

The ICU In Vivo: Critical Illness Is Top Sport

Can Ince



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Declared interests

I have the following financial relationships to disclose:

CEO & CTO (Can Ince & Matthias Hilty) & Stockholder in:

Active Medical BV

(MicroTools and clinical microcirculation products and services)

The logo for Active Medical features the company name in a bold, red, lowercase sans-serif font. The word 'active' is followed by an underscore, and 'medical' is in a larger font size. Below the main text, the tagline 'unlocking the microcirculation' is written in a smaller, red, italicized sans-serif font.

active_medical
unlocking the microcirculation

I am a physiologist !

Outline

Exercise is medicine.

Unfitness predicts bad outcome.

Exercise can help you survive.

Critical illness, exercise and outcome.

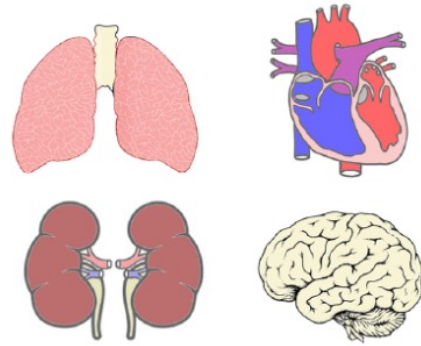
Extreme physiology and adaptation.

the ICU in vivo

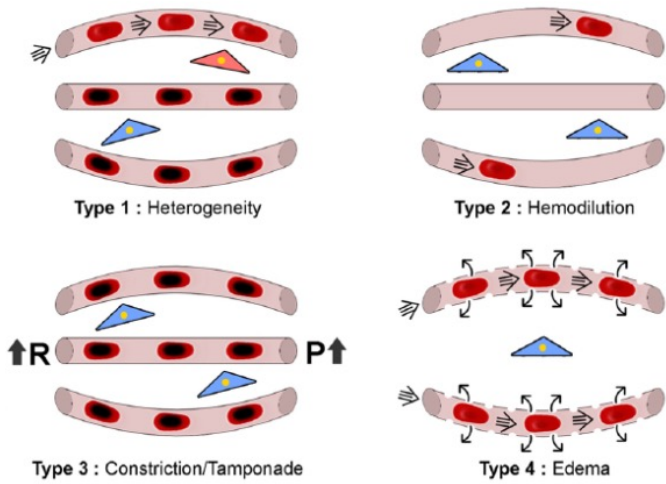
Can Ince



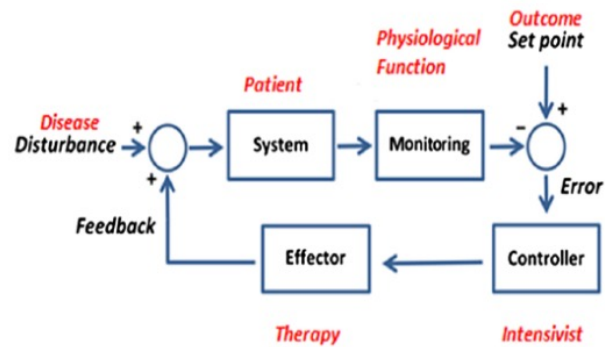
I. Frailty and Physiological Reserve



II. Organ Function Response to Therapy



III. Hemodynamic Coherence



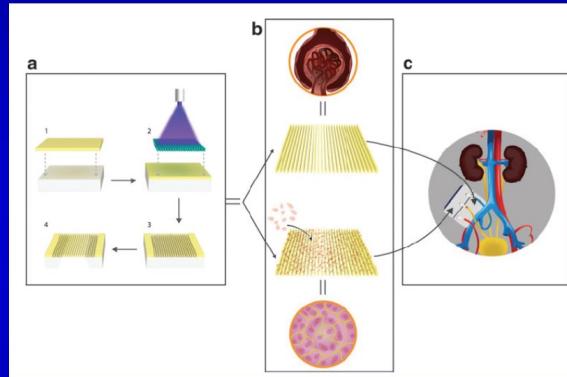
IV. Integration and Feedback

the ICU in vivo

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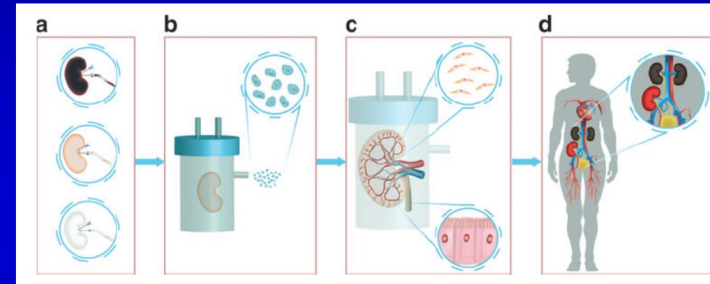
Update on Renal Replacement Therapy: Implantable Artificial Devices and Bioengineered Organs

Chiara Attanasio, PhD,¹ Marcela T. Latancia, MSc,² Leo E. Otterbein, PhD,² and Paolo A. Netti



“microelectromechanical systems”

silicon nanopore membranes



detergent perfusion of the kidney

scaffold seeding with proper cell lines

Inside the bioreactor, the bioengineered organ is maintained

laboratory-grown kidney will be successfully transplanted into patients


The first chamber is hemofilter, removing toxins, excess water, and salts. Second chamber acts as a bioreactor with SNMs seeded with renal proximal tubule cells which selectively reabsorb water and salts allowing the excretion of toxins through the bladder.

Implantable renal assist device (iRAD)

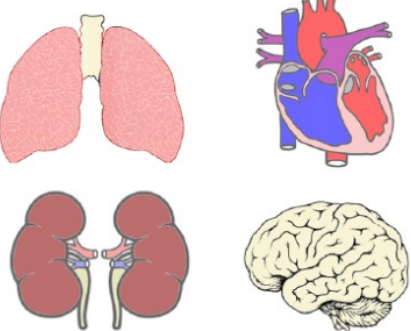
TISSUE ENGINEERING: Part B
Volume 00, Number 00, 2016

the ICU in vivo

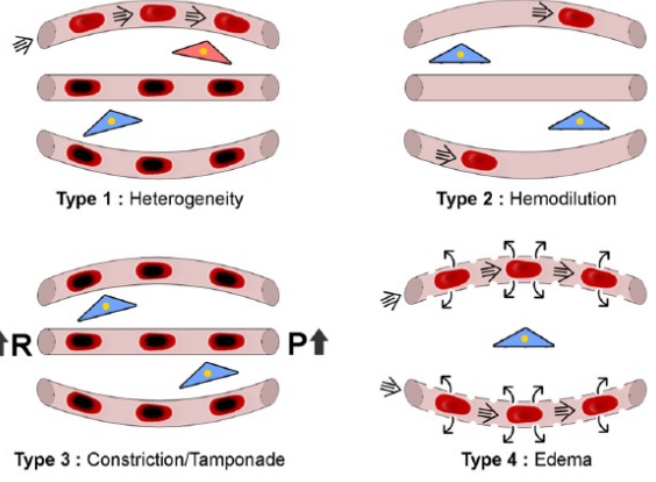
Can Ince



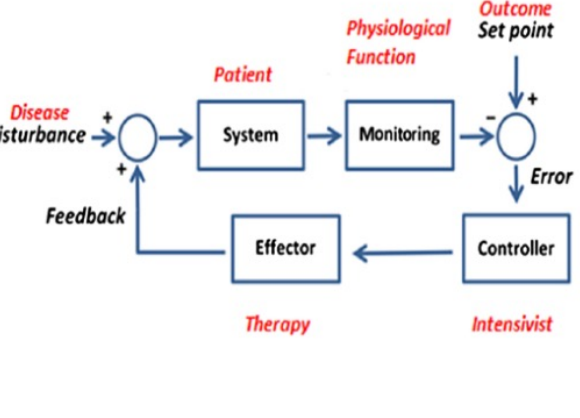
I. Frailty and Physiological Reserve



II. Organ Function Response to Therapy



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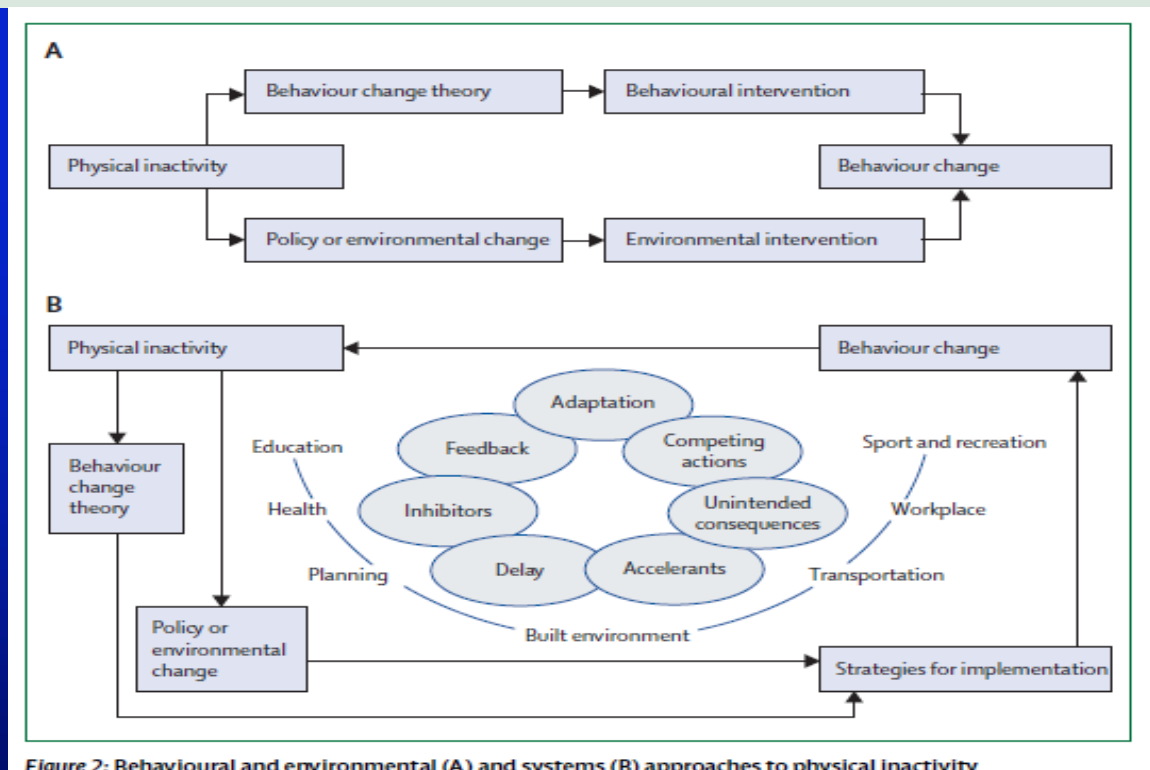
IV. Integration and Feedback

The pandemic of physical inactivity: global action for public health

Harold W Kohl 3rd, Cora Lynn Craig, Estelle Victoria Lambert, Shigeru Inoue, Jasem Ramadan Alkandari, Grit Leetongin, Sonja Kahlmeier, for the Lancet Physical Activity Series Working Group*

Physical inactivity is the fourth leading cause of death worldwide.

