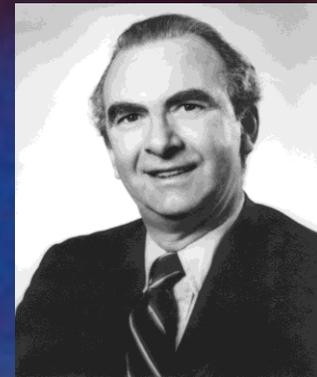


UW-Madison

John Rankin Laboratory of Pulmonary
Medicine

jdempsey@wisc.edu



Neural Feedback Influences on Exercise Physiology, Pathophysiology and Performance: Known and Unknown

(UW Rankin Lab of Pulmonary Medicine)



Markus Amann



Lee Romer



David Pegelow



Les Proctor



Craig Harms



Gregory Blain



Keisho Katayama



Dorothy Ainsworth



Curt Smith



Barb Morgan



Bruce Johnson



Bill Sheel



Mike Stickland



Claudette St. Croix

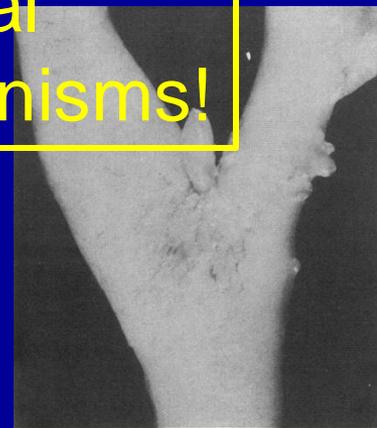
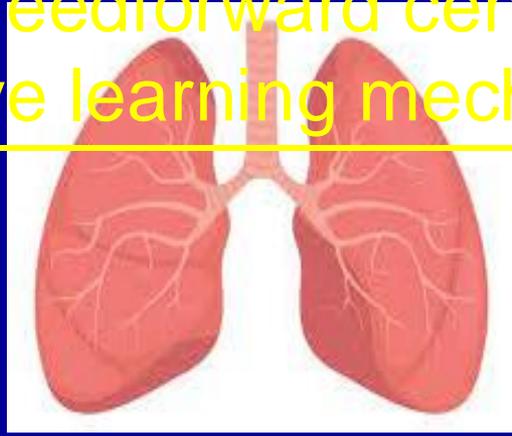
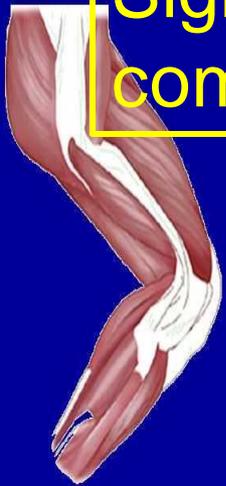


Jordan Miller

Neural Mechanisms Regulating Exercise Physiology

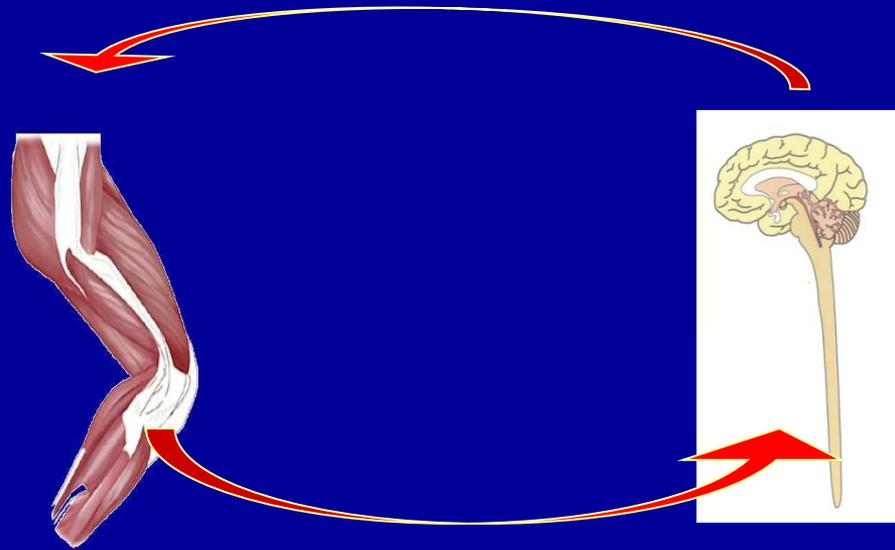
- Hyperpnea, breathing pattern, bronchodilation
- MAP, muscle vascular conductance/blood flow
- Pacing strategy, fatigue, exercise performance

Obligatory Feedback Mechanisms?
Significant roles for feedforward central command/associative learning mechanisms!



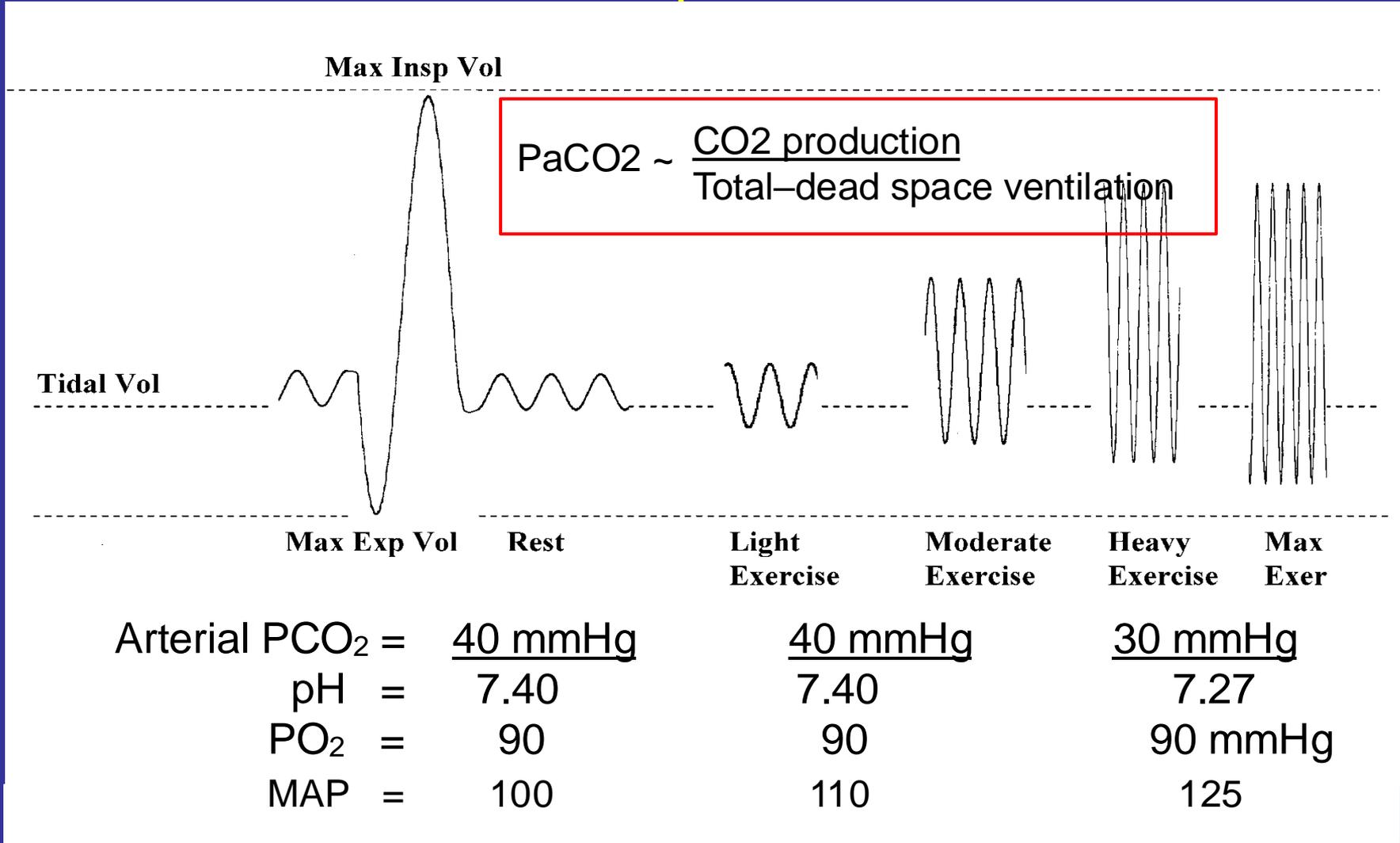
Approach: Reversibly Block/Reduce Each Input During Physiologic Exercise

Locomotor Muscle Group III, IV Afferents



- Gp III mechanosensitive/Gp IV metabosensitive
 - **ACTIVATED:** Rhythmic or static muscle contractions via muscle metabolites, venous distension.
- III-IV interactions; supraspinal projections
- Are muscle afferents obligatory to cardiovent exercise response?

Mediation of Eucapnic Hyperpnea, Breathing Pattern, Vasc Resistance ? Is Muscle Afferent Feedback Required??



IntraThecal Fentanyl, μ Opiate Receptor Agonist

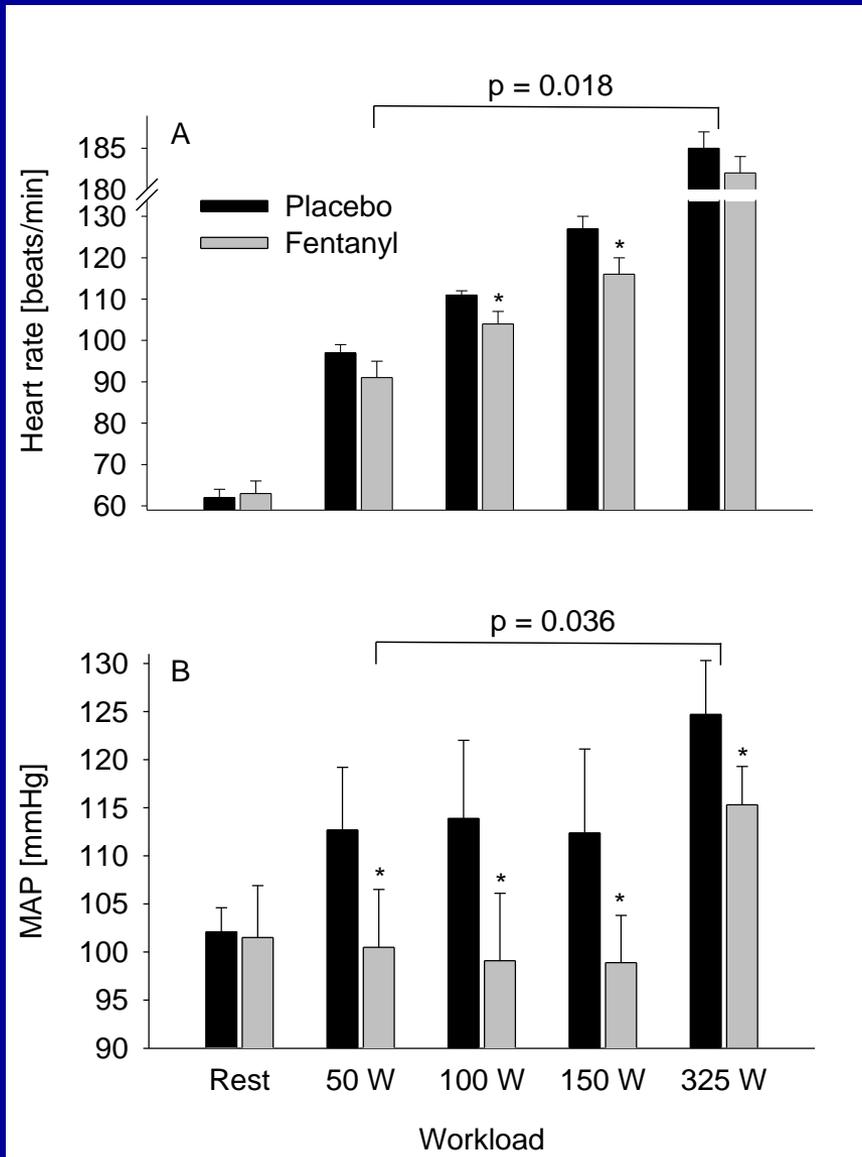
- Opiate agonist \downarrow metaboreceptor-induced pressor response (Hill, Kaufman)
- Only muscle afferents blocked- MVC, Qtw unaffected
- Fentanyl contained within spinal compartment



(Amann et al. 2006-2024)

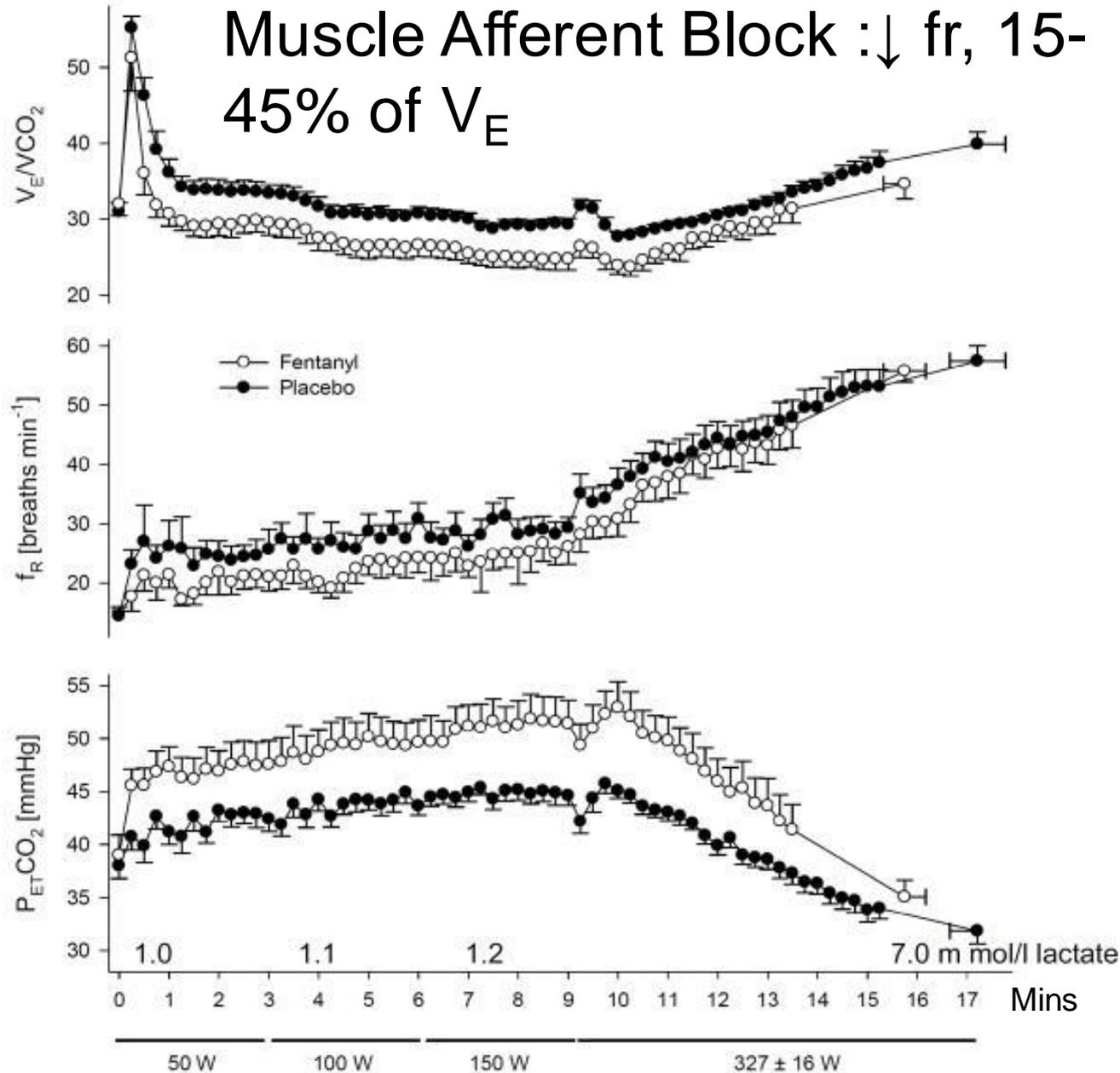


Afferent Block = ↓ Steady State CV Response to Cycling



Aff block = persistent ↓
in HR and MAP, ↑ limb
vascular conductance,
↓ cardiac output

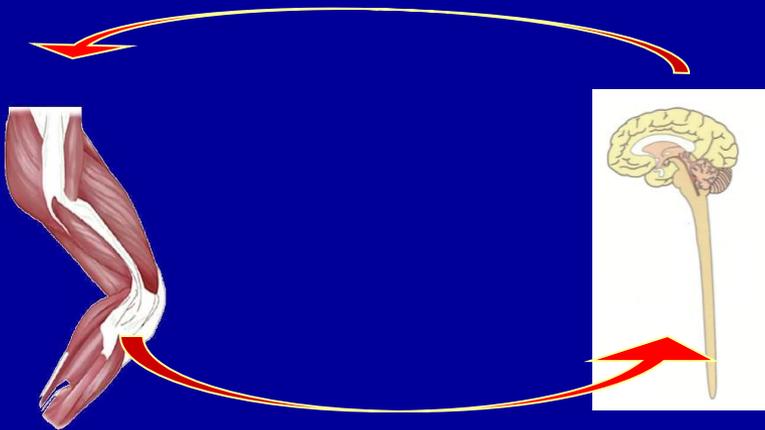
Muscle Afferent Block : \downarrow fr, 15-45% of V_E



... controversial /pushback!!

