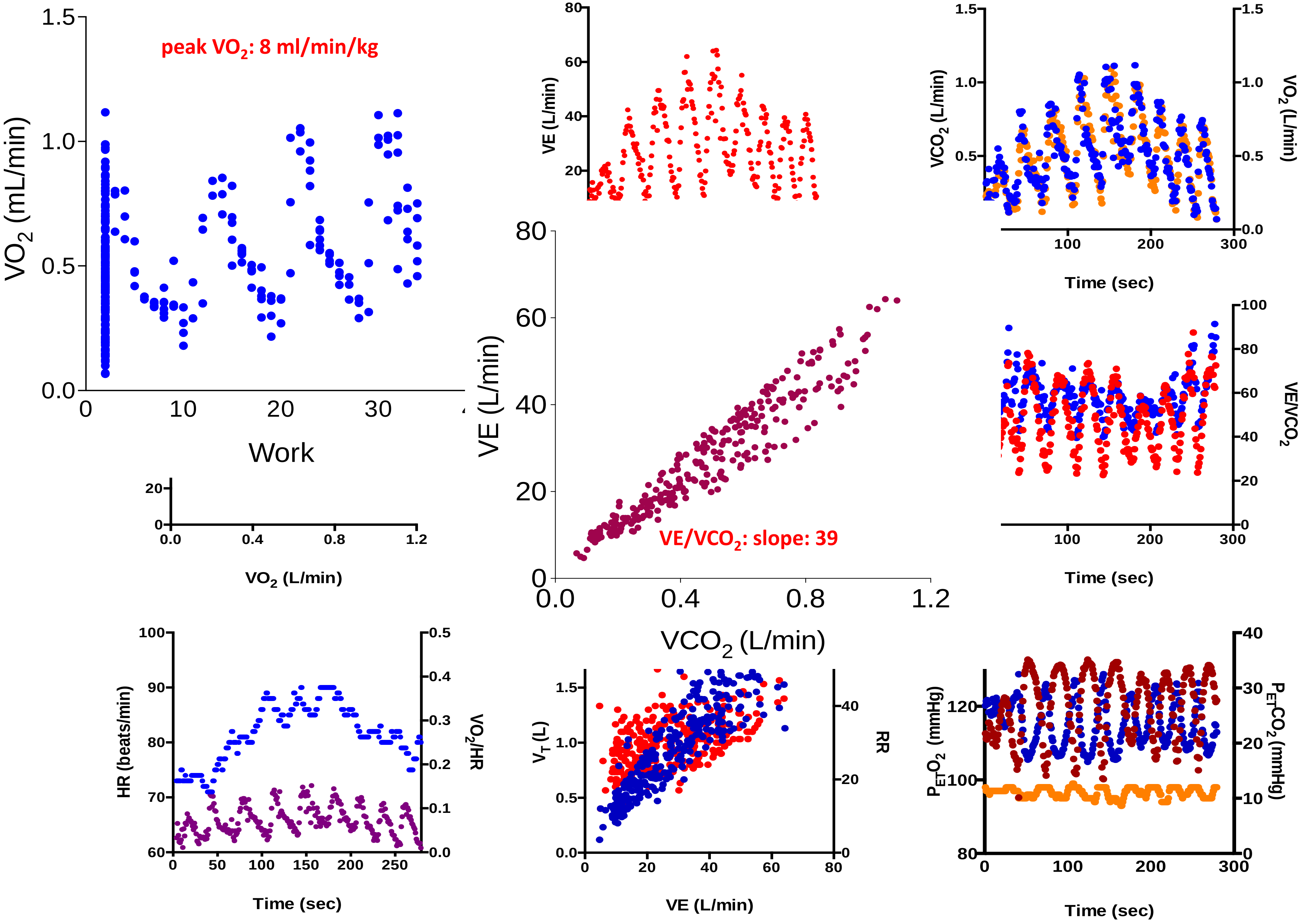
*:Group B and C vs Group A peak

The 9-plot Analysis

Ramp protocol
(8 watt/min)