Panel 1: Physical activity surveillance: if it is important, it must be measured

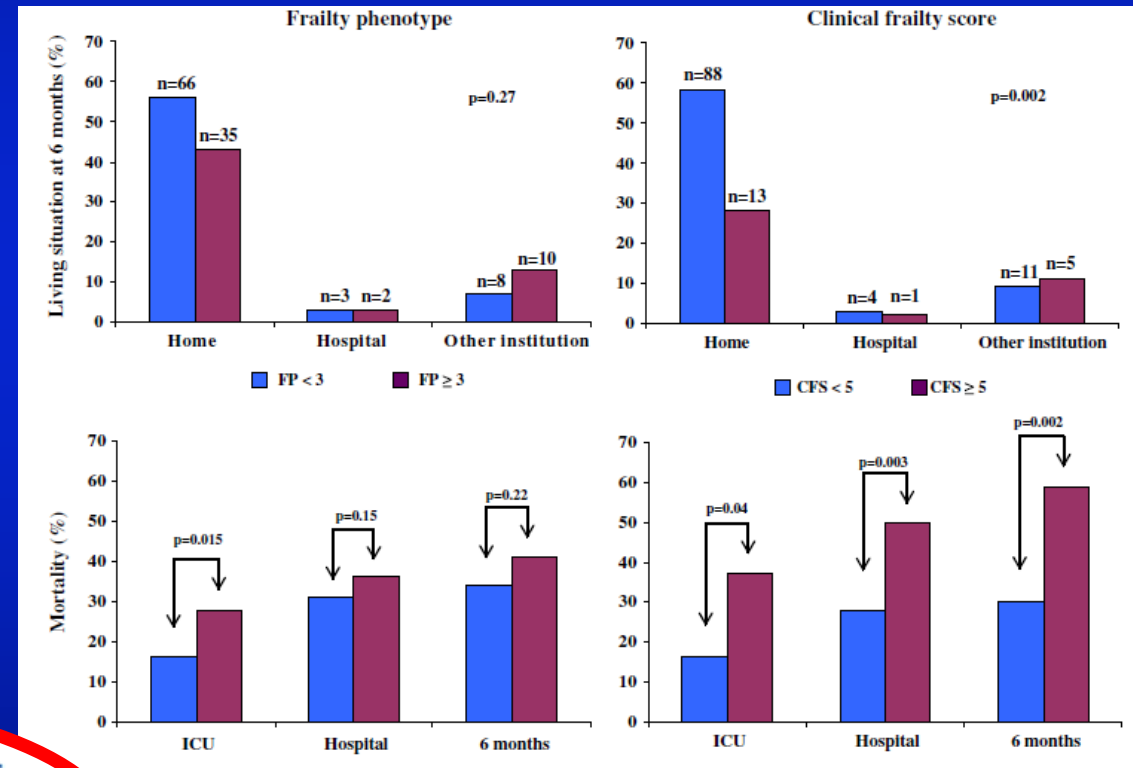
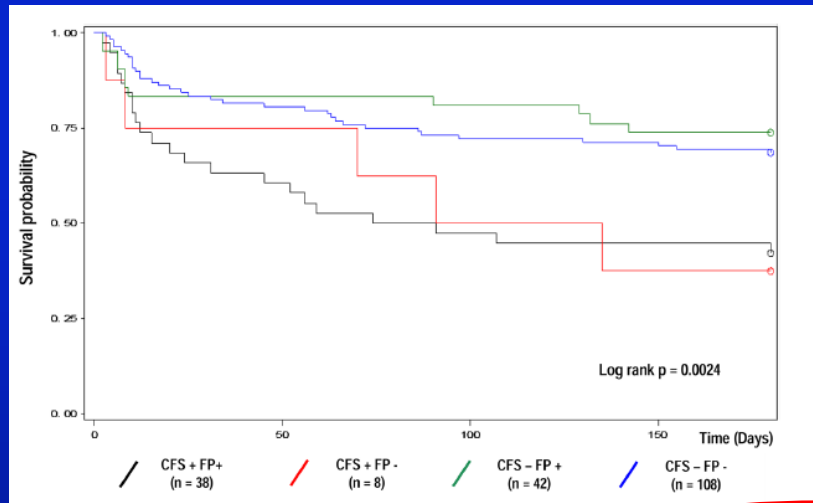


Lancet 2012; 380: 294-305

Prevalence and impact of frailty on mortality in elderly ICU patients: a prospective, multicenter, observational study

Pascale Le Maguet
 Antoine Roquilly
 Sigismond Lasocki
 Karim Asehnoune
 Elsa Carise
 Marjorie Saint Martin
 Olivier Mimoz
 Grégoire Le Gac
 Dominique Somme
 Catherine Cattenoz
 Fanny Feuillet
 Yannick Malledant
 Philippe Seguin

The aim of our study was to determine the prevalence of frailty and the impact of frailty on mortality in a prospective cohort of patients aged 65 years or more who were admitted to ICUs.

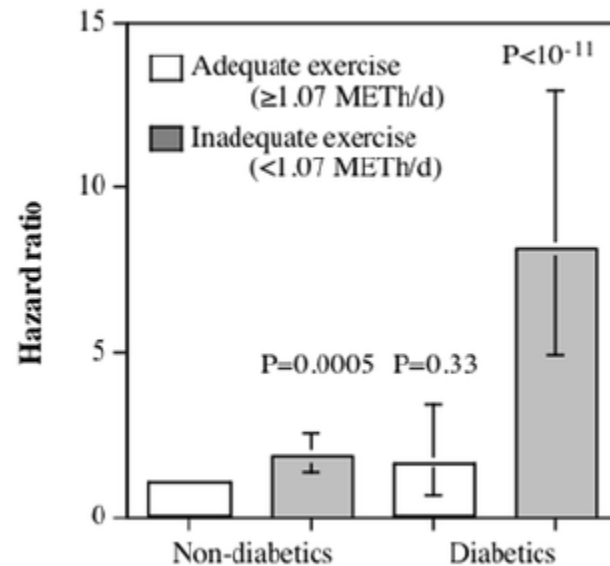


Conclusions: Frailty is a frequent occurrence and is independently associated with increased ICU and 6-month mortalities. Notably, the

CFS predicts outcomes more effectively than the commonly used ICU illness scores.

Inadequate Exercise as a Risk Factor for Sepsis Mortality

Paul T. Williams



PLOS ONE:

Inadequate exercise is a risk factor for sepsis mortality, particular in diabetics.

energy expenditure in terms of metabolic equivalents (MET), where one MET is the energy expended sitting at rest ($3.5 \text{ ml O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, 1 MET-hour ~1 km run)

Conclusions

These results suggest that inadequate exercise is associated with a doubling of the risk for sepsis mortality. Given that the incidence of sepsis is increasing [3], these results suggest that getting people to exercise could be immediately effective in reducing the disease incidence.

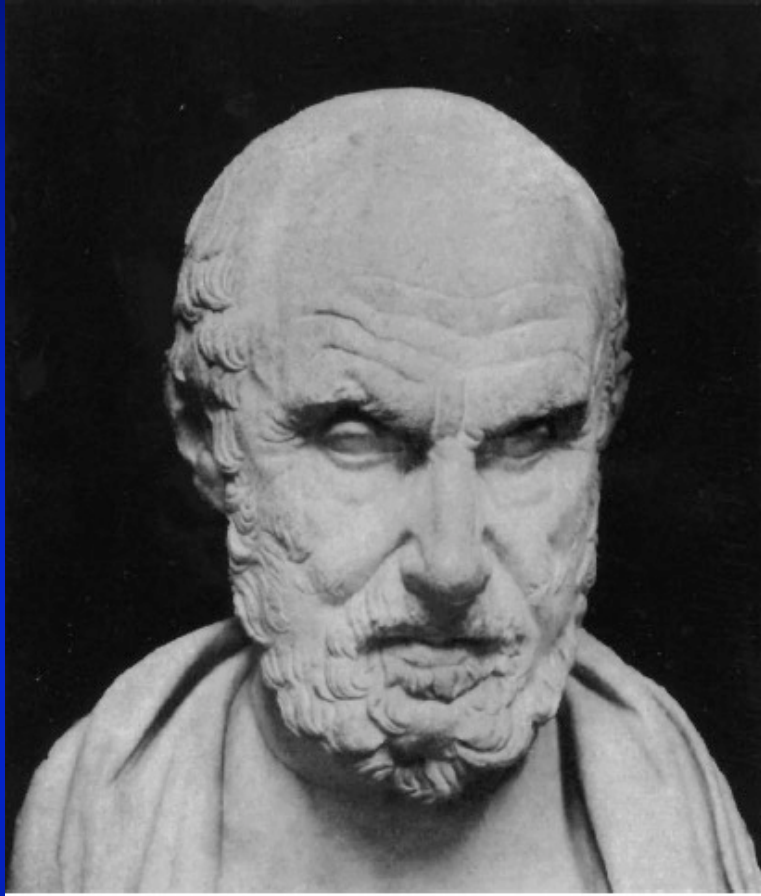
EXERCISE IS MEDICINE®: A Global Health Initiative



A CRITICAL CALL TO ACTION Exercise is Medicine® (EIM) is a global health initiative managed by the American College of Sports Medicine (ACSM (<http://acsm.org>)) that is focused on encouraging primary care physicians and other health care providers to include physical activity when designing treatment plans for patients. EIM is committed to the belief that physical activity is integral in the prevention and treatments of diseases and should be regularly assessed and “treated” as part of all medical care.

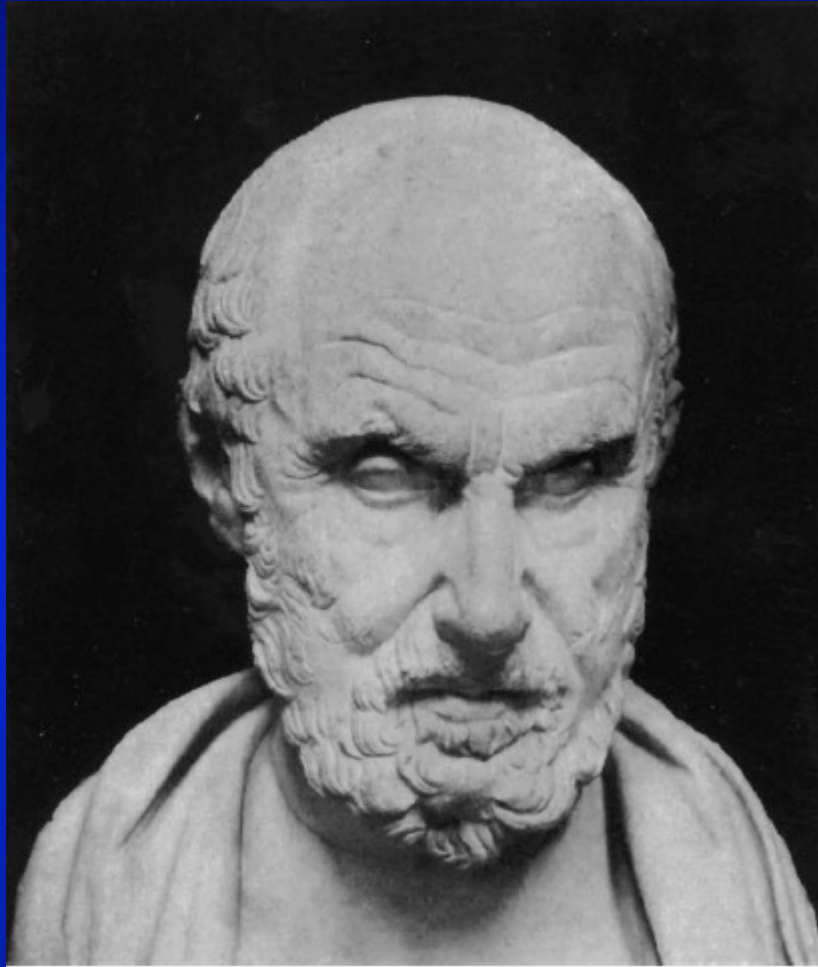
Nov 5, 2007

Hippocrates (460–370 BCE) of Cos.