...Additional hypothesis testing experiments

Summary: Group III-IV muscle afferents are required for exercise-induced sympathoexcitation, \uparrow MAP, breathing frequency/hyperpnea, airway bronchodilation!!



Importance of:

- Muscle mass involved
- Exercise intensity/duration
- Limitation: Only partial afferent block
- Pathophysiology- CHF/Hypertension

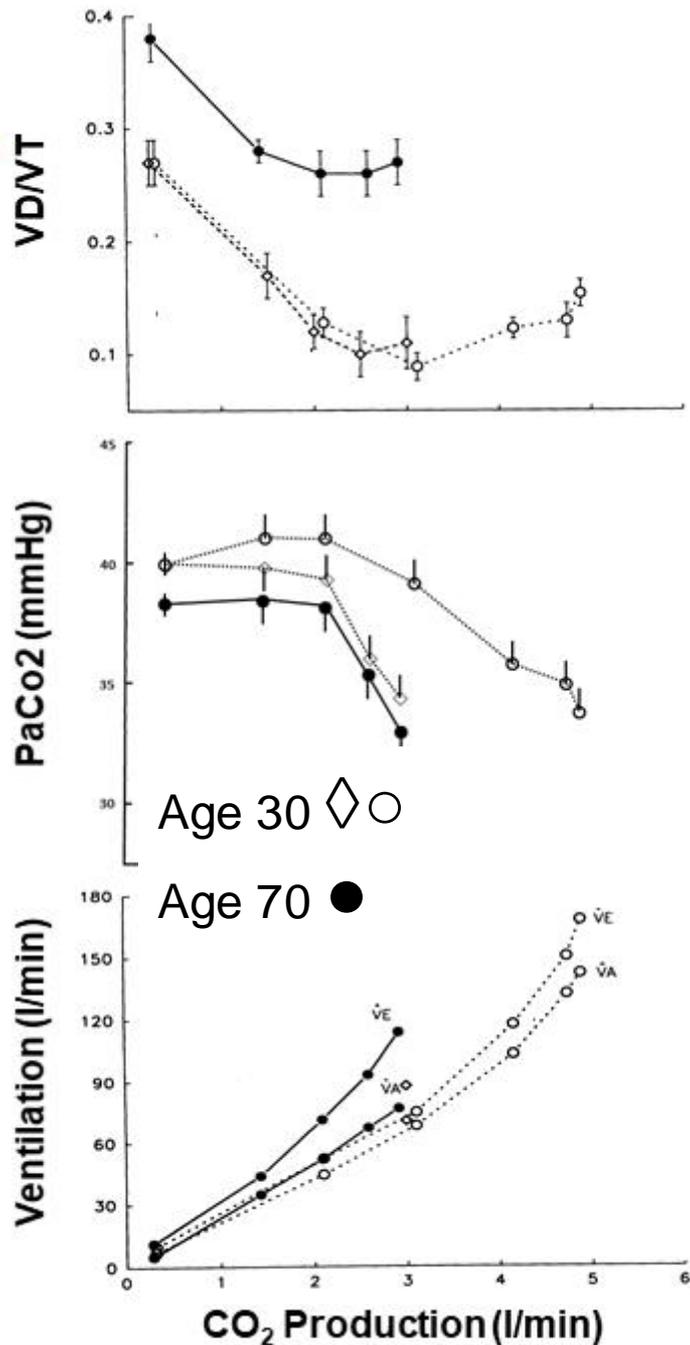
Lots of Unknowns Remain!

Near-Eucapnic Exercise Hyperpnea ???

- Relative contributions of feedback/feedforward stimuli? Stimuli interactions?
- Is “VCO₂” sensed?...where/how?
- Adjusting V_E to adapt to changes in V_d:V_t?
- Breathing pattern regulation?
- Role for long-term associative learning/neural plasticity via trial and error, resulting in a memory engram encoding the hyperpnea in the cerebellum? (Somjen 1990; Welch ,2024)

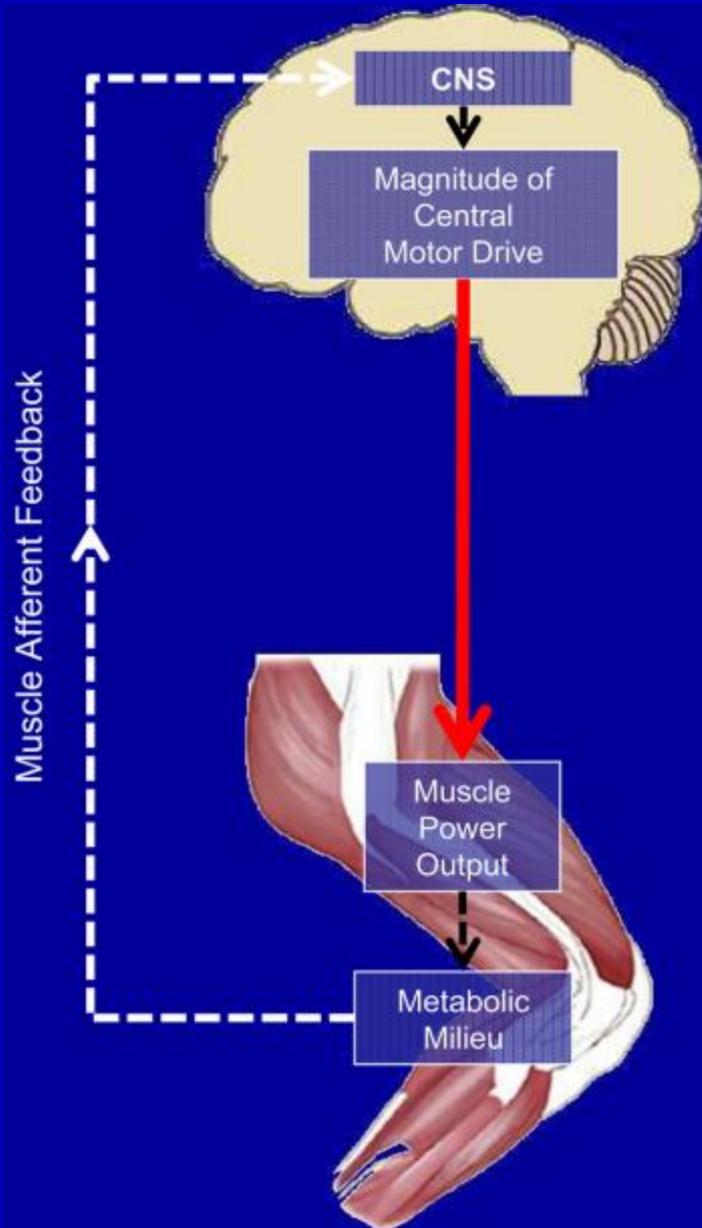
Plasticity in Exercise Hyperpnea with Aging?..

...how does the controller “sense” a changing V_d/V_t , so that $\dot{V}_E:\dot{V}_{CO_2}$ is adjusted to preserve the $\dot{V}_A:\dot{V}_{CO_2}$ proportional link ?



Johnson et al., 1994

MUSCLE AFFERENTS AFFECT PERFORMANCE?



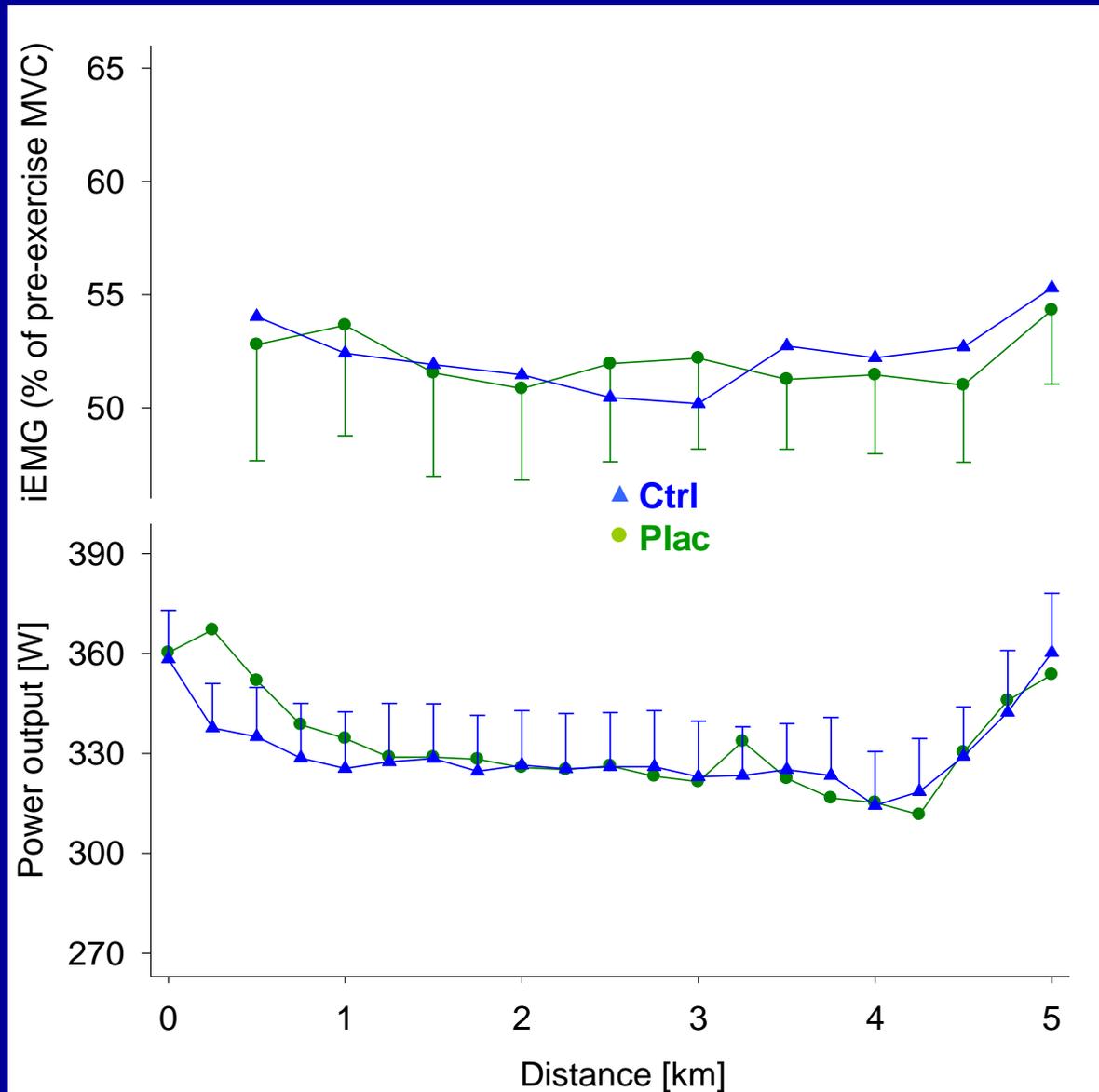
Postulate: Muscle afferent feedback constrains central drive to locomotor muscles which limits excessive muscle fatigue/ performance!

Test- Time Trial:

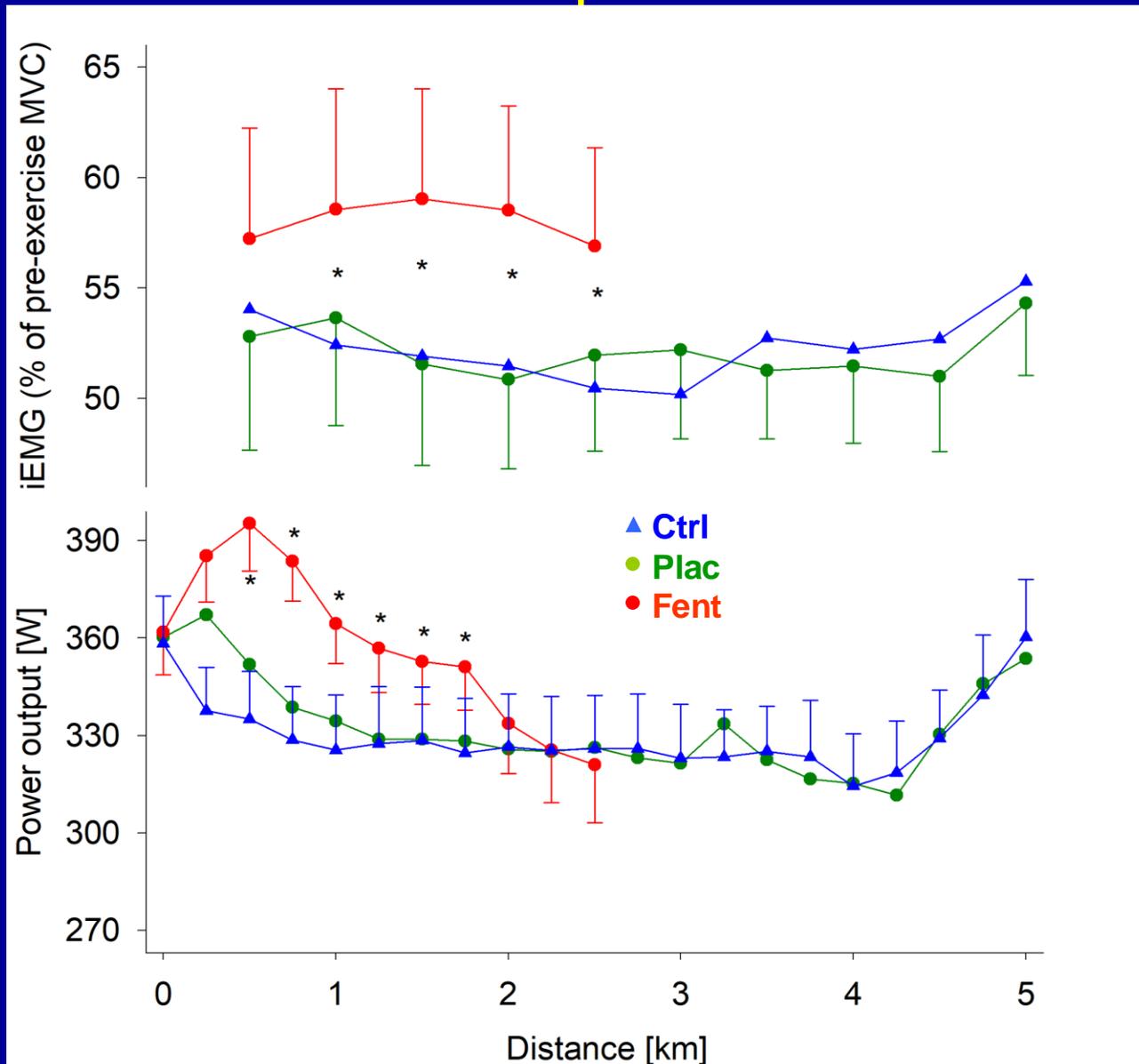
Muscle afferent blockade effects on pacing, power output, fatigue (Q_{tw}), muscle metabolites and performance??