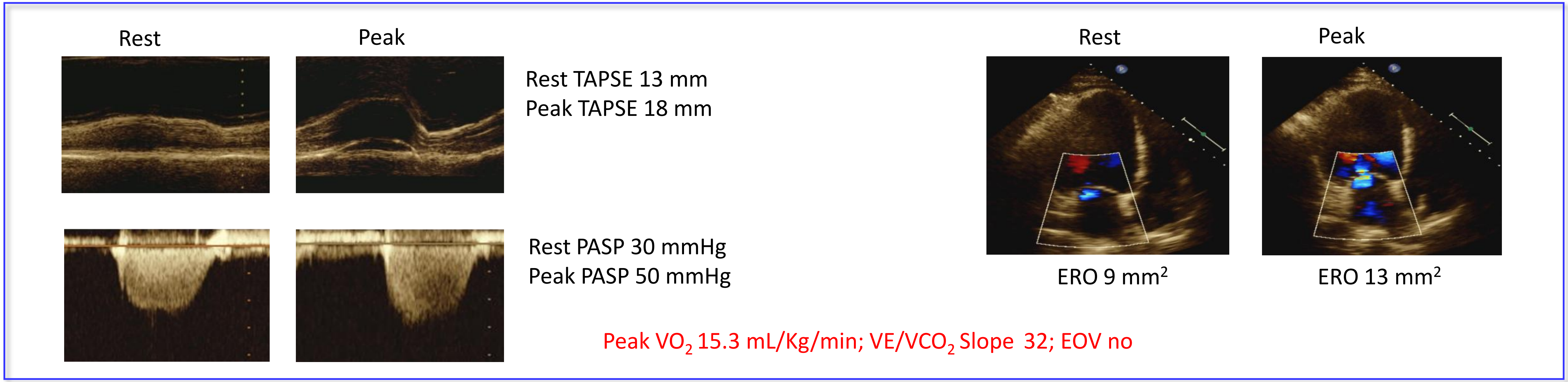
Max workload: 45 watt

Symptom-limited test terminated because of DYSPNEA and Significant RV-PA UNCOUPLING

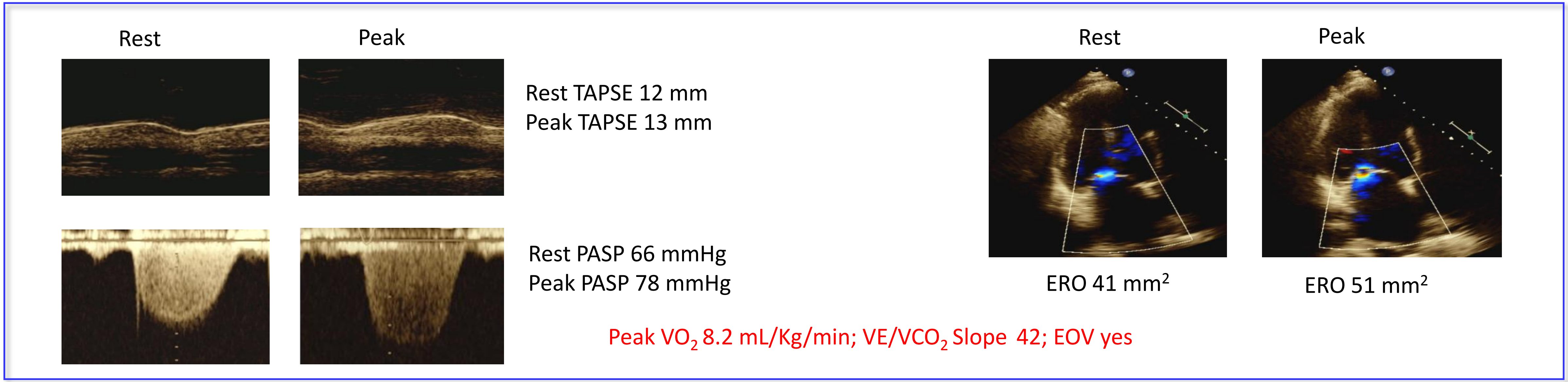


Guazzi M et al JACC 2017 in press

Group B



Group C



Exercise Training in Heart Failure

1. Training Intensity (% of VO2 max or max HR)
2. Type of training (endurance, resistance, combined)
3. Methods of training (continuous or steady state, intermittent, interval)
4. Training modality (concentric vs eccentric)
5. Training target (systemic vs regional training, e.g. respiratory training)
6. Training control (supervised/non supervised)
7. Training location (hospital based, outpatient, home based)

Moderate intensity endurance training has been proven prognostic benefits
→ reduced hospitalization rate[1], mortality[2,3]

[1] O' Connor CM et al, JAMA 2009;301:1439-1450
[2] Keteyan SJ et al JACC 2012;60:1899-1905
[3] Piepoli MF et al BMJ 2004;328:189

Conclusions and Outlook

- **“CPET imaging”** seems now an evolving step to better phenotyping advanced HFrEF.
- **Mitral regurgitation** is a sort of “central redistributor” of O_2 delivery whose mechanistic implications on exercise are of novel interest for either extraction (exhaustion at maximum), RV to PC uncoupuling (increased load) and exercise ventilation inefficiency
- **RV pump failure** comes up as an early and quite underestimated mechanical cause of impaired performance and exhaustion.
- **ET training in HF:** the evidence is just for continuous, moderate intensity, supervised modalities