I say then, that this question [regimen] is a most excellent one and allied to many others, some of the most vital importance in the art [medicine], for that it can contribute much to the recovery of the sick, and to the preservation of health in case of those gymnastic[athletic] exercise and is useful to whatever one wish to apply it.

Hippocrates (460–370 BCE) of Cos.



I say then, that this question [regimen] is a most excellent one and allied to many others, some of the most vital importance in the art [medicine], for that it can contribute much to the recovery of the sick, and to the preservation of health in case of those gymnastic[athletic] exercises, and is useful to whatever one wish to apply it.

Claudius Galenus (129–210 CE) or Galen of Pergamon.



The form of exercise deserving our attention is therefore that which has the capacity to provide health of the body, harmony of the part, and virtue in the soul, and these things are true of the exercise with the small ball.

cardiopulmonary exercise testing (CPET)



CPET integrates expired oxygen and carbon dioxide concentrations with the measurement of ventilatory flow thus deriving oxygen uptake ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) under varying external workloads.

to help identify high risk patients: $\dot{V}O_2$ peak/max,¹² anaerobic threshold (AT),^{5 8 9 13} and ventilatory equivalent for carbon dioxide ($\dot{V}_E/\dot{V}CO_2$).^{9 14} Consequently, these three variables are

Heart Rate Recovery Predicts Clinical Worsening in Patients with Pulmonary Arterial Hypertension

Omar A. Minai¹, Ravi Gudavalli², Srinivas Mummadi¹, Xiaobo Liu³, Kevin McCarthy¹ and Raed A. Dweik¹

Methods: HRR1 was defined as the difference in heart rate at the end of 6MW test and at 1 minute after completion of the 6MW test.

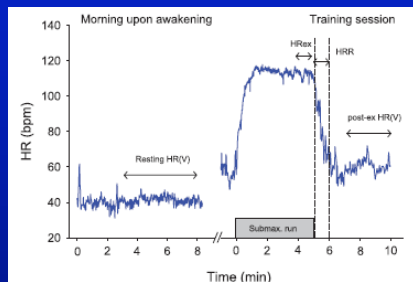
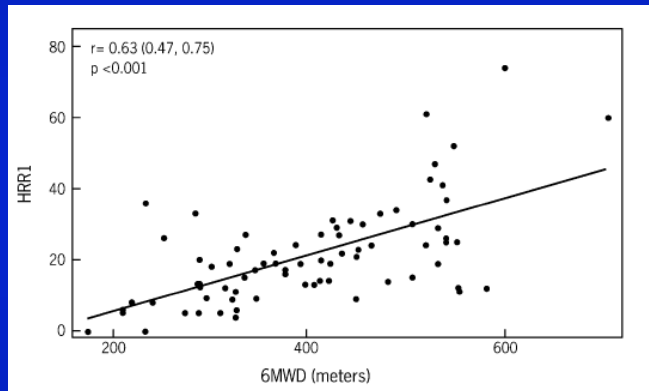
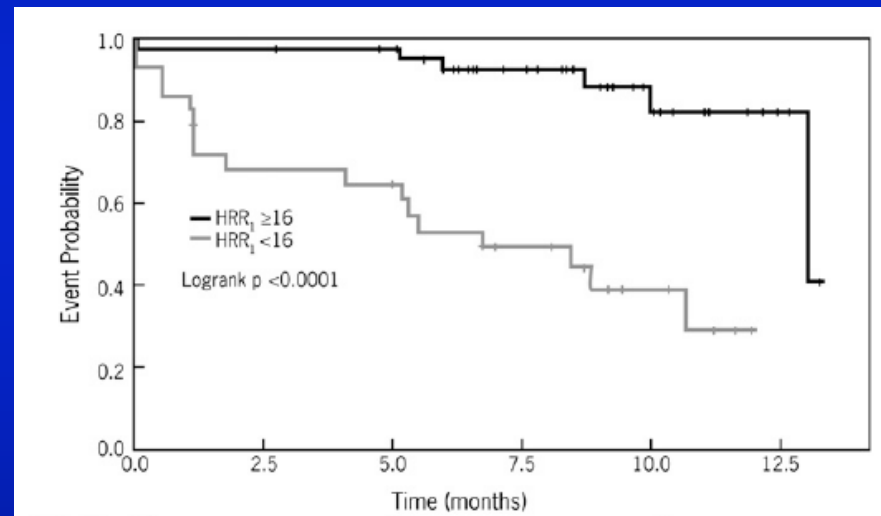


FIGURE 2 | Example of the different heart rate (HR) recording conditions during the day time. HR(ex), exercise HR; HRR, HR recovery over 60s; HRV, HR variability.



HRR ₁ < 16	29	17	5
HRR ₁ ≥ 16	44	41	14

Figure 2. Kaplan-Meier curve showing that patients with reduced heart rate recovery in 1 minute (HRR1) (< 16 beats) had an increased propensity to have clinical worsening and had shorter time to clinical worsening compared with patients with HRR1 ≥ 16 beats.

Recordings of resting (indices capturing beat-to-beat changes in heart rate, reflecting cardiac parasympathetic activity) and submaximal exercise (30-to-60-s average)

Cardiopulmonary exercise testing predicts 5 yr survival after major surgery†

M. Colson^{1*}, J. Baglin², S. Bolsin¹ and M. P. W. Grocott³

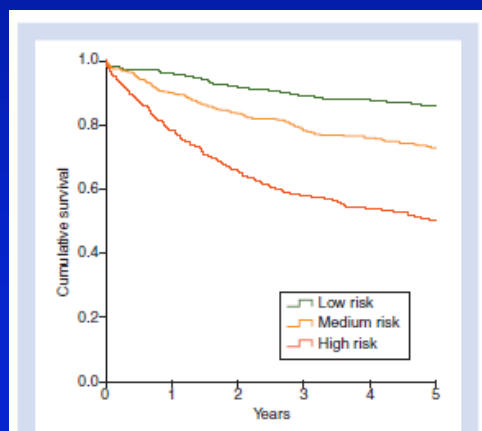


Fig 2 Survival by risk category. The Kaplan-Meier 5 yr survival curves across assigned risk categories based on BMA. The survival curves show a clear relationship between risk and survival.

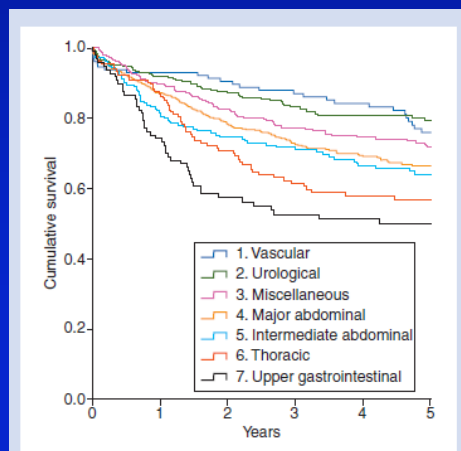


Fig 1 Survival by surgery type. The Kaplan-Meier 5 yr survival curves across the seven major surgery types.

Database of 1725 patients with cardiopulmonary exercise testing (CPET) who had major surgery.

Table 2 Single variable analysis. Area under the ROC curve linking the sensitivity and specificity of selected single CPET variables in predicting survival endpoints

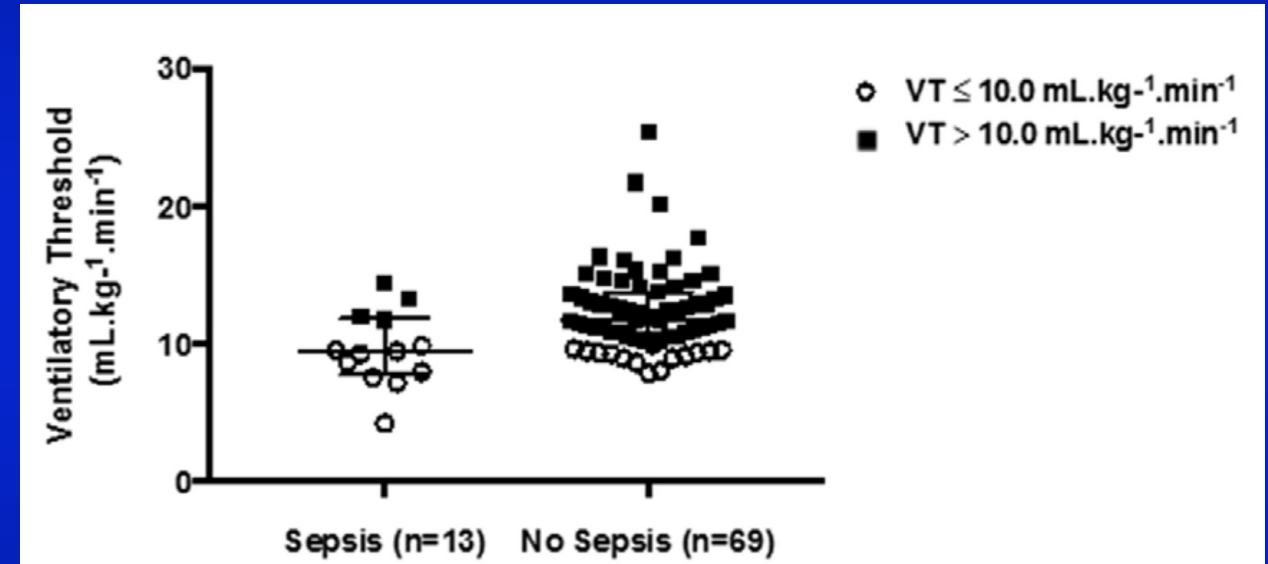
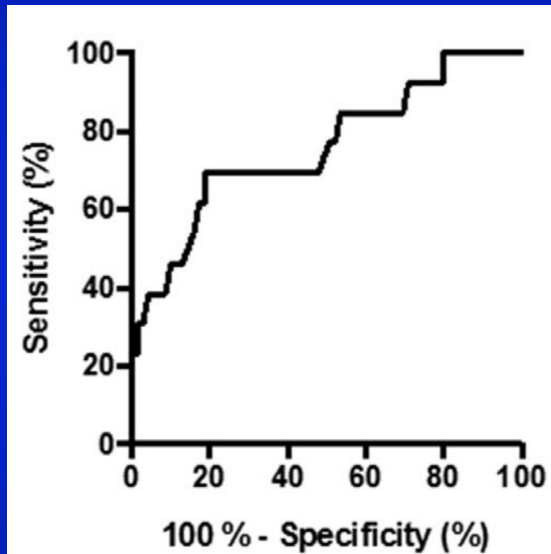
Outcome	AT-V _{O₂} kg ⁻¹	AT-V _E /V _{CO₂}	OUES	Age
30-day mortality	0.551	0.633	0.509	0.559
One-year mortality	0.474	0.648	0.406	0.594
Five-year mortality	0.502	0.645	0.571	0.581