- (Amman, Blain, Hureau et al, 2008-24)

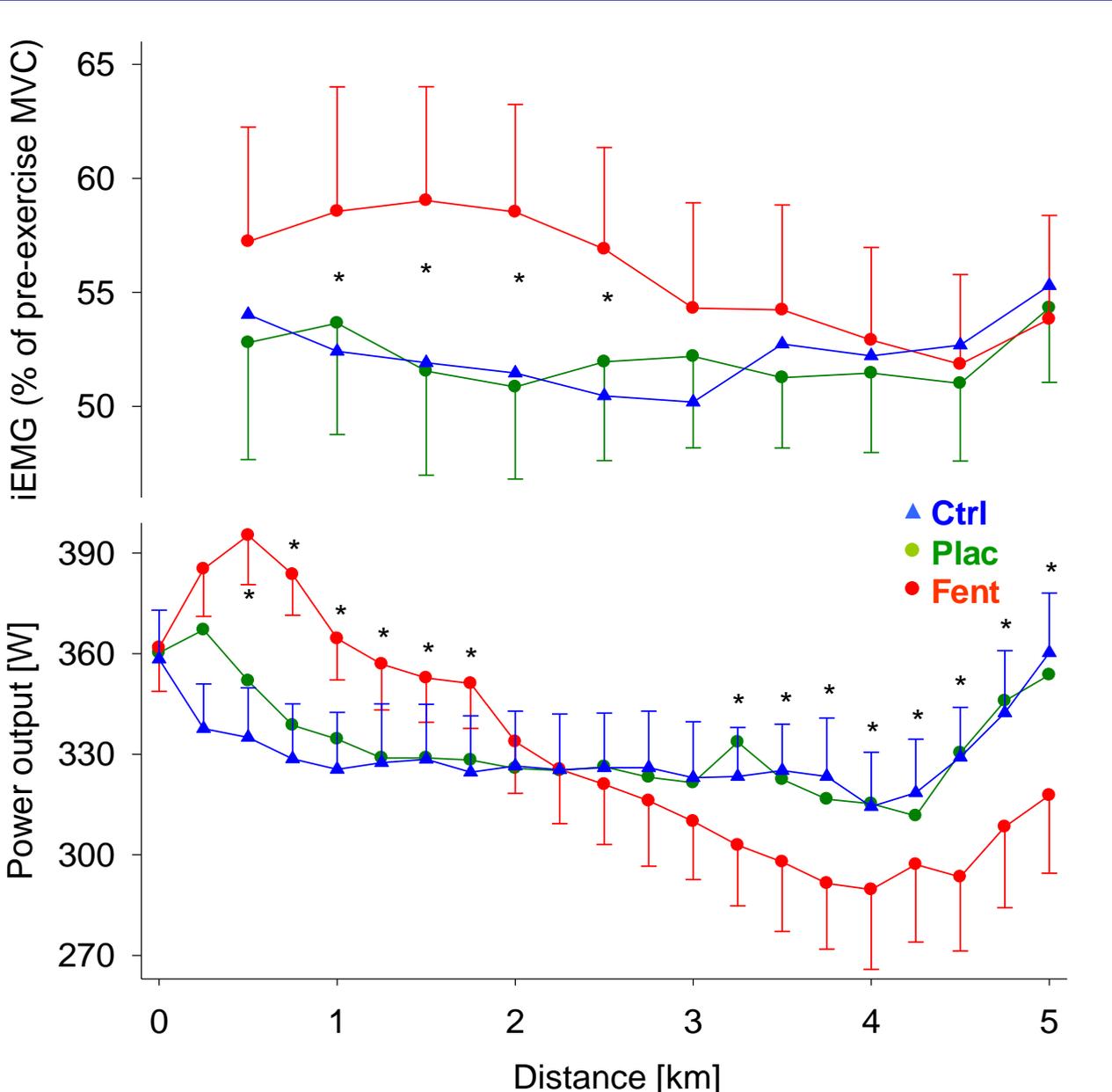
Muscle Afferent Effects on “Choosing” the Level of Central Motor Drive and Power Output During Time Trial Exercise



Fent Block : 1st 2.5 km = ↑ Central Motor Drive/Power Output

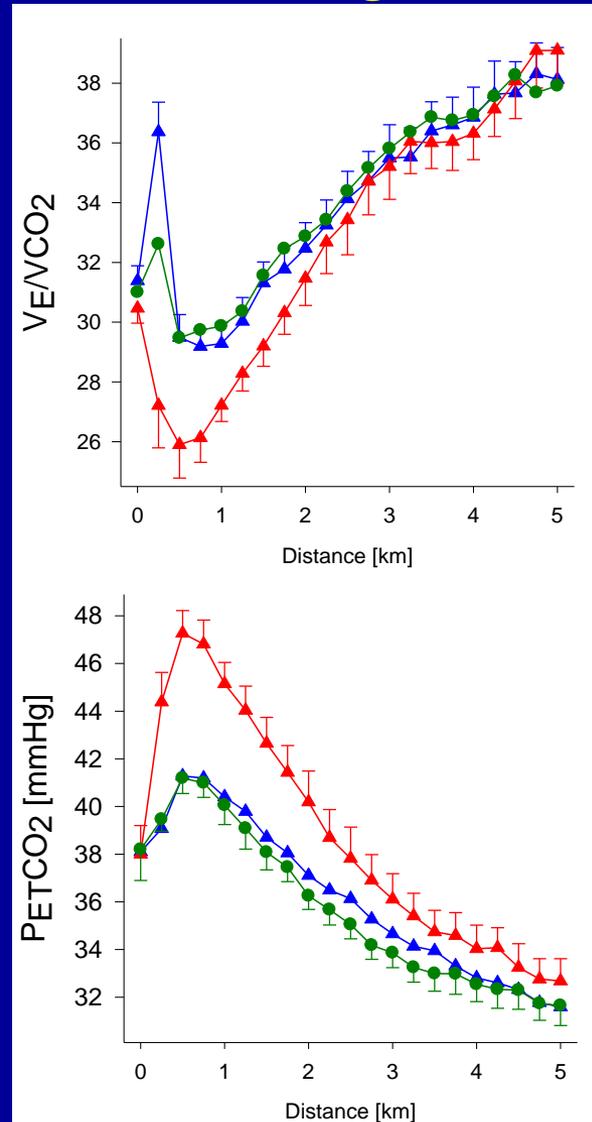
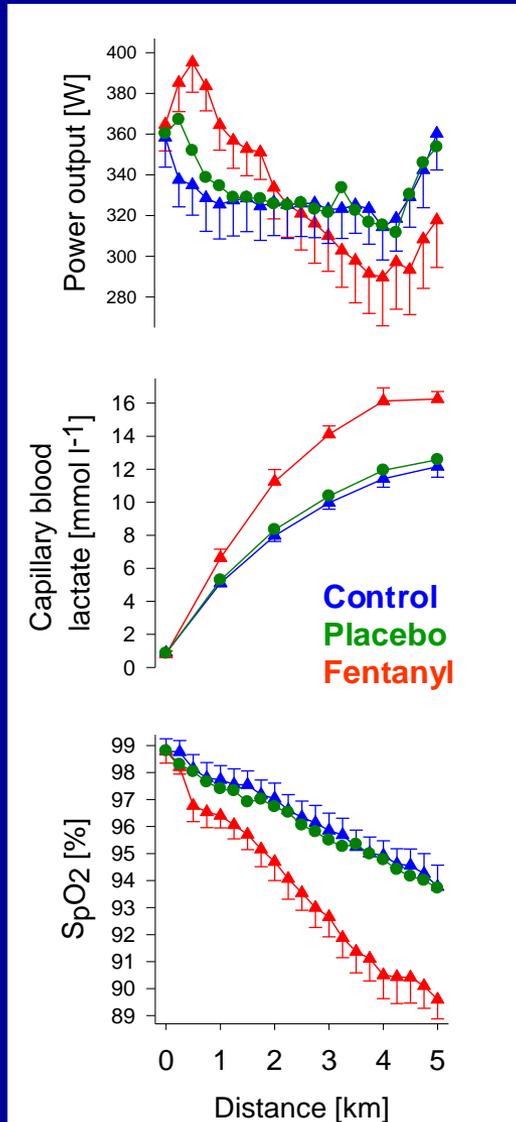


Fent Block: 2nd 2.5 km, → Central Motor Drive and ↓ Power Output



Muscle afferent Feedback influence:
- on pacing strategy!(even in experienced racers)
- on Exercise performance??

Performance and Afferents? Confounding Effects on O₂ transport of Hypoventilation/ HbO₂ Desaturation during Fentanyl time trial



..so, need to combine muscle afferent block with preserved O₂ transport (\uparrow FIO₂)

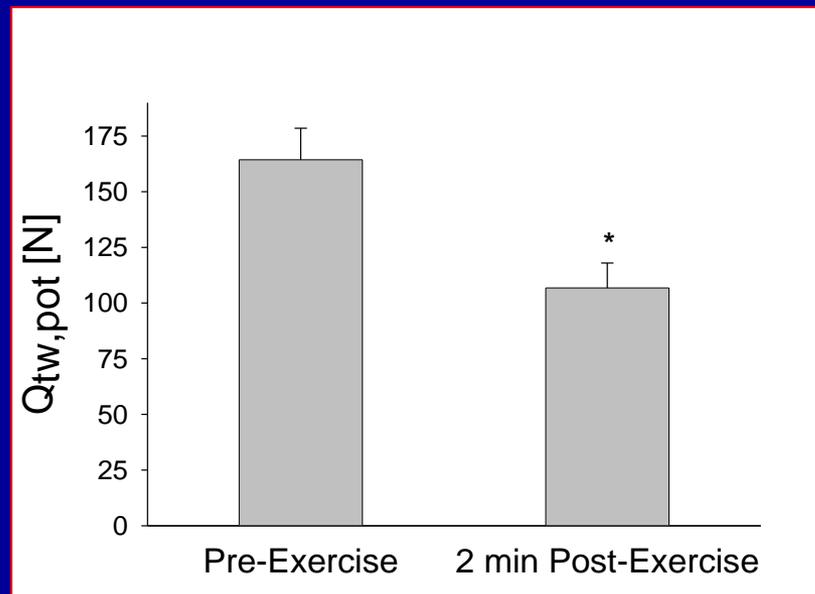
...(+ quantify post exercise muscle fatigue via Q_{tw})
(Hureau et al, 2018)

Peripheral Muscle Fatigue: Supramaximal Magnetic Femoral Nerve Stimulation

Potentiated twitch force ($Q_{tw,pot}$)

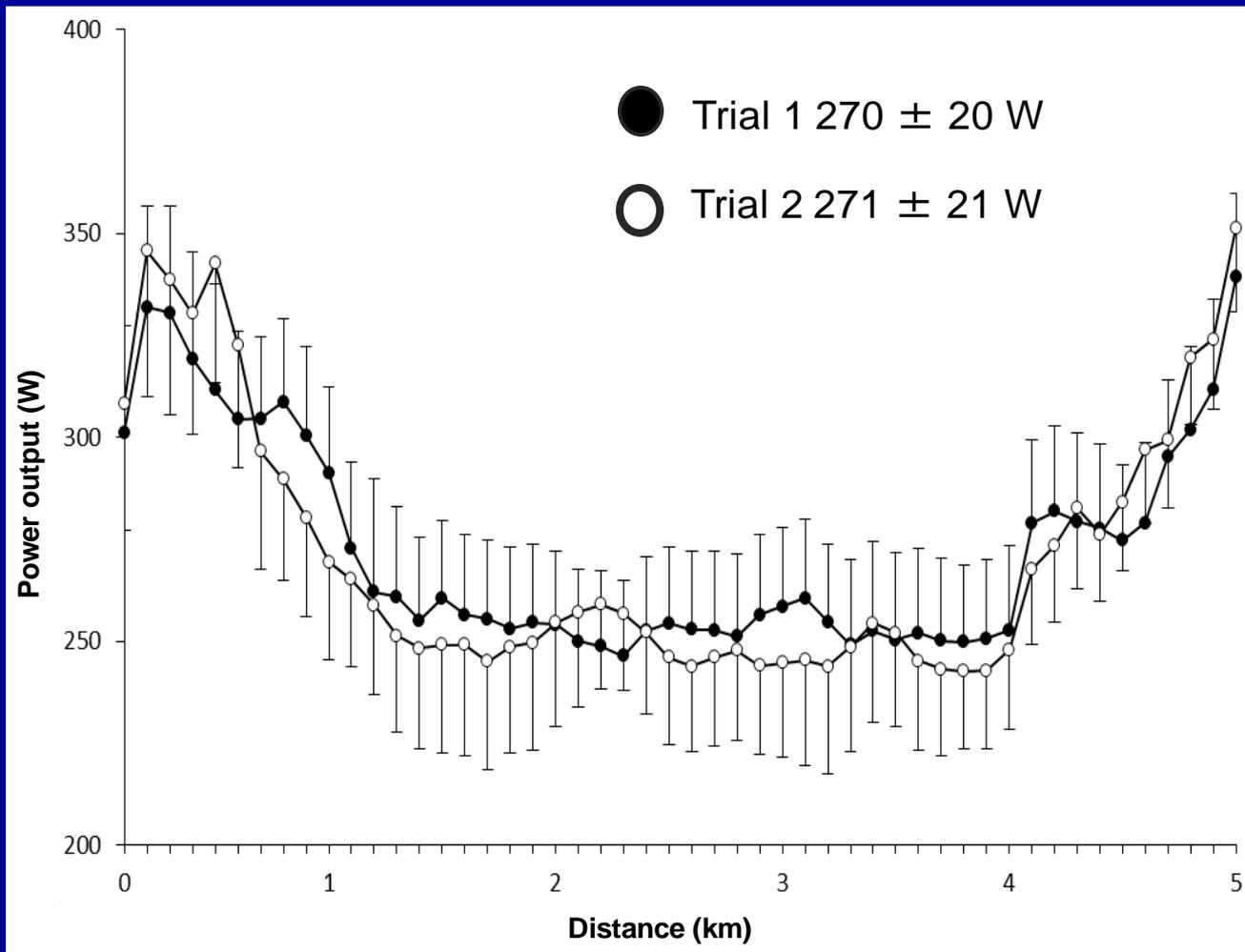


ΔQ_{tw} :pre-vs post 5K
time trial-Control
hyperoxia vs Fent
hyperoxia



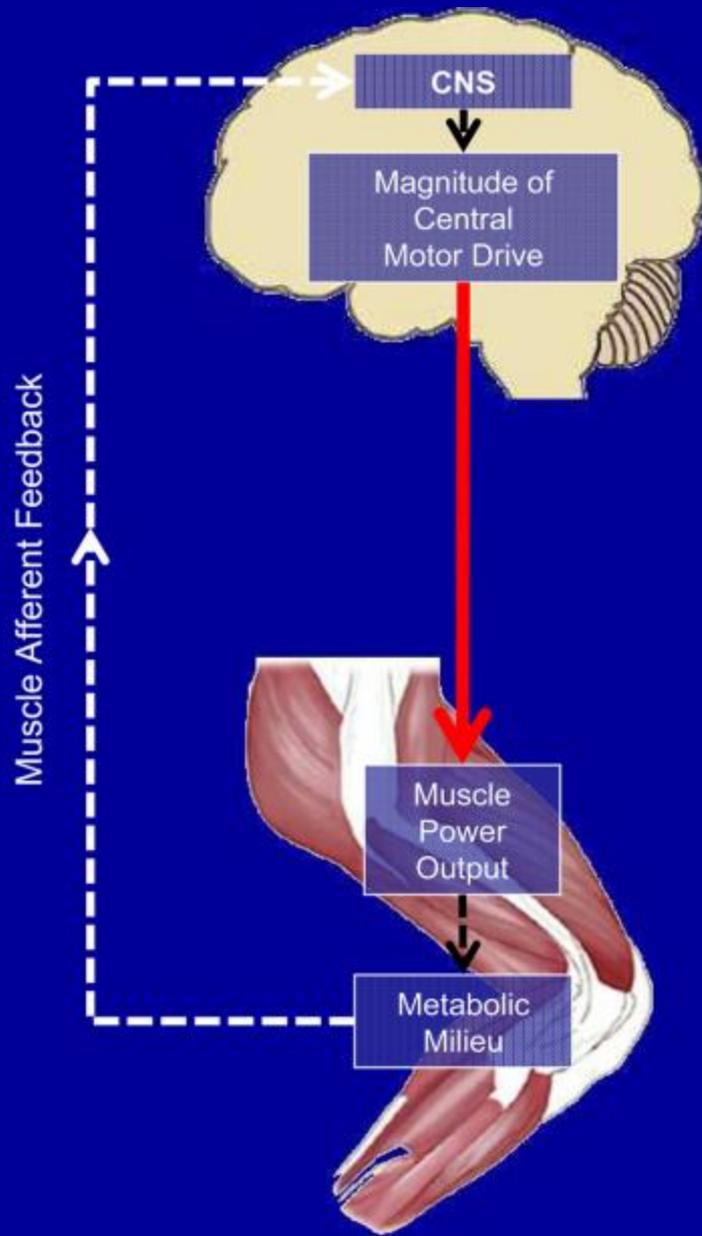
Day-to-day Time Trial Performance Reliability-Control Conditions

Time to completion 491 ± 13 s vs 489 ± 13 s (ICC 0.99)



Muscle Afferent Block in Hyperoxia Improves Sustained Neural/ Power Output/Time Trial Performance

Afferent block \uparrow muscle fatigue (38% $\uparrow \Delta Q_{tw}$, pre-vs. post-exercise)(Hureau,2018)



Conclusions:

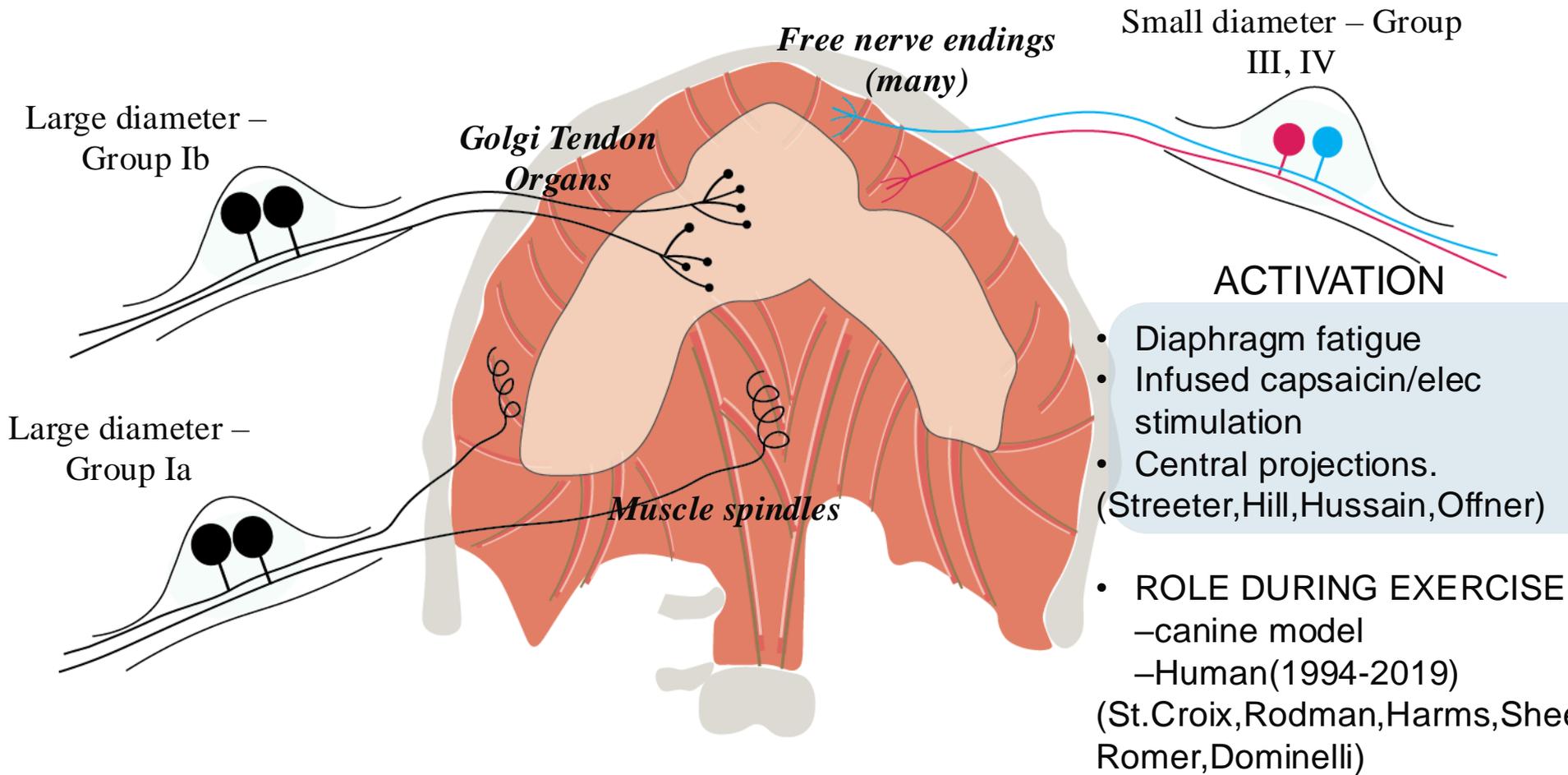
Muscle Afferent Feedback Influences Early Pacing decisions, Constrains Central Locomotor Neural/ Power Output, Limits Muscle Fatigue and Performance

Other Performance Determinants:

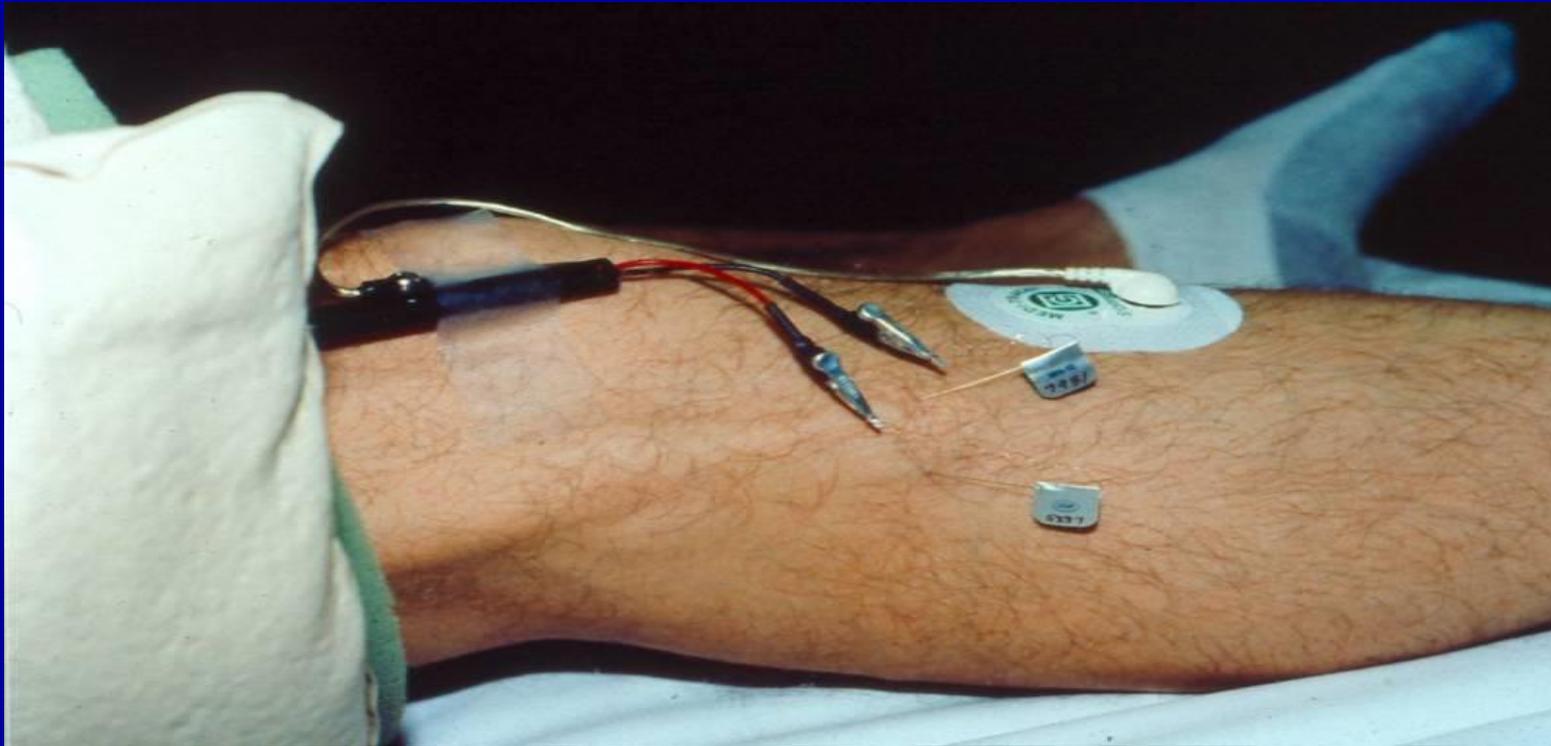
Psychobiological self-regulation of power output via perceived exertion/motivation; Associative learning via past experiences

(Marcora, 2016; Baumeister 2007; McCormick 2015)

SMALL MYELINATED AND UNMYELINATED PHRENIC AFFERENTS

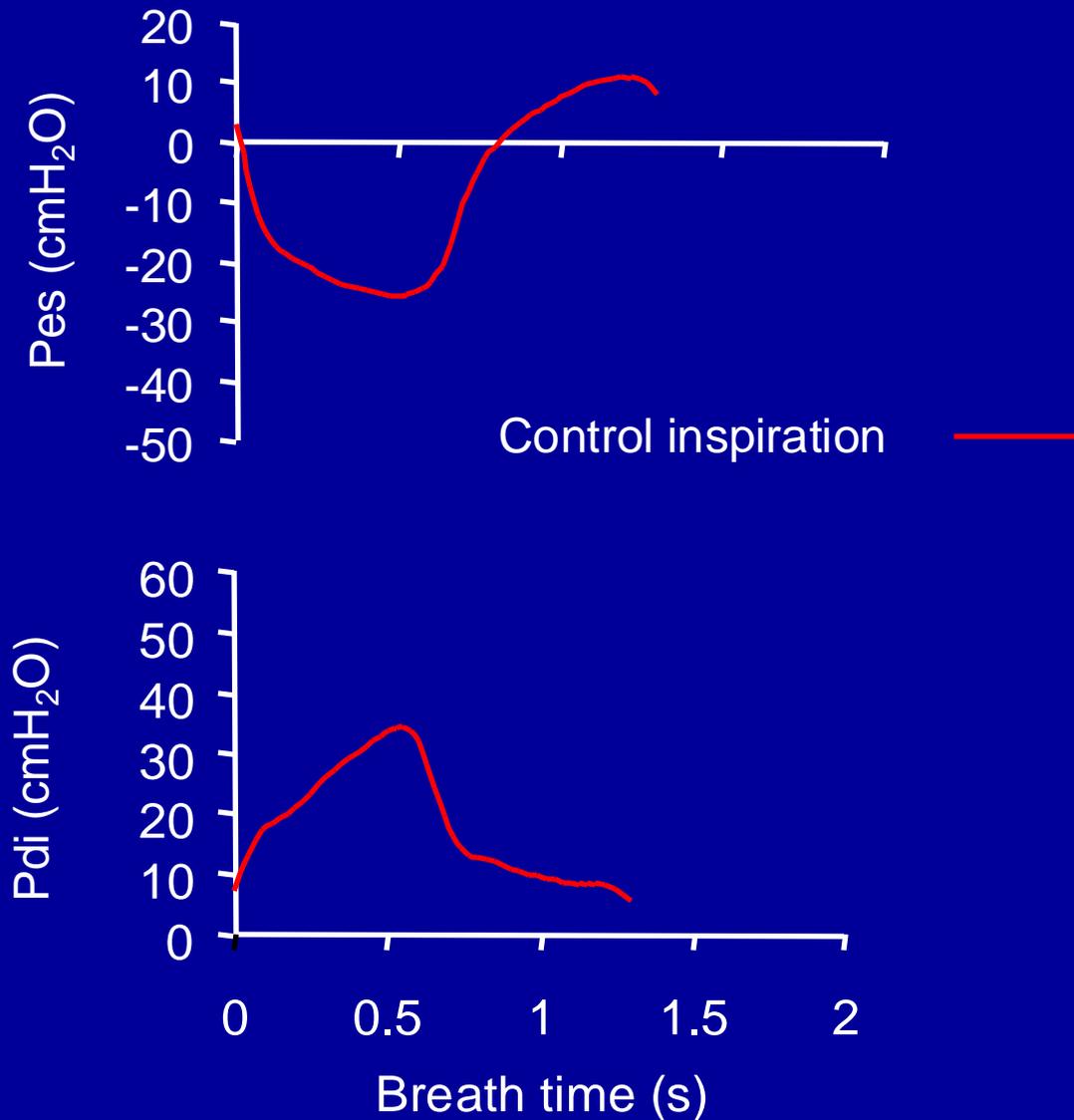


MSNA

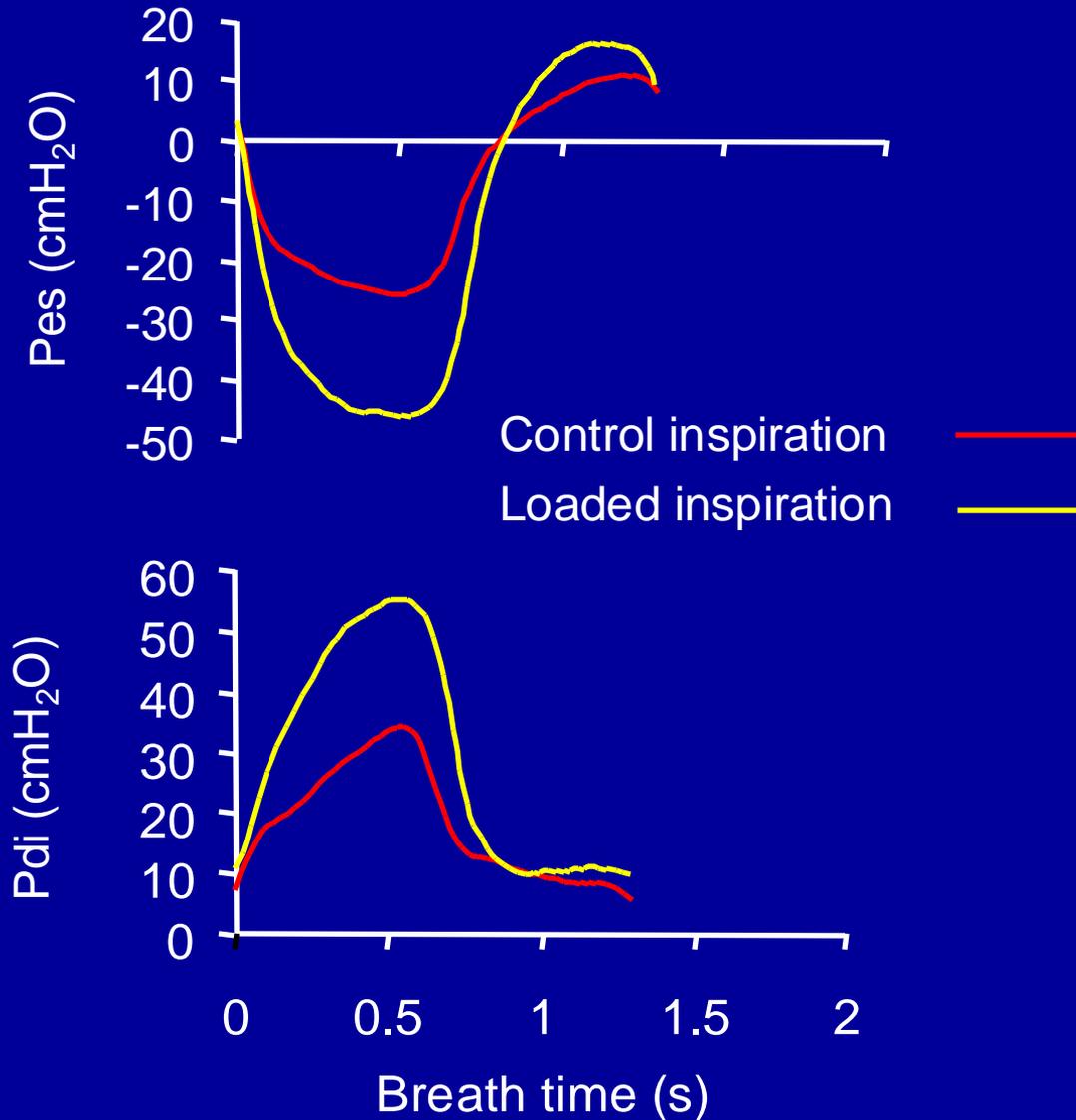


Reflex Effects of \uparrow diaphragm work / fatigue?
(St. Croix 2000)