Table 1 Definitions. CPET-variable terms used in this paper, with measurement units where applicable

Term	Definition	Measurement unit
Age	Patient age on date of surgery	yr
AT	Anaerobic threshold	
BMI	Body mass index: patient weight divided by their height squared	kg m ⁻²
FVCR	Forced vital capacity as a ratio to that predicted by the relevant European Respiratory Society algorithm	
HR	Heart rate	beats min ⁻¹
OUES	Oxygen uptake efficiency slope	
Overall-IR	Ratio of inspiration time to total test time	
P _{E_{CO₂}}	End-tidal carbon-dioxide concentration	%
P _{E_{O₂}}	End-tidal oxygen concentration	%
RER	Respiratory exchange ratio of carbon dioxide production to oxygen consumption	
TV	Tidal volume	litre
US	Unloaded section - these value are averaged over the entire unloaded section of the test	
V _{CO₂}	Carbon dioxide production rate	litre min ⁻¹
V _E	Pulmonary minute ventilation	litre min ⁻¹
V _{O₂}	Oxygen consumption rate	litre min ⁻¹

Poor Cardiorespiratory Fitness Is a Risk Factor for Sepsis in Patients Awaiting Liver Transplantation

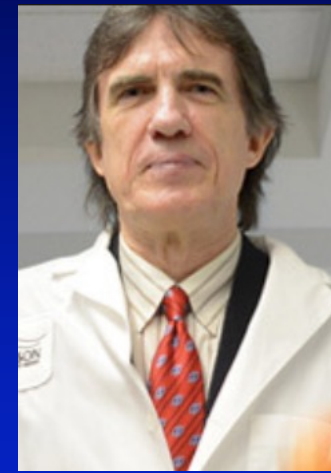
Matthew P. Wallen, PhD,¹ Aidan J. Woodward, MBBS,^{2,3} Adrian Hall, MBBS,⁴ Tina L. Skinner, Jeff S. Coombes, PhD,¹ and Graeme A. Macdonald, PhD^{2,3,5}



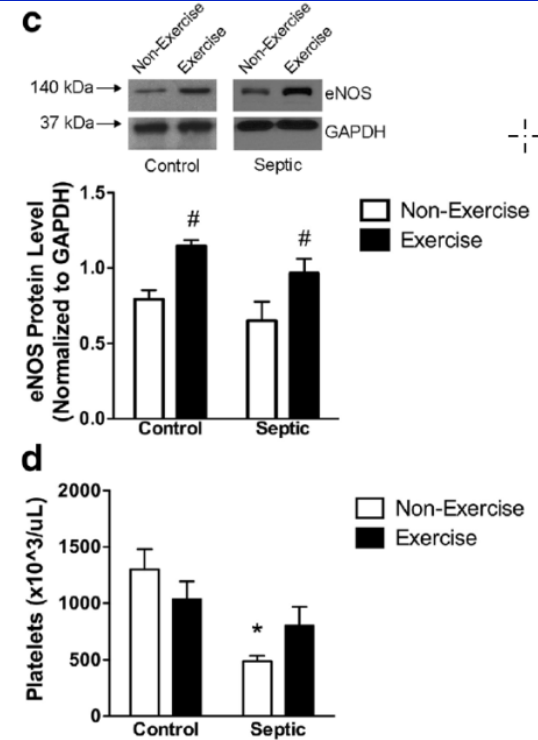
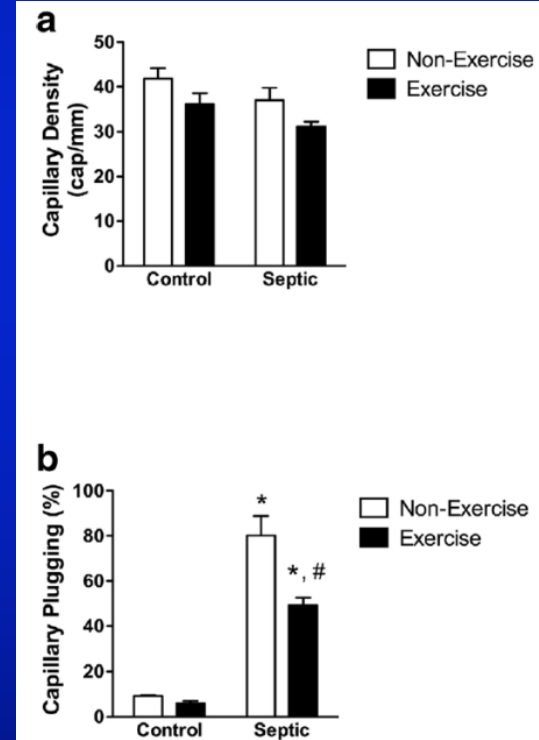
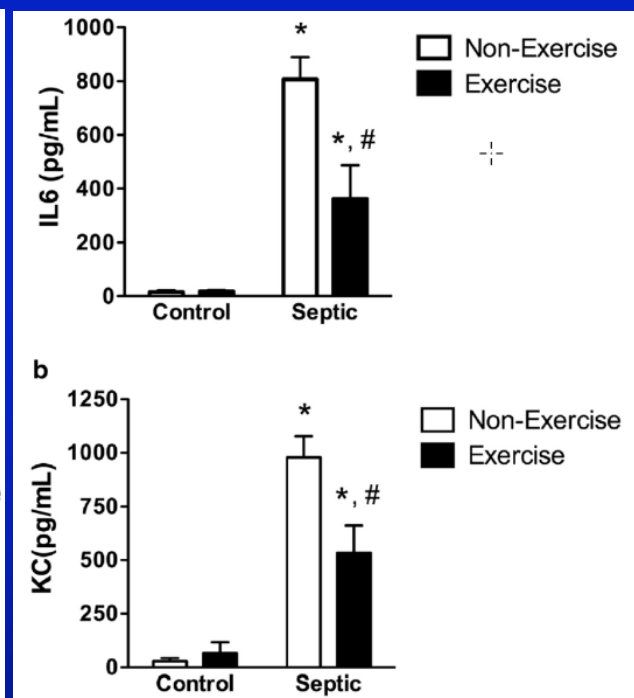
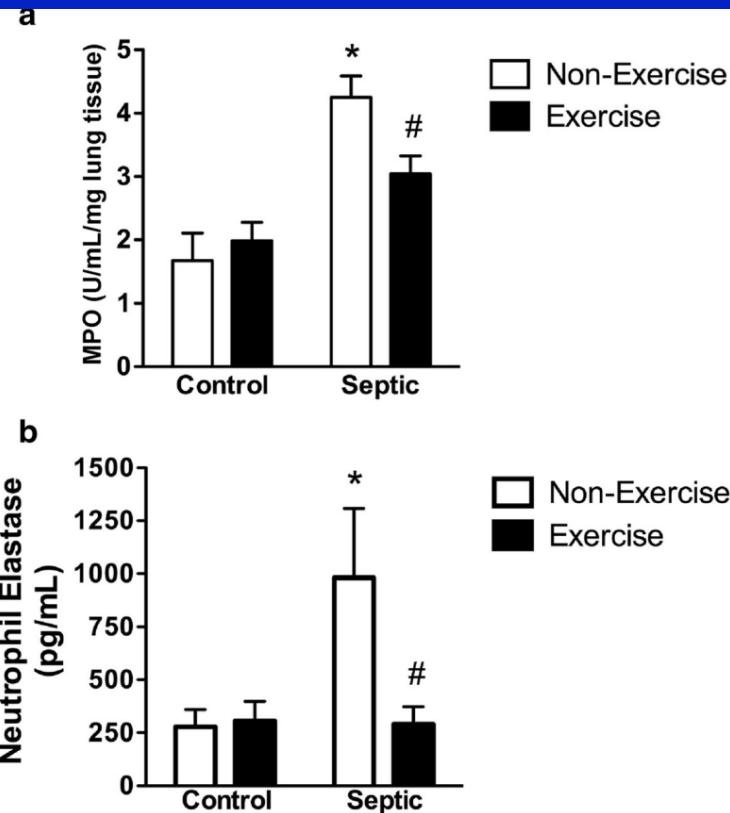
Sensitivity and specificity analysis of ventilatory threshold (VT) for predicting the diagnosis of sepsis

VT there is a nonlinear increase in ventilation with an increase in workload and is associated with the onset of increased anaerobic metabolism.

Voluntary running exercise protects against sepsis-induced early inflammatory and pro-coagulant responses in aged mice



Karel Tymi^{1,8}, Scott Swarbreck¹, Cynthia Pape^{1,4}, Dan Secor¹, James Koropatnick^{2,5,6,7}, Qingping Feng¹, Ruud A. W. Veldhuizen^{1,3,4,5} and Sean E. Gill^{1,3,4,5*}

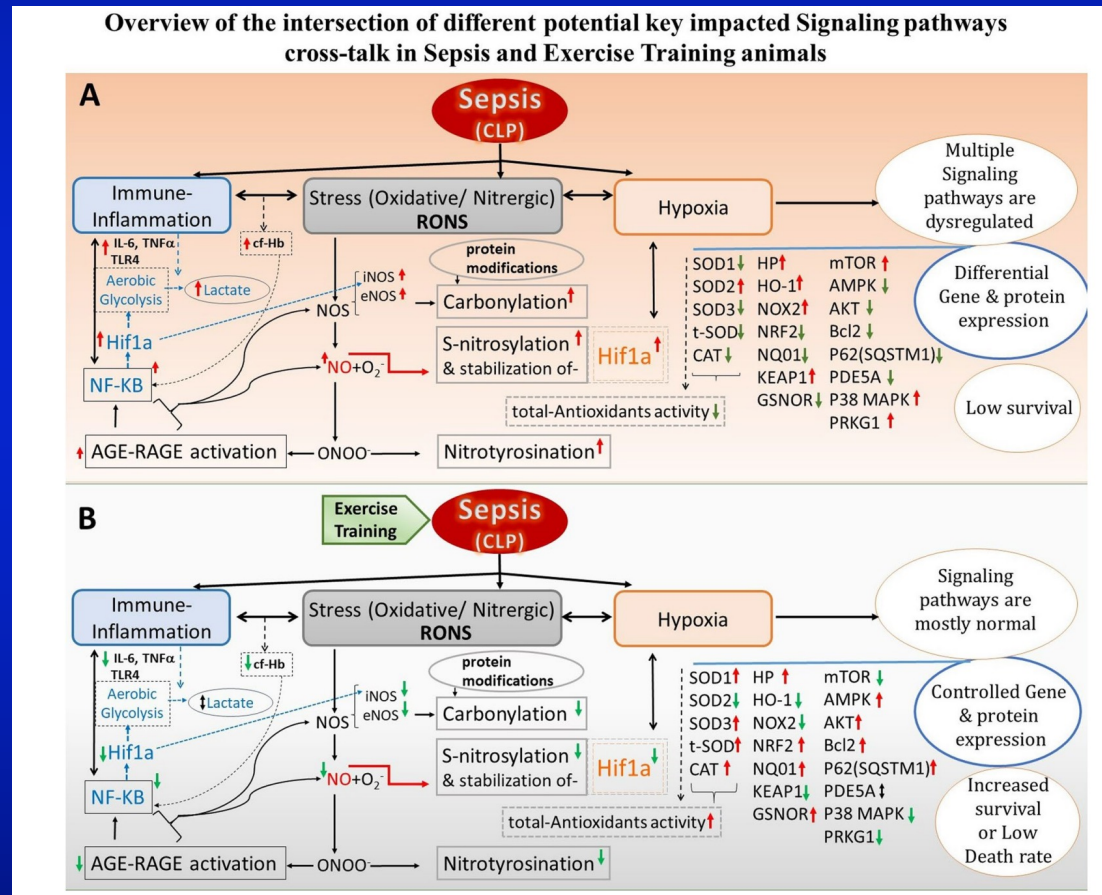


Critical Care (2017) 21:210

Moderate exercise-induced dynamics on key sepsis-associated signaling pathways in the liver