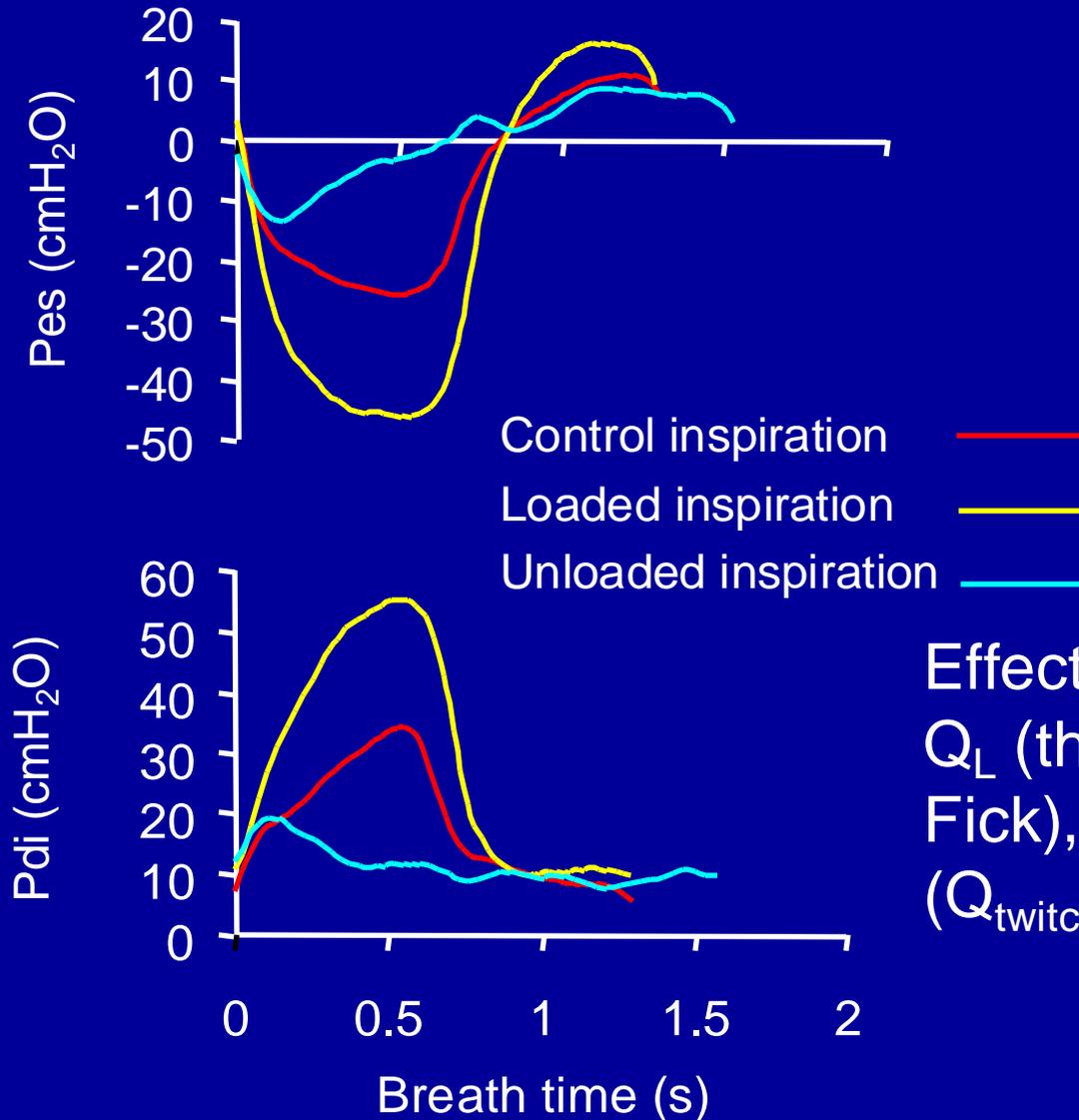
Testing Role of Diaphragm Metaboreflex in Humans Cycle Exercising at High Intensity



↑ WOB (Inspiratory Resistive Load)

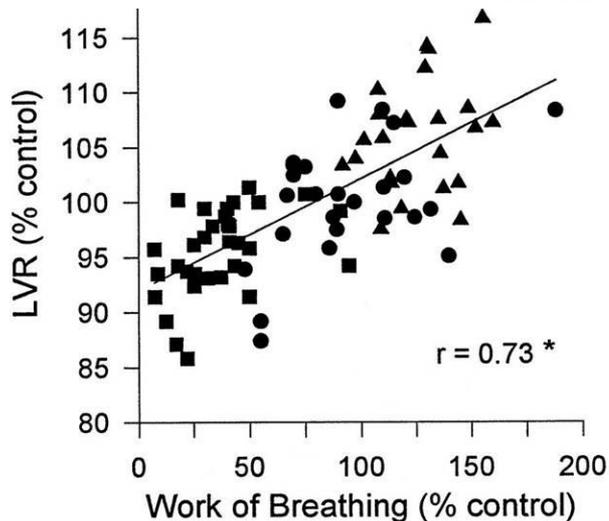
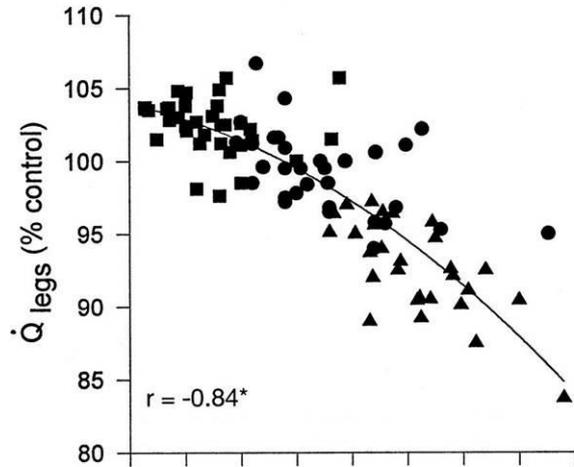


↓ WOB (Mechanical Ventilator)



Effects on: Dia Fatigue (Q_{TW}), Q_L (thermo dilution), CO (direct Fick), Limb muscle fatigue (Q_{twitch}), exercise performance?

↕ Work of Breathing:↕ CV Effects in Hi Intensity Exercise

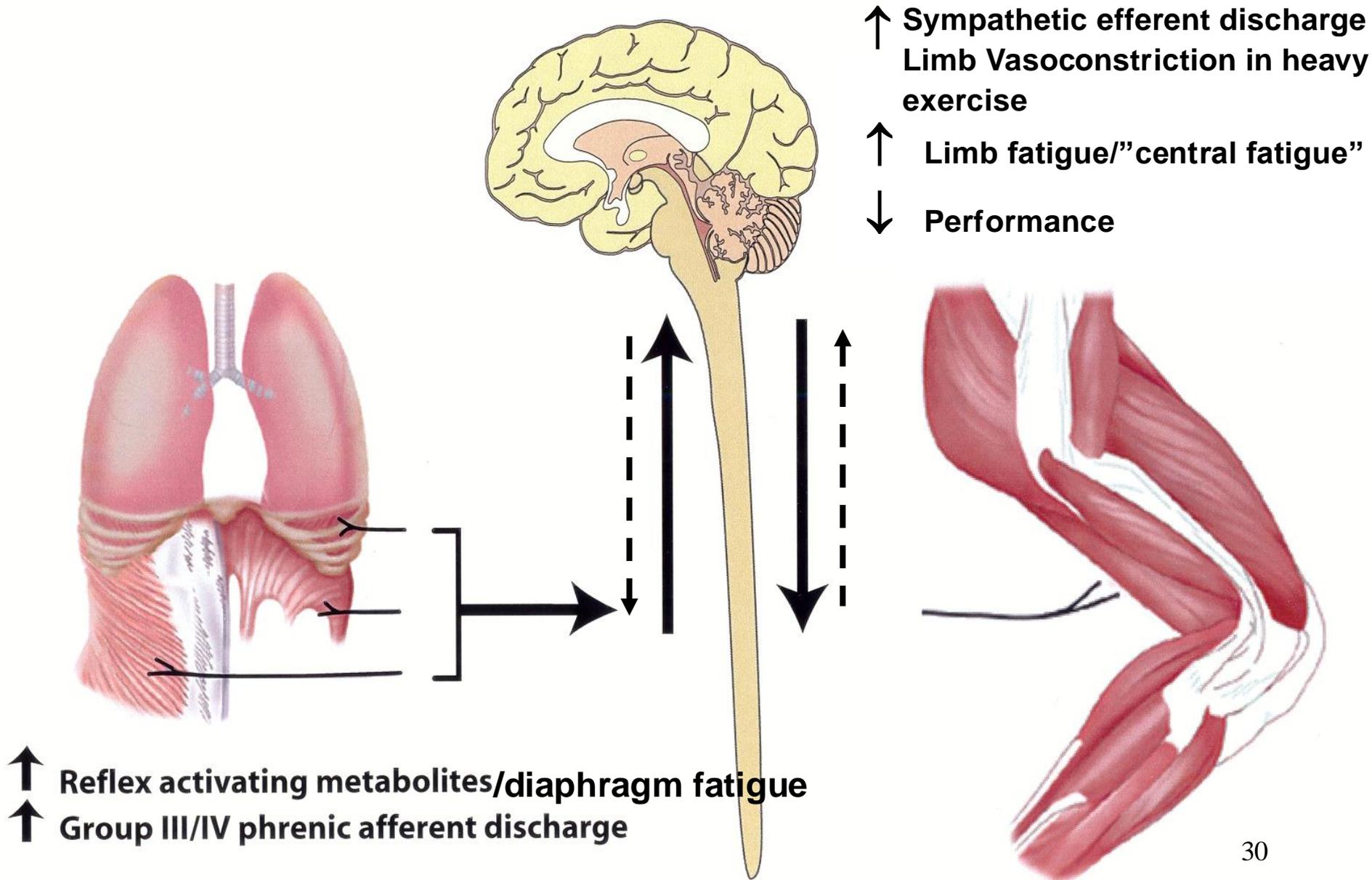


↓ WOB = prevent di fatigue; ↓ MSNA, Limb Vasc. Resist, CO, ↑ Limb Blood Flow, ↓ Limb fatigue/ ↑ exercise performance

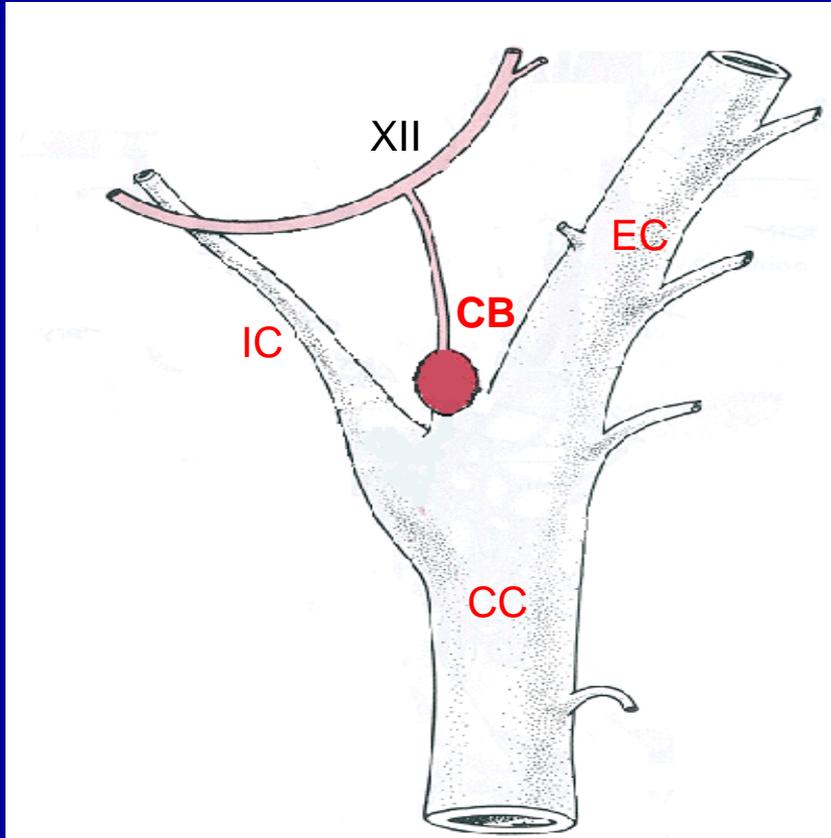
(Reduced sympatholysis in Diaph vs limb vasc ?)

(Harms, St. Croix, Romer, Miller, Sheel, Babcock, Johnson [1994-2002])-2017-Dominelli;2023,Angus

SUMMARY: RESPIRATORY MUSCLE METABOREFLEX



CAROTID CHEMOREFLEX IN EXERCISE

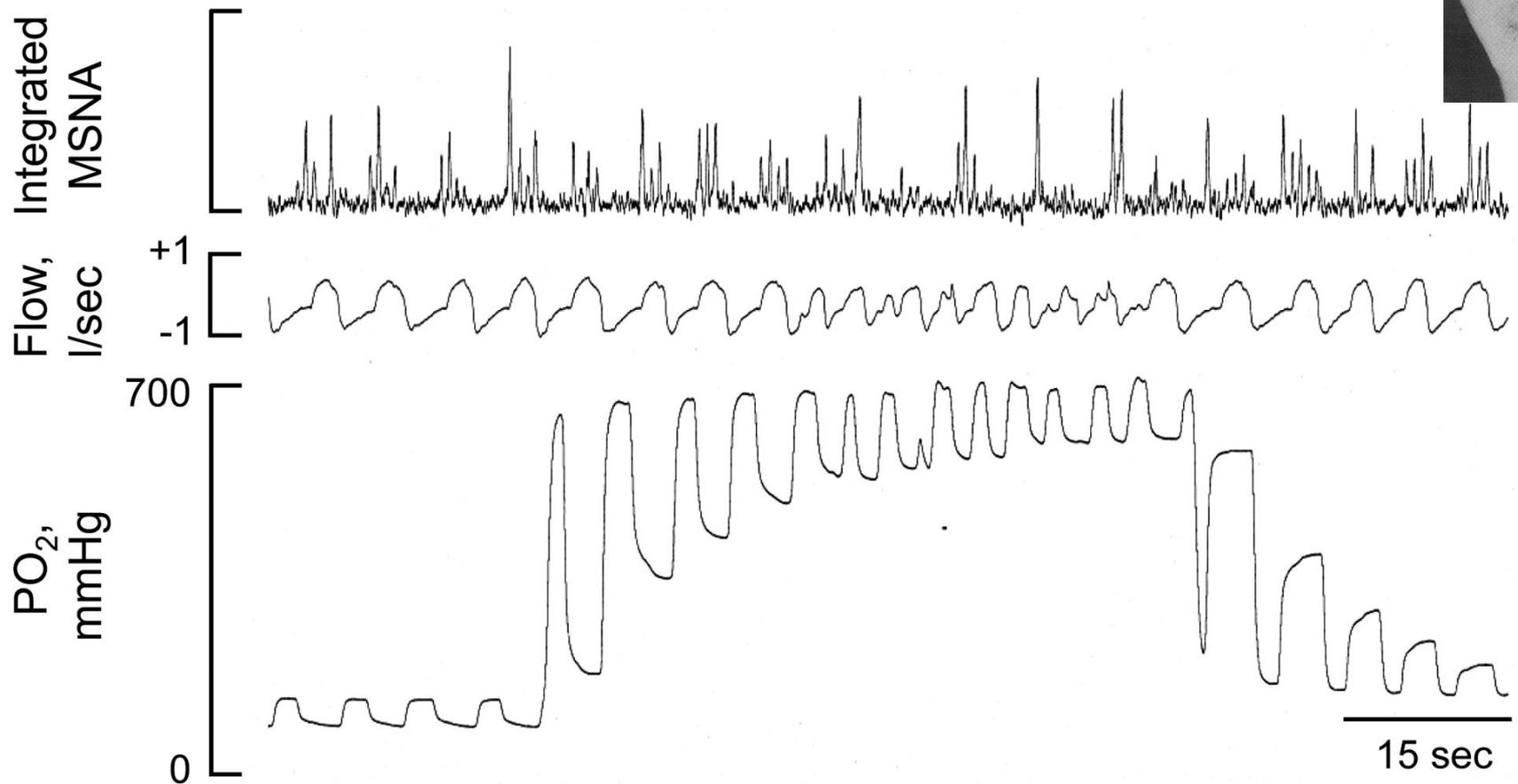


Effects of Car Chemo Tonic Activity

- Effects on VE, SNA, Vasc Conductance
- Canines/Humans
- Plasticity/Pathophysiology