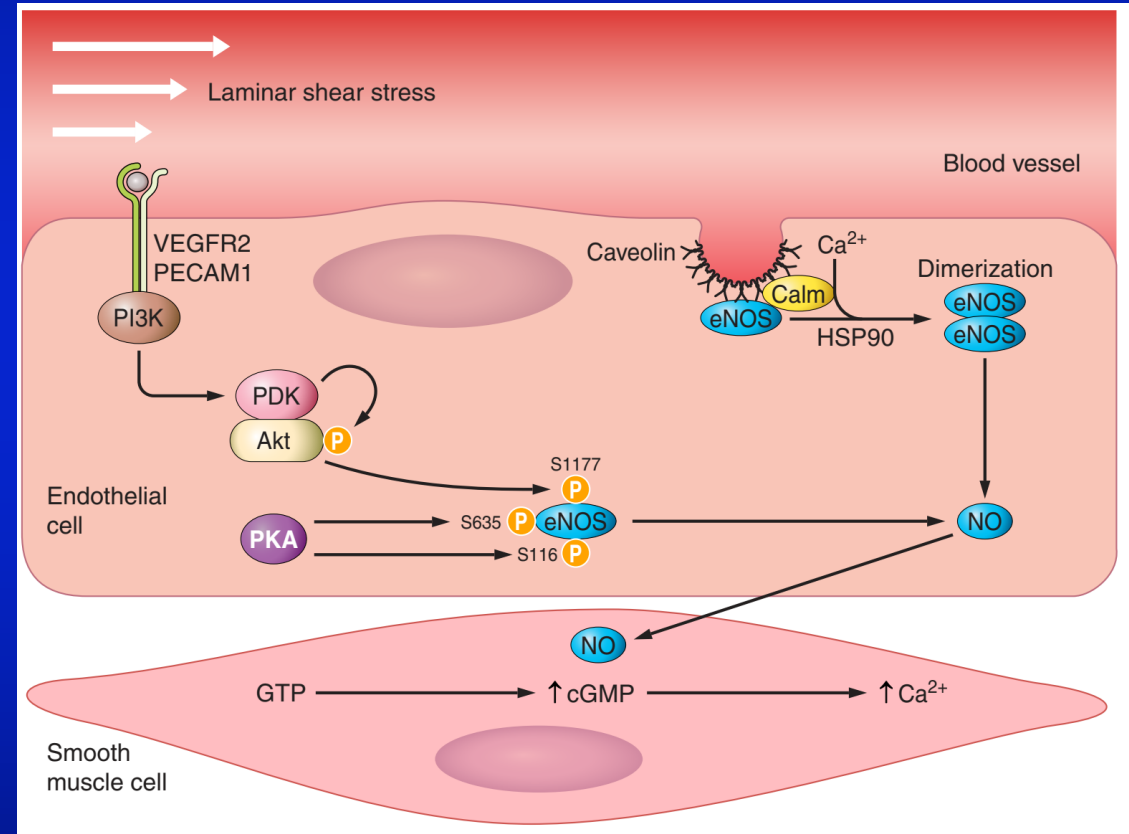
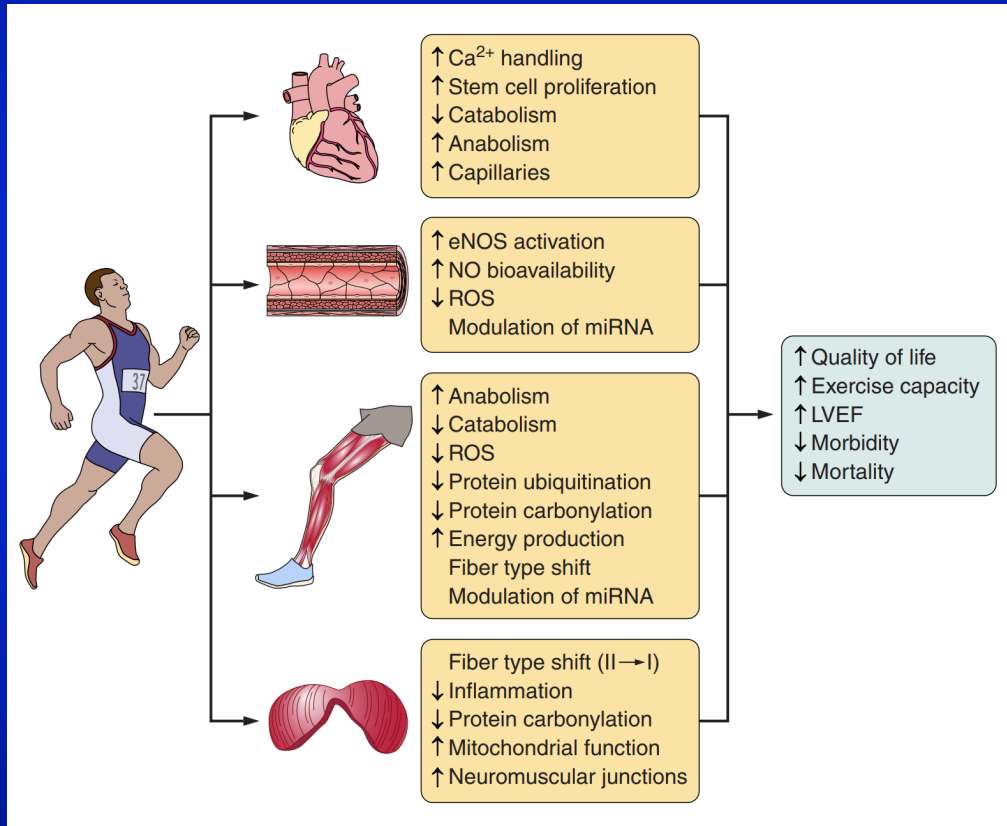


Hari Prasad Osuru^{1*}, Keita Ikeda¹, Navya Atluri¹ and Robert H. Thiele^{1*}



Molecular effects of exercise training in patients with cardiovascular disease: focus on skeletal muscle, endothelium, and myocardium

Volker Adams,¹ Bernhard Reich,² Madlen Uhlemann,¹ and Josef Niebauer²

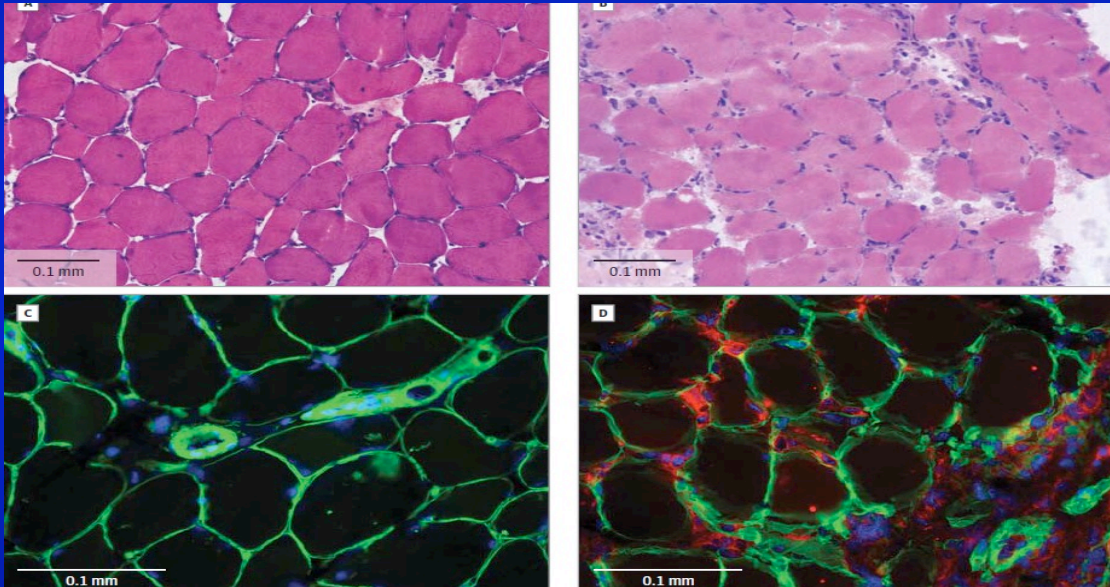


Am J Physiol Heart Circ Physiol 313: H72–H88, 2017.