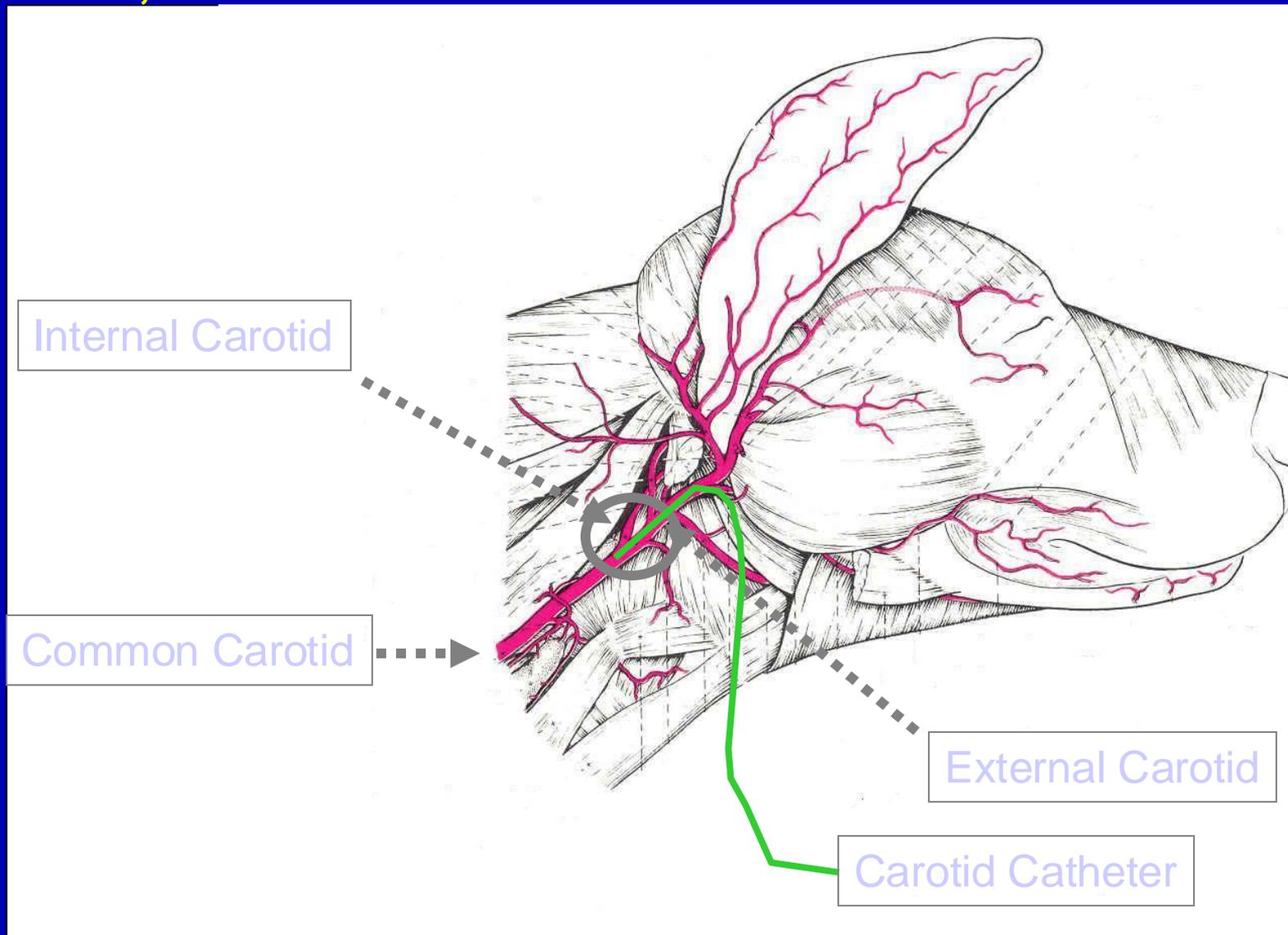
(1996-2017)

Transient Hyperoxia Quantifies Tonic Chemo-receptor Activity Effects on VE,MSNA



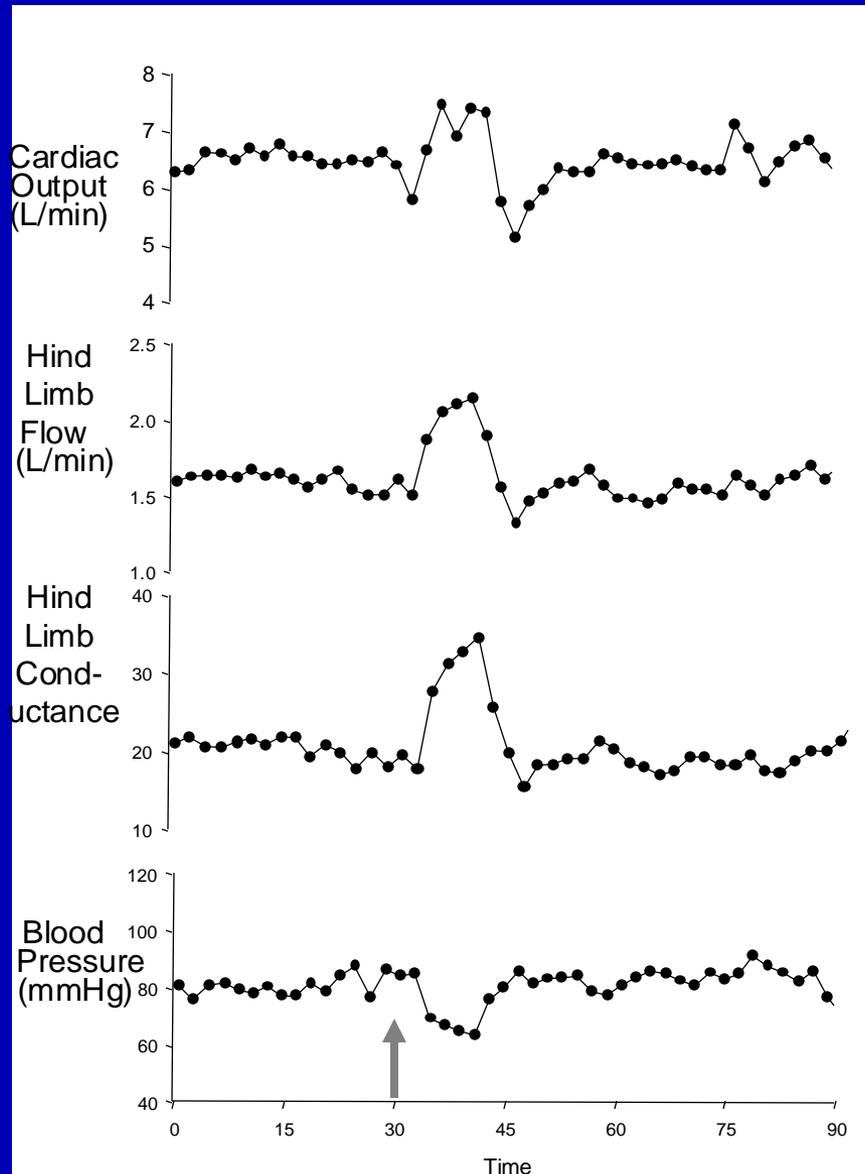
Prasad,2020;
Hypertensive
Pts with OSA)

Transient Inhibition of Carotid Chemos at Rest, Exercise in Health and CHF Canines



Inhibit CB via Local CB dopamine / hyperoxic saline

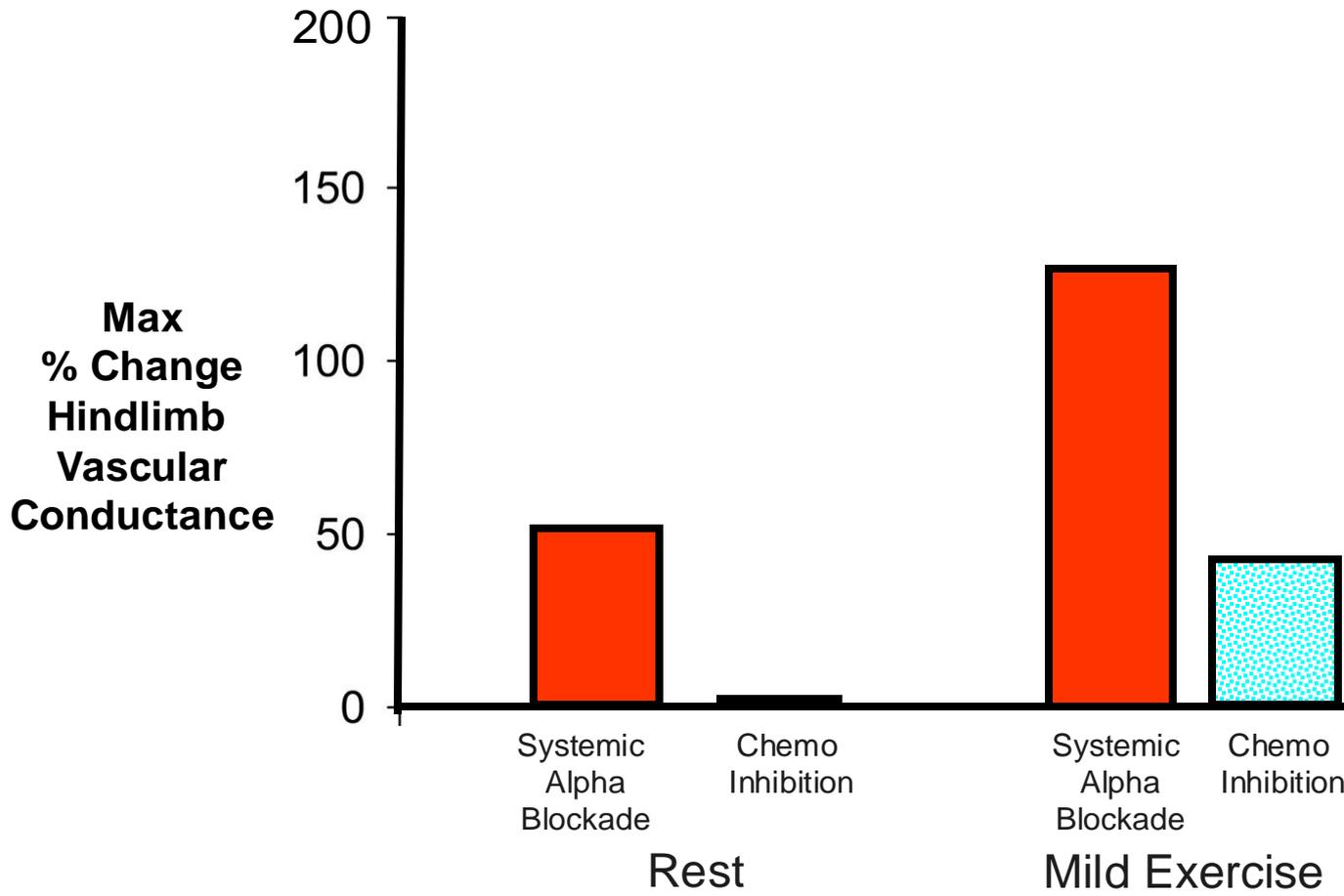
10 $\mu\text{g}/\text{kg}$ Dopamine, 4.0 mph, 10% grade



Vasodilatory effects
of transient DA/
hyperoxia prevented
via adrenergic
blockade, CBX

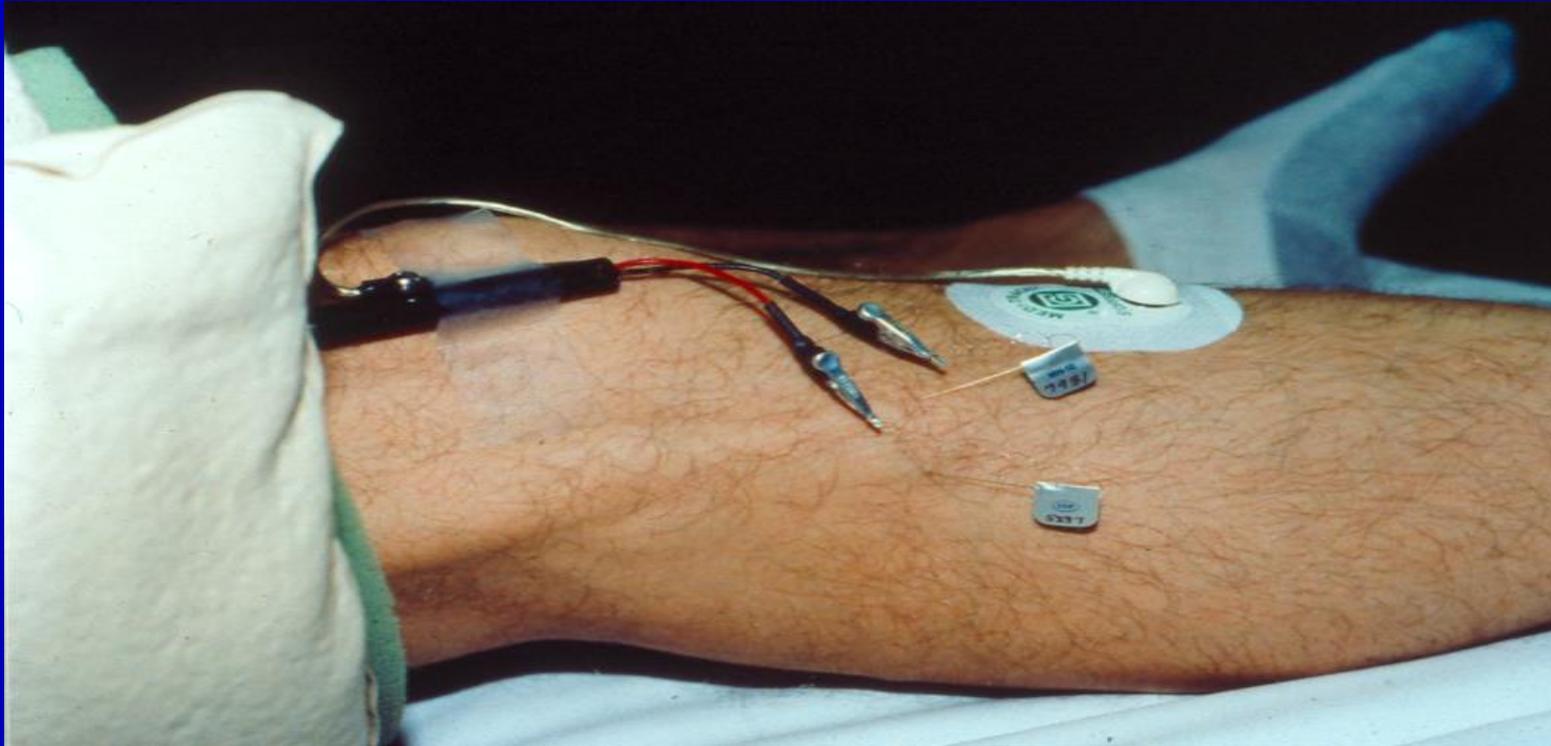
... effects of CB tonic
activity on sympathetic
tone-rest vs exercise?