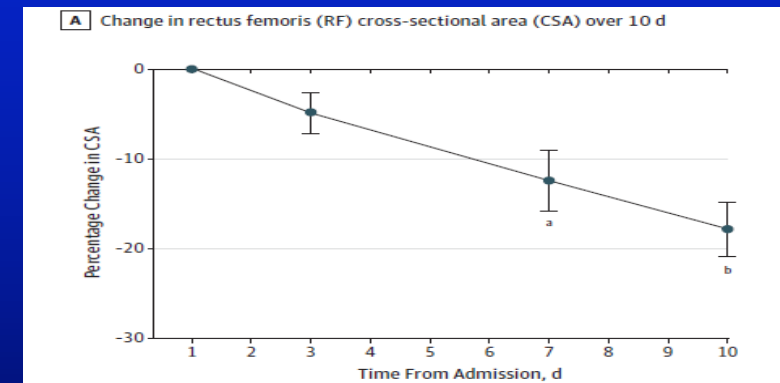
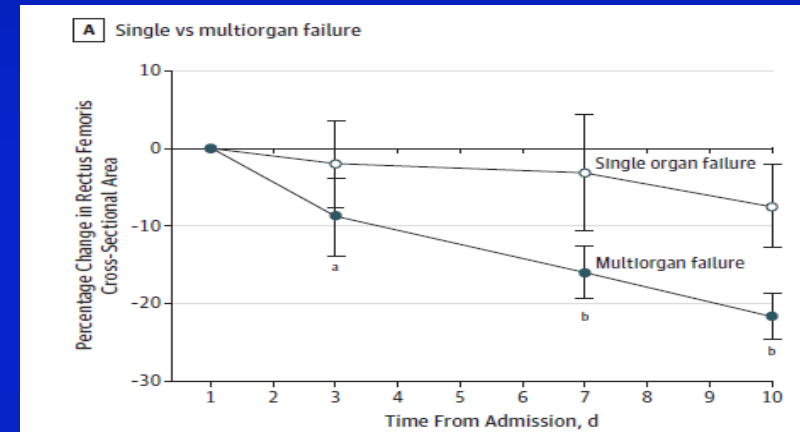
Acute Skeletal Muscle Wasting in Critical Illness



Zudin A. Puthuchery, MRCP; Jaikity Rawal, MRCS; Mark McPhail, PhD; Bronwen Connolly, BSc; Gamunu Ratnayake, MRCP; Pearl Chan, MBBS; Nicholas S. Hopkinson, PhD; Rahul Padhke, PhD; Tracy Dew, MSc; Paul S. Sidhu, PhD; Cristiana Velloso, PhD; John Seymour, PhD; Chibeza C. Agley, MSc; Anna Selby, PhD; Marie Limb, PhD; Lindsay M. Edwards, PhD; Kenneth Smith, PhD; Anthea Rowleron, PhD; Michael John Rennie, PhD; John Moxham, PhD; Stephen D. R. Harridge, PhD; Nicholas Hart, PhD; Hugh E. Montgomery, MD

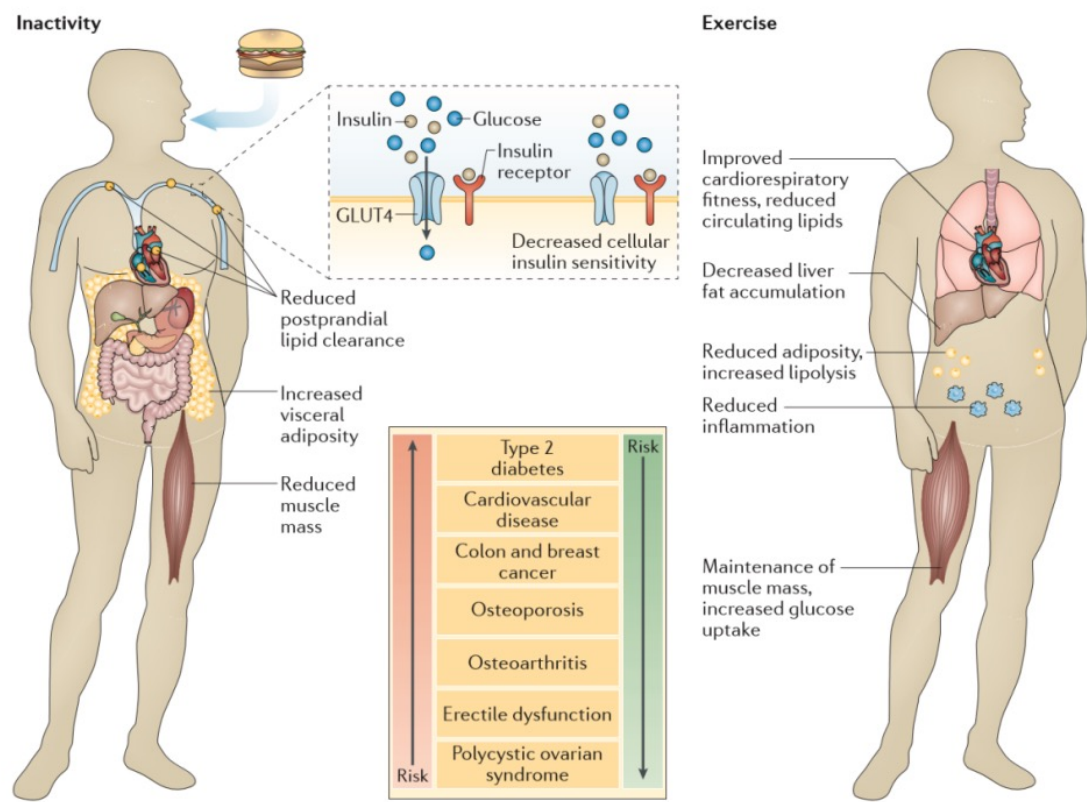


Healthy muscle is seen on day 1 (A, C) with necrosis and a cellular infiltrate on day 7 (B, D). This infiltrate was CD68 positive on immunostaining, indicating macrophage origin (red). A, B are hematoxylin and eosin stain, and C, D was



The ever-expanding myokinome: discovery challenges and therapeutic implications

Martin Whitham and Mark A. Febbraio



Myokine

A cytokine or peptide that is produced by skeletal muscle cells and subsequently released into the circulation to exert paracrine or endocrine effects.

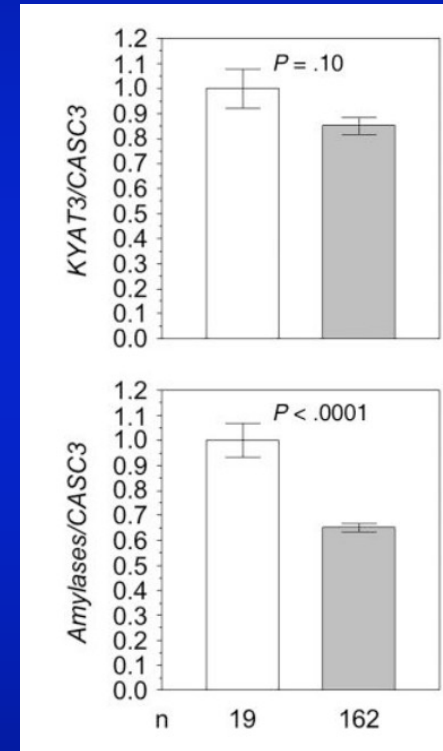
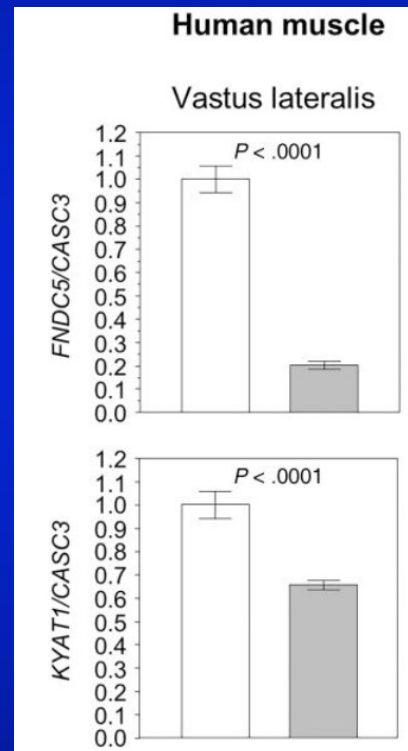
Myokine	Method of discovery	Validation as a secreted factor	Purported myokine function
Irisin	<i>In vitro</i> gene expression array and secreted protein bioinformatics of PGC1 α -overexpressing muscle cells	Quantitative analysis of post-exercise plasma in mice (western blot) and humans (targeted mass spectrometry)	Browning of adipose tissue
Meteorin-like 1	Combined gene expression and mass spectrometry analysis of PGC1 α -overexpressing primary muscle cells	Delayed protein appearance in wild-type mice carrying out downhill running exercise	Browning of adipose tissue
Myonectin	Serendipitously, while characterizing metabolic function of CTRP family of proteins	Increased concentration of myonectin in serum of mice carrying out 2 weeks of voluntary running wheel activity	Improved hepatic fatty acid uptake
Musclin	Screening of cDNA libraries specific for secreted proteins	Increased gene and plasma expression in mice subjected to daily treadmill exercise versus control mice. Systemic treatment of musclin rescued phenotype in <i>Ostn</i> -knockout mice	Increased mitochondrial biogenesis
SPARC	Gene expression arrays of muscle derived from mice exercised for 4 weeks versus controls	Exercise time-course analysis in mice and humans. Secretion from primary muscle cells <i>in vitro</i>	Reduces precursor lesions of colorectal adenocarcinoma on the surface of the colon

proteins termed 'myokines'

skeletal muscle is an endocrine organ capable of secreting

Skeletal Muscle Myokine Expression in Critical Illness, Association With Outcome and Impact of Therapeutic Interventions

Ilse Vanhorebeek,¹ Jan Gunst,^{1,2} Michaël P. Casaer,^{1,2} Inge Derese,¹ Sarah Derde,¹ Lies Pauwels,¹ Johan Segers,³ Greet Hermans,^{1,4} Rik Gosselink,³ and Greet Van den Berghe^{1,2}



□ Healthy ■ Critically ill

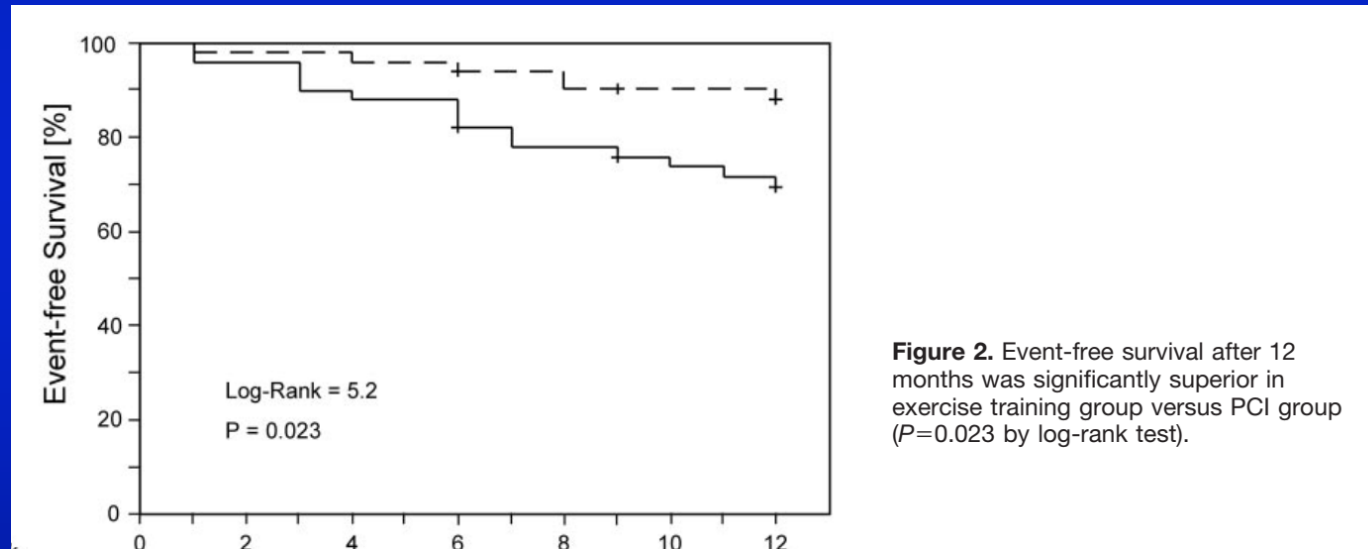
Conclusion: Expression of the studied myokines was affected by critical illness and associated with clinical outcomes, with limited effects of interventions that attenuate muscle wasting or weakness.