Sympathetic Tone: Effects of α Blockade vs Chemoreceptor Inhibition: HEALTHY CANINE (EF 55%)



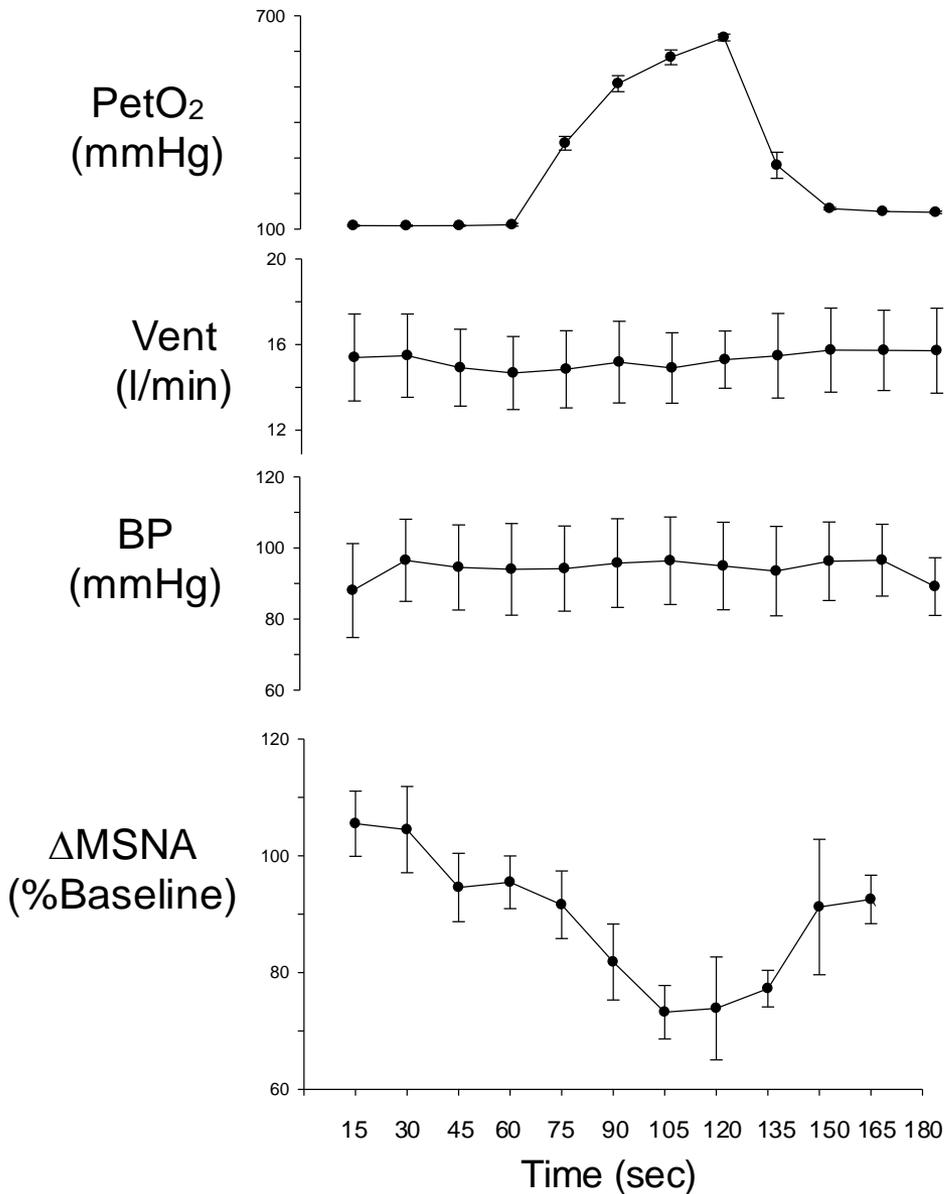
Enhanced CB tonic activity in exercising canine/human

MSNA



Effects of Mild intensity arm exercise + transient hyperoxia in healthy humans (Stickland et al. 2008)

Transient Hyperoxia: Exercise (2008)



Transient hyperoxia, iv dopamine = 30% ↑ limb vasc. conductance, Q_L (Stickland, 2011)

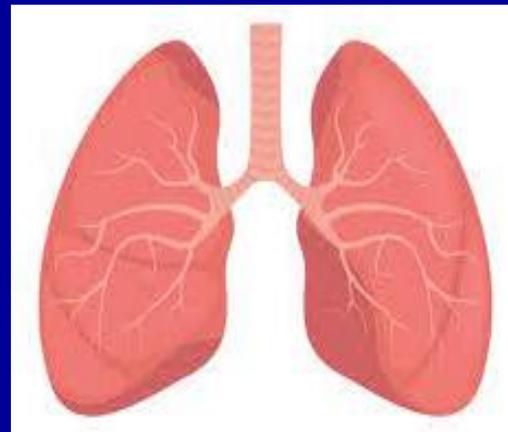
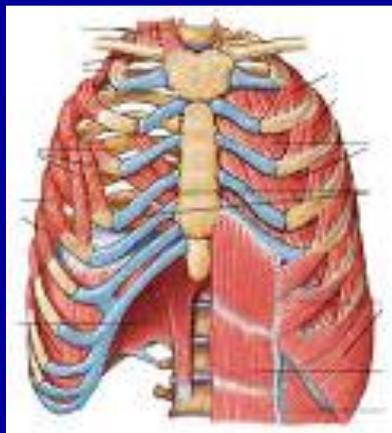
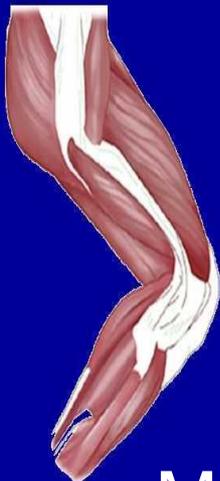
Pathophysiology: Excessive Car Chemoreceptor Activity/Tonicity in CHF/Hypertension /COPD

- Human CHF = ↑ car chemo tonic activity, MSNA, sleep disordered breathing, exercise tachypnea
- Dog and rabbit models of CHF via 6 wks of cardiac pacing = ↑ carotid sinus nerve activity, ↑ renal SNA, limb vasc resistance, MAP
- ↓ carotid blood flow/shear stress ↑ chemoreceptor activity
- “Treat” high car chemo tonic activity in hypertension/CHF??

SUMMARY- Obligatory Neural Feedback Mechanisms in Exercise

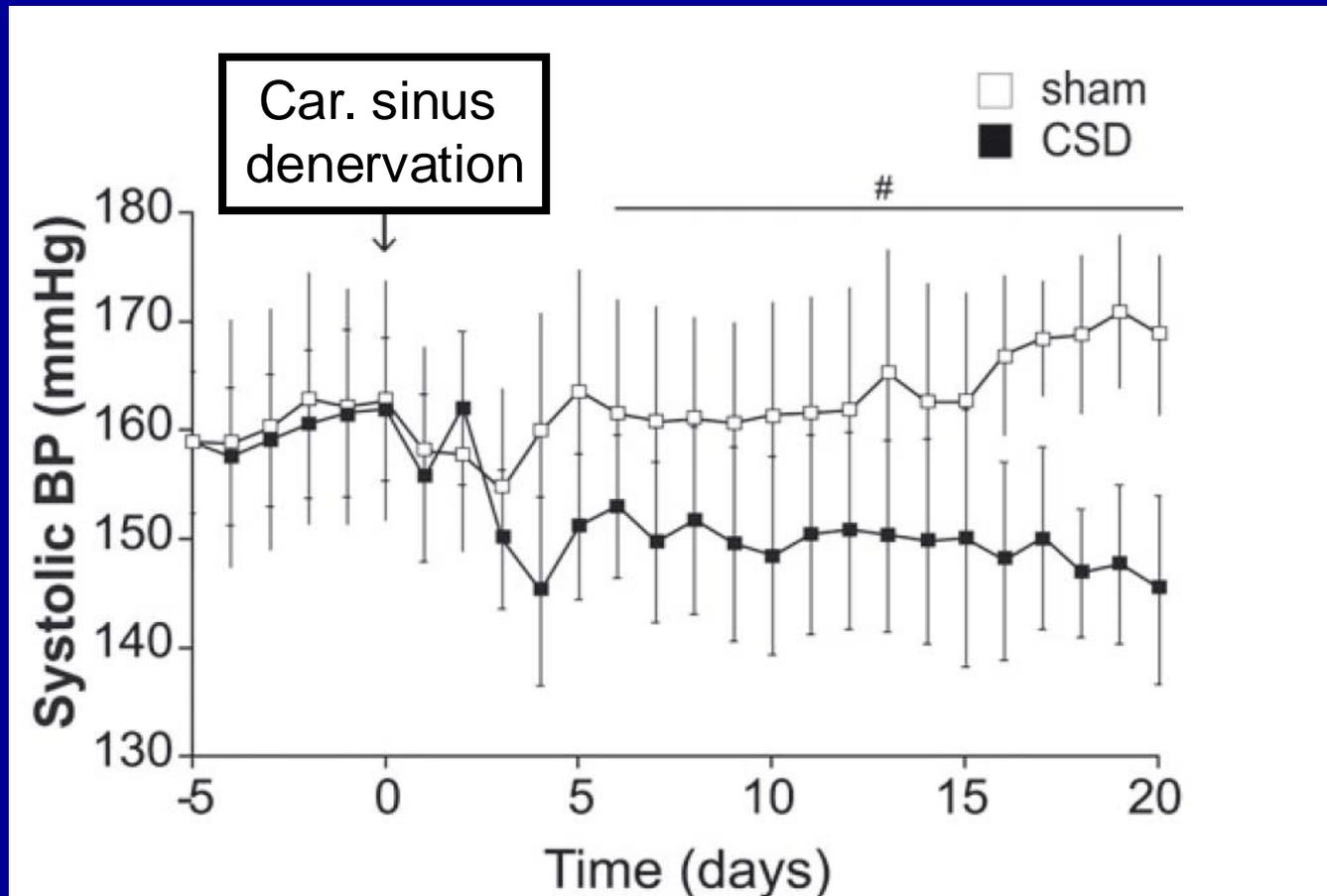
Physiology: O₂ / Acid –base homeostasis, work of breathing, MSNA /blood flow distribution, central locomotor output/fatigue/exercise performance.

Patho-Physiology: -Excessive muscle afferent/carotid chemoreceptor sensitivities in CHF, Hypertension, COPD, OSA.



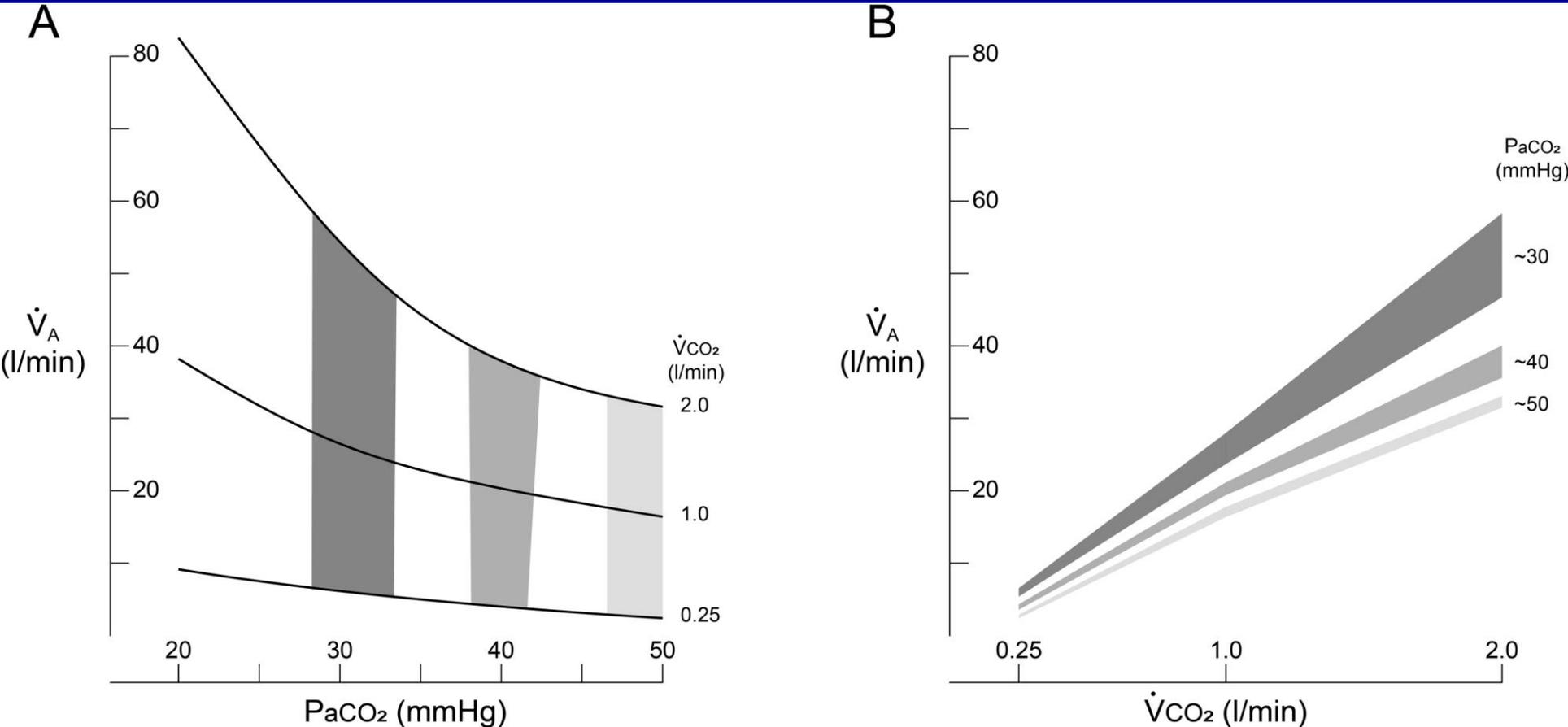
Many Unknowns remain!!

Hypertension is significantly dependent on the carotid body input in the spontaneously hypertensive rat.
(Abdala et al., 2012)



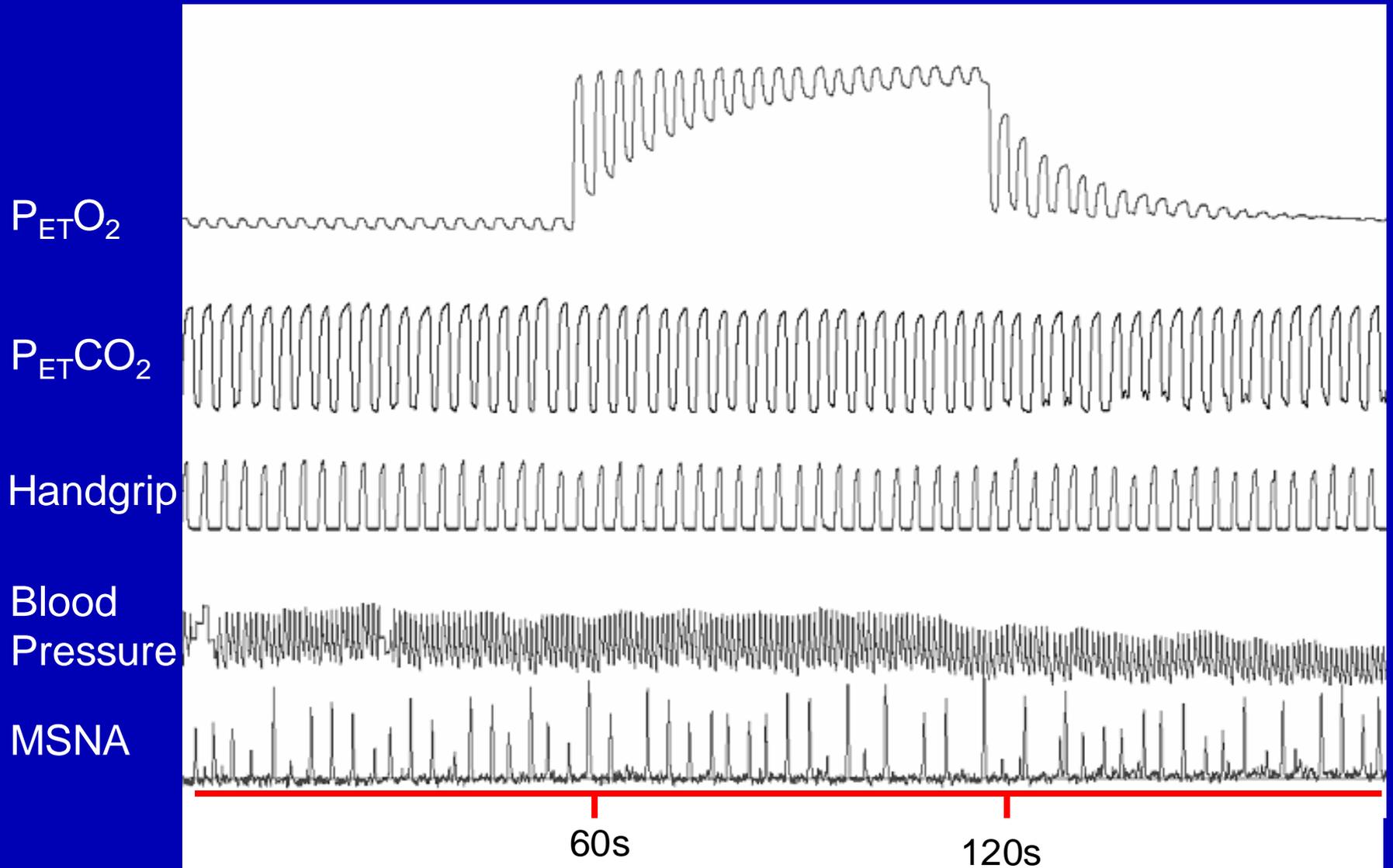
...role for (selective) CBX in drug resistant hypertension??