Percutaneous Coronary Angioplasty Compared With Exercise Training in Patients With Stable Coronary Artery Disease

A Randomized Trial

Rainer Hambrecht, MD; Claudia Walther, MD; Sven Möbius-Winkler, MD; Stephan Gielen, MD; Axel Linke, MD; Katrin Conradi, MD; Sandra Erbs, MD; Regine Kluge, MD; Kai Kendziorra, MD; Osama Sabri, MD; Peter Sick, MD; Gerhard Schuler, MD

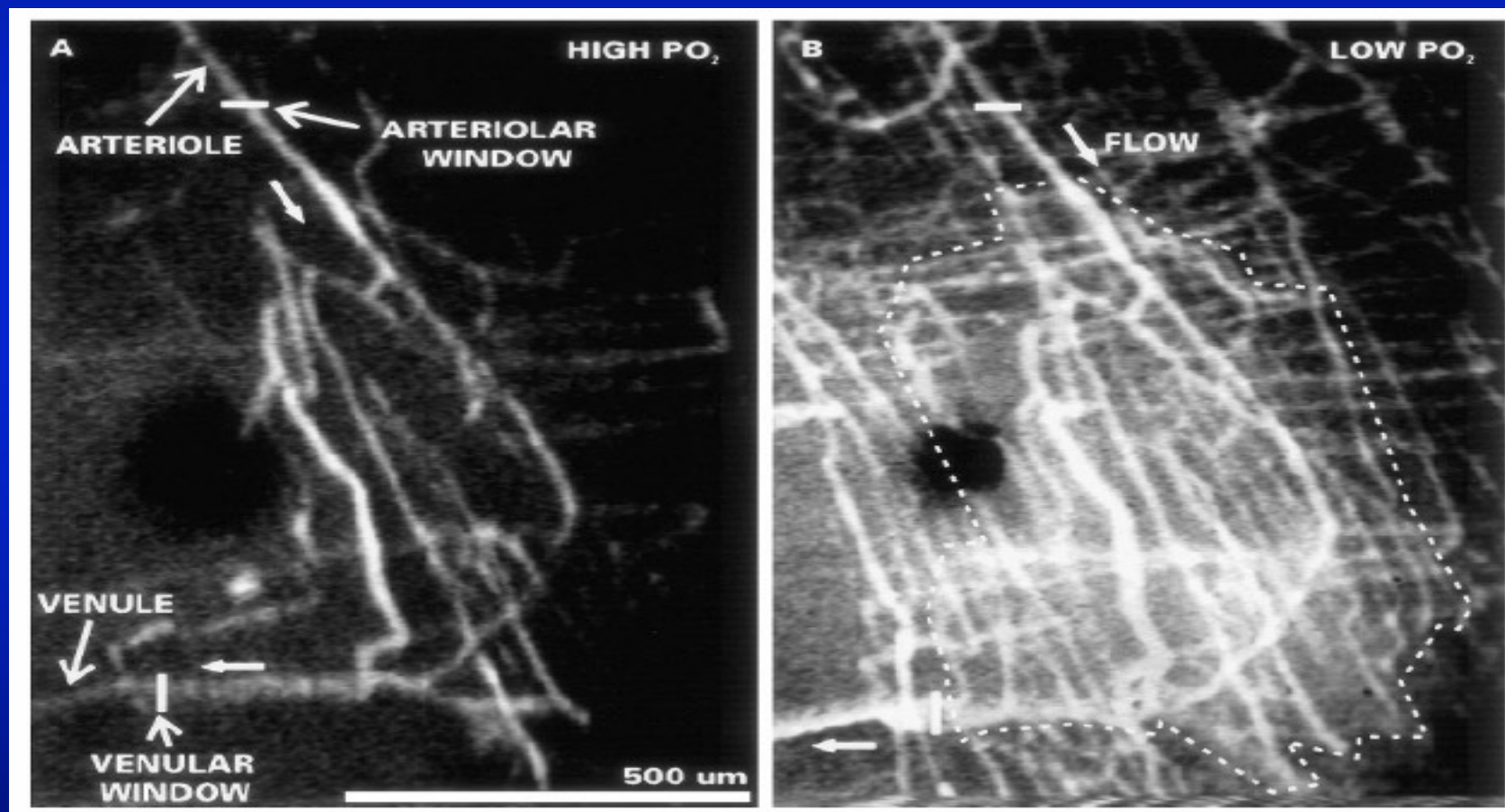
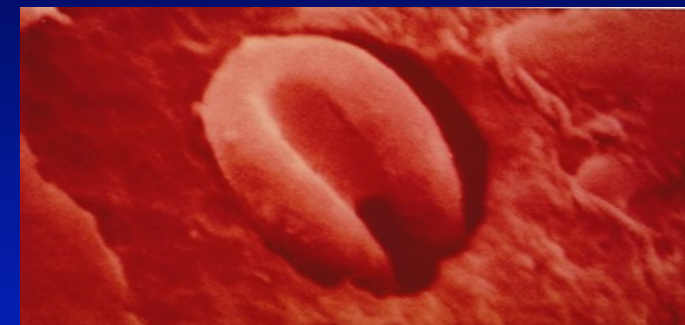
a randomized study to compare the effects of exercise training versus standard percutaneous coronary intervention (PCI) with stenting on clinical symptoms



Conclusions—Compared with PCI, a 12-month program of regular physical exercise in selected patients with stable coronary artery disease resulted in superior event-free survival and exercise capacity at lower costs, notably owing to reduced rehospitalizations and repeat revascularizations. (*Circulation*. 2004;109:1371-1378.)

Capillary recruitment in response to tissue hypoxia and its dependence on red blood cell deformability

KAUSHIK PARTHASARATHI AND HERBERT H. LIPOWSKY



Am. J. Physiol. 277 (Heart Circ. Physiol. 46): H2145–H2157, 1999.

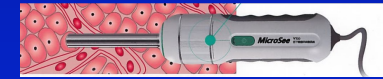
Imaging the Microcirculation Physiology at the Bedside



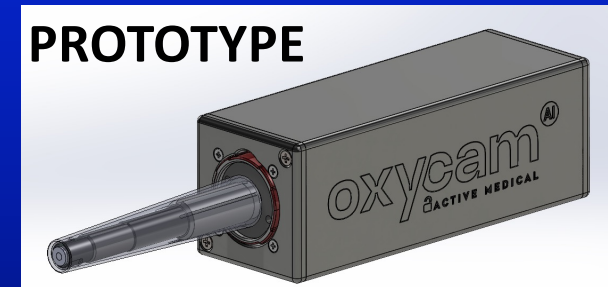
Orthogonal Spectral (OPS) imaging



Incident dark field (IDF) imaging

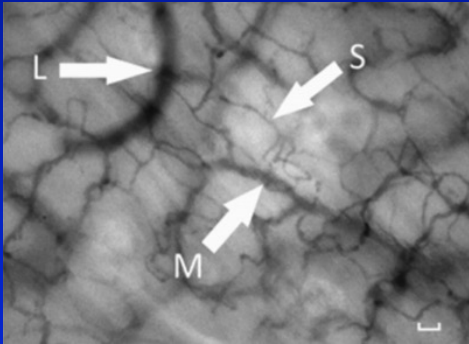


Sidestream dark field (SDF) imaging



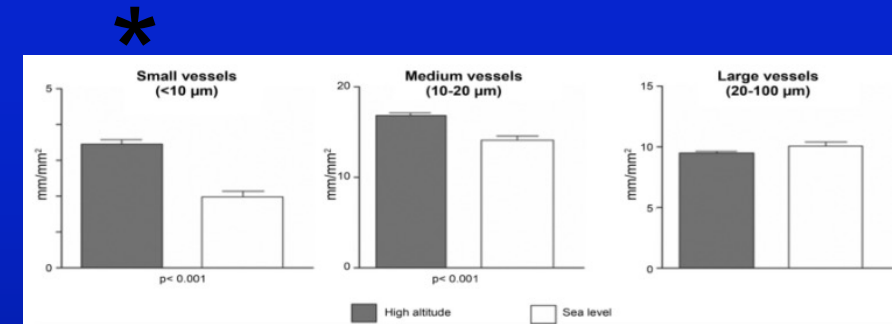
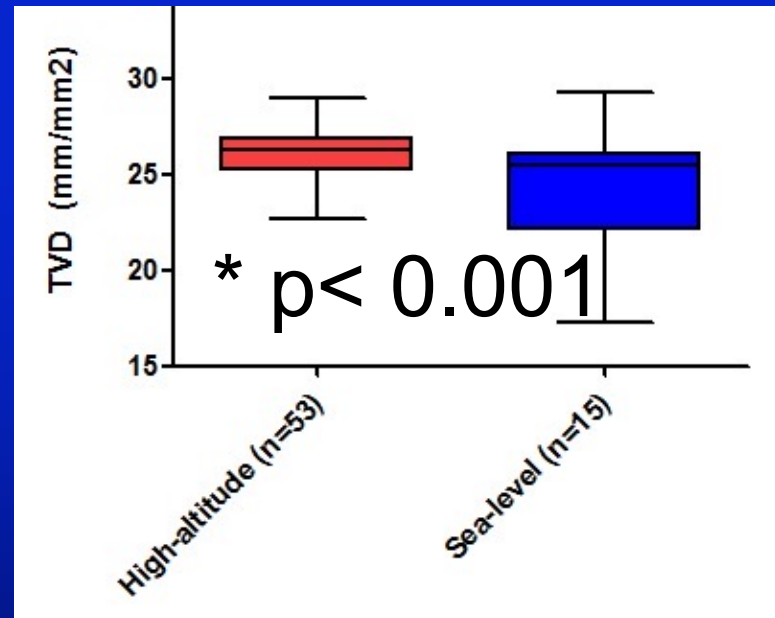
Incident dark field (IDF)
plus O2 saturation imaging

Pregnancy at high altitude in the Andes leads to increased total vessel density in healthy newborns



Norina N. Gassmann,^{1,2*} Hugo A. van Elteren,^{2*} Tom G. Goos,^{2,3} Claudia R. Morales,⁴ Maria Rivera-Ch,^{4,5} Daniel S. Martin,⁶ Patricia Cabala Peralta,⁷ Agustin Passano del Carpio,⁷ Saul Aranibar Machaca,⁷ Luis Huicho,^{5,8} Irwin K. M. Reiss,² Max Gassmann,^{1,8*} and Rogier C. J. de Jonge^{2*}

Total vessel density in term neonates at high altitude (Puno 3827 m)



Irwin Reiss, Max Gassman

J Appl Physiol 121: 709–715, 2016.

Adaptation of the microcirculation to hypoxia

The response of the microcirculation to hypoxia is to increase its oxygen extraction capacity by increasing its TVD and thereby shortening its diffusive distance.



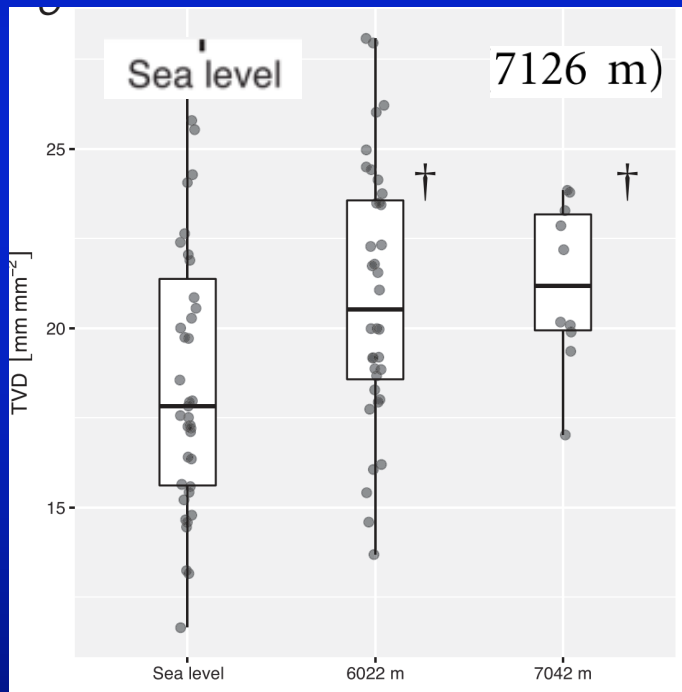
Matthias Hilty

Recruitment of non-perfused sublingual capillaries increases microcirculatory O₂-extraction capacity throughout ascent to 7126 m

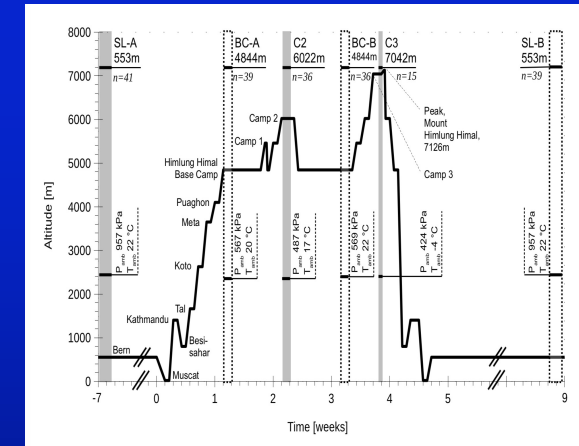
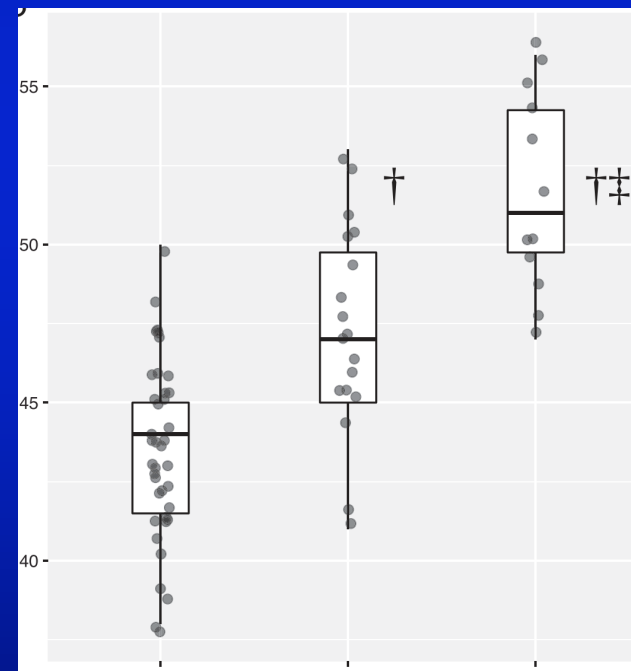
Matthias Peter Hilty^{1,4} , Tobias Michael Merz^{3,6} , Urs Hefti⁵, Can Ince⁴, Marco Maggiorini¹ and Jacqueline Pichler Hefti^{2,3}



Total vessel density



Hematocrit



Mount Himlung Himal Nepal (7126 m)

Microvascular recruitment at high altitude

COVID-19

The mystery of the pandemic's 'happy hypoxia'

Doctors debate how to treat patients with low blood oxygen but without trouble breathing

Jennifer Couzin-Frankel

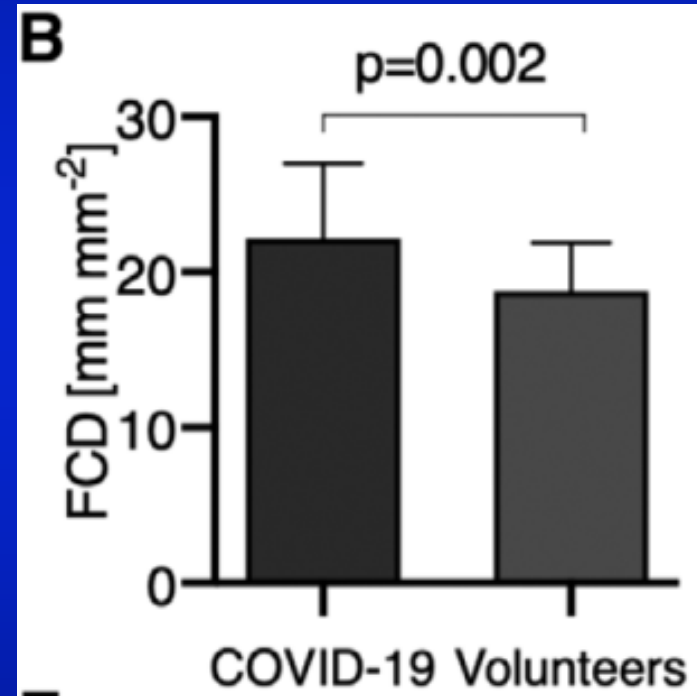
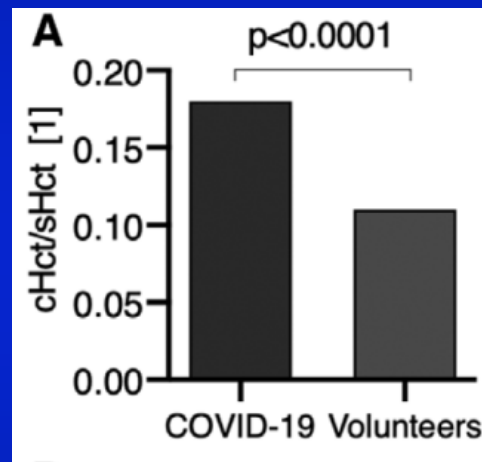
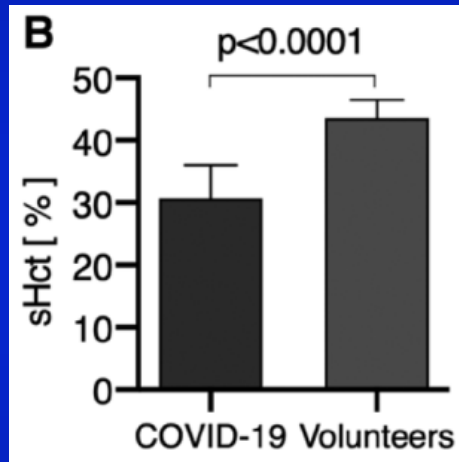


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Capillary Leukocytes, Microaggregates, and the Response to Hypoxemia in the Microcirculation of Coronavirus Disease 2019 Patients

Adaptive microcirculatory mechanisms in response to COVID-19 hypoxia

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 Henrik Endeman, MD, PhD¹



RBC move from the systemic to the microcirculation

The density of sublingual capillaries (functional capillary density; FCD) are elevated in COVID-19



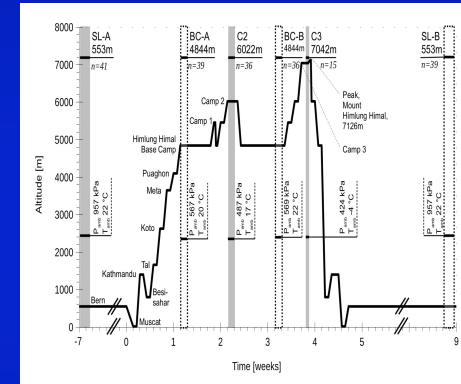
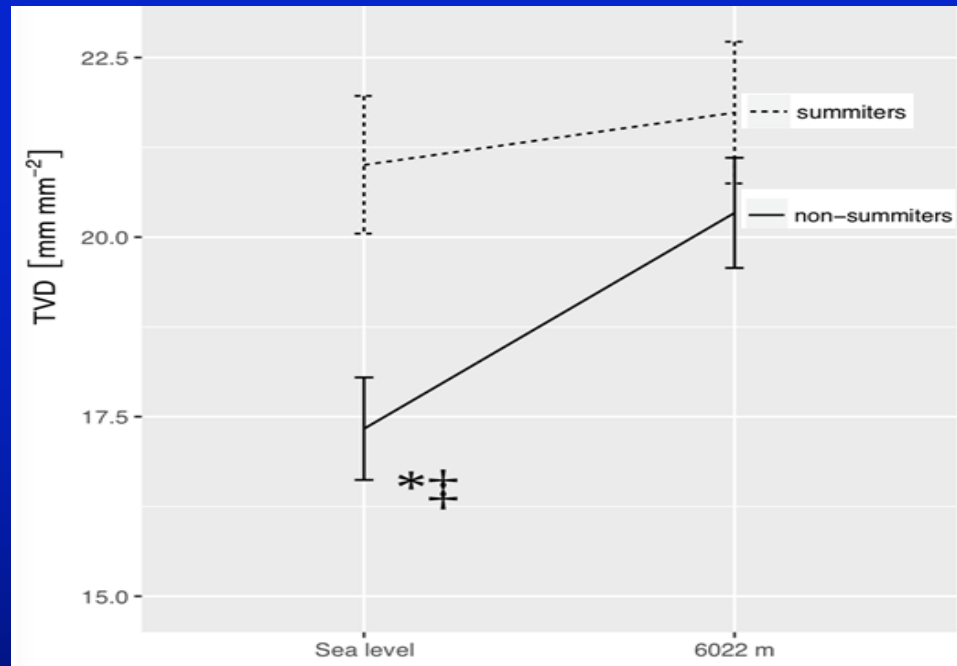
Recruitment of non-perfused sublingual capillaries increases microcirculatory O₂-extraction capacity throughout ascent to 7126 m

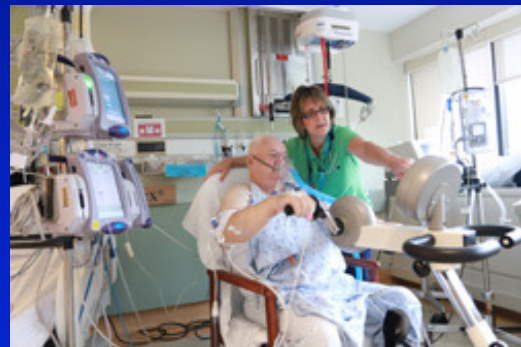
Hilty M, Merz T, Hefti U, Ince C, Maggiorini M, Pichler J
Swiss-EXPED 2013 Himalayan High Altitude Research Expedition



Matthias Hilty

Capillary density at sea level and high altitude





Exercise is Medicine



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Thank you for the invitation !