Isocapnic Exercise Hyperpnea Adjusted to Change in Resting Setpoint ($\text{PaCO}_2 \sim \dot{V}\text{CO}_2/\dot{V}_A * K$)

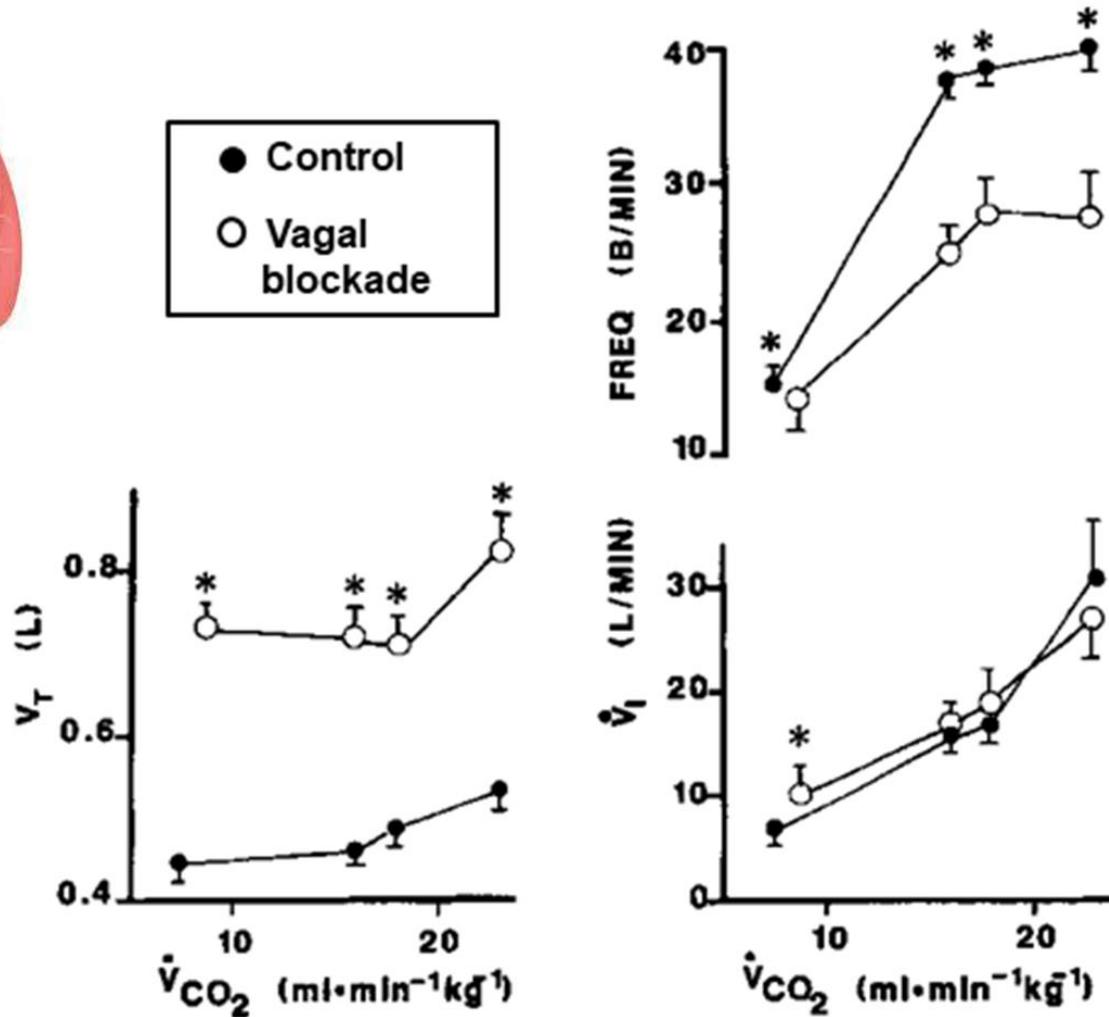
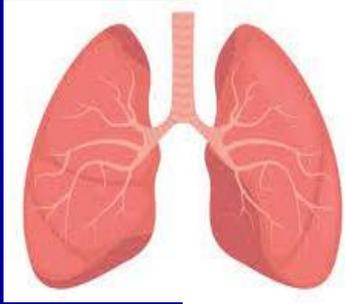


How does controller adjust $\dot{V}_A:\dot{V}\text{CO}_2$ response to changing resting setpoint/plant gain?

Rhythmic Handgrip Exercise + Transient Hyperoxia ($F_{I}O_2 \sim 1.0$)

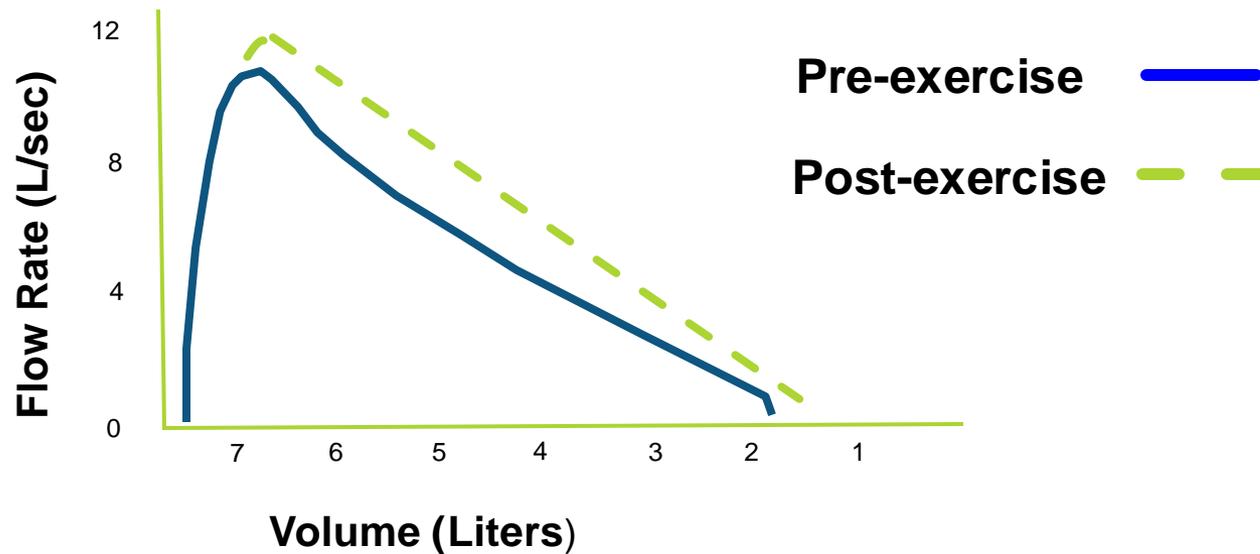


Lung Stretch Receptor Feedback Affects on Breathing Pattern/



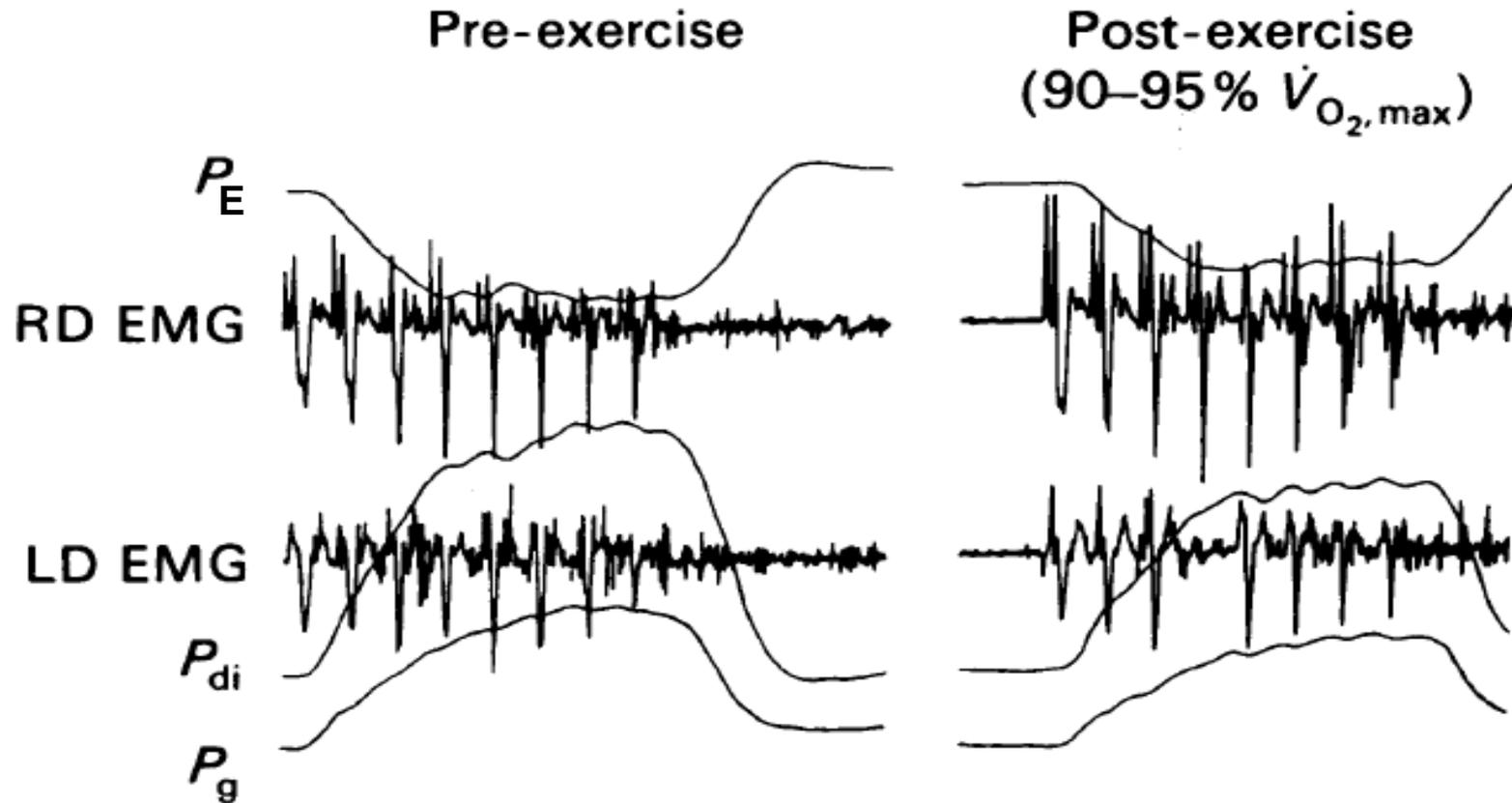
Ainsworth, 1992; Winning, 1985; Scirba, 1988

EXERCISE-INDUCED BRONCHODILATION



...occurs via withdrawal of cholinergic tone to airway smooth muscle by locomotor muscle afferent feedback (Kaufman, 1982-'88-anesthetized canines). Exercising humans??

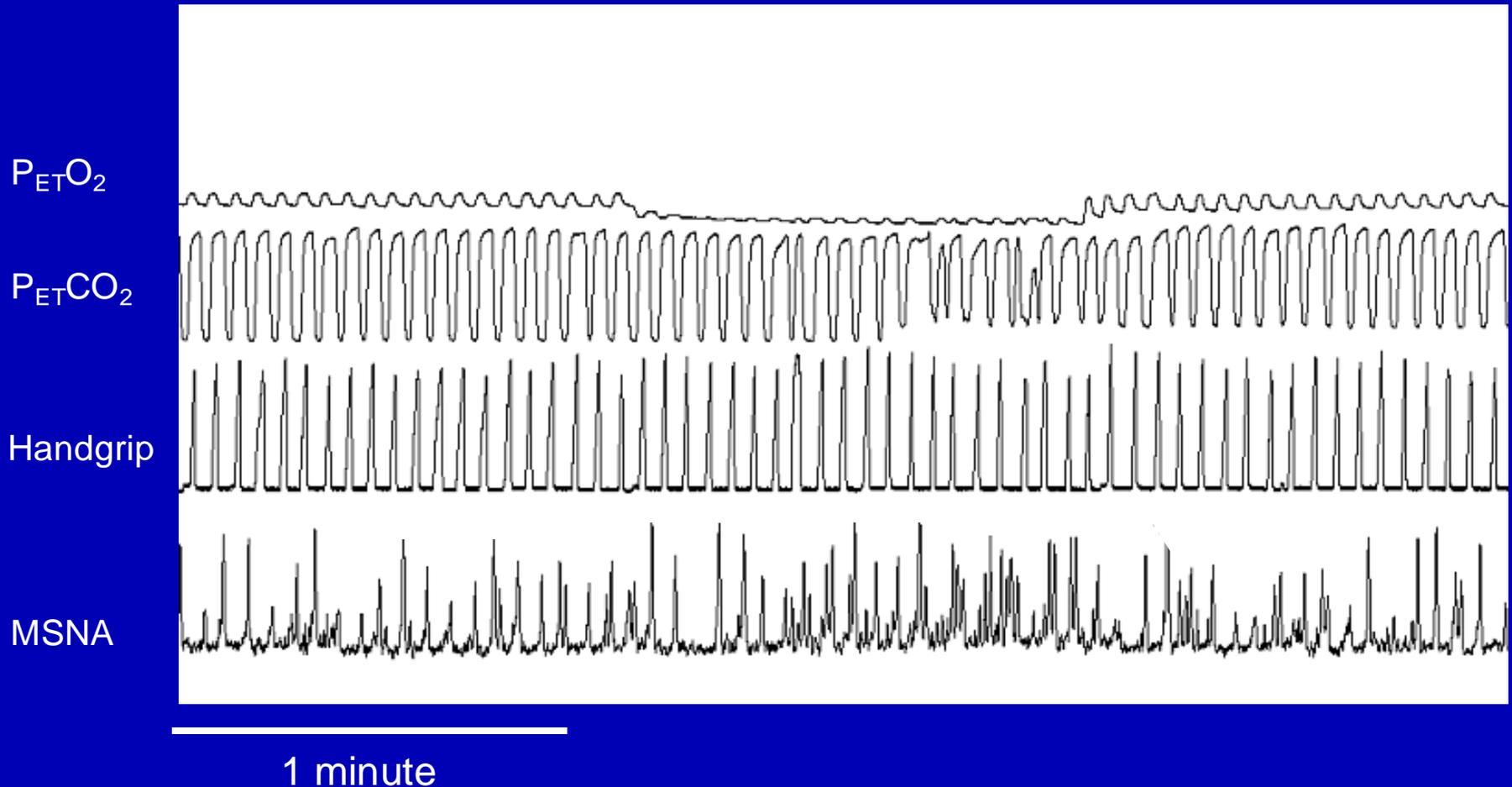
Underbuilt Diaphragm: Long-lasting Fatigue following High Intensity Endurance Exercise (supramaximal phrenic nerve stim, 1-20 Hz)



Cardiovascular consequences of diaphragm metabolite accumulation/ fatigue?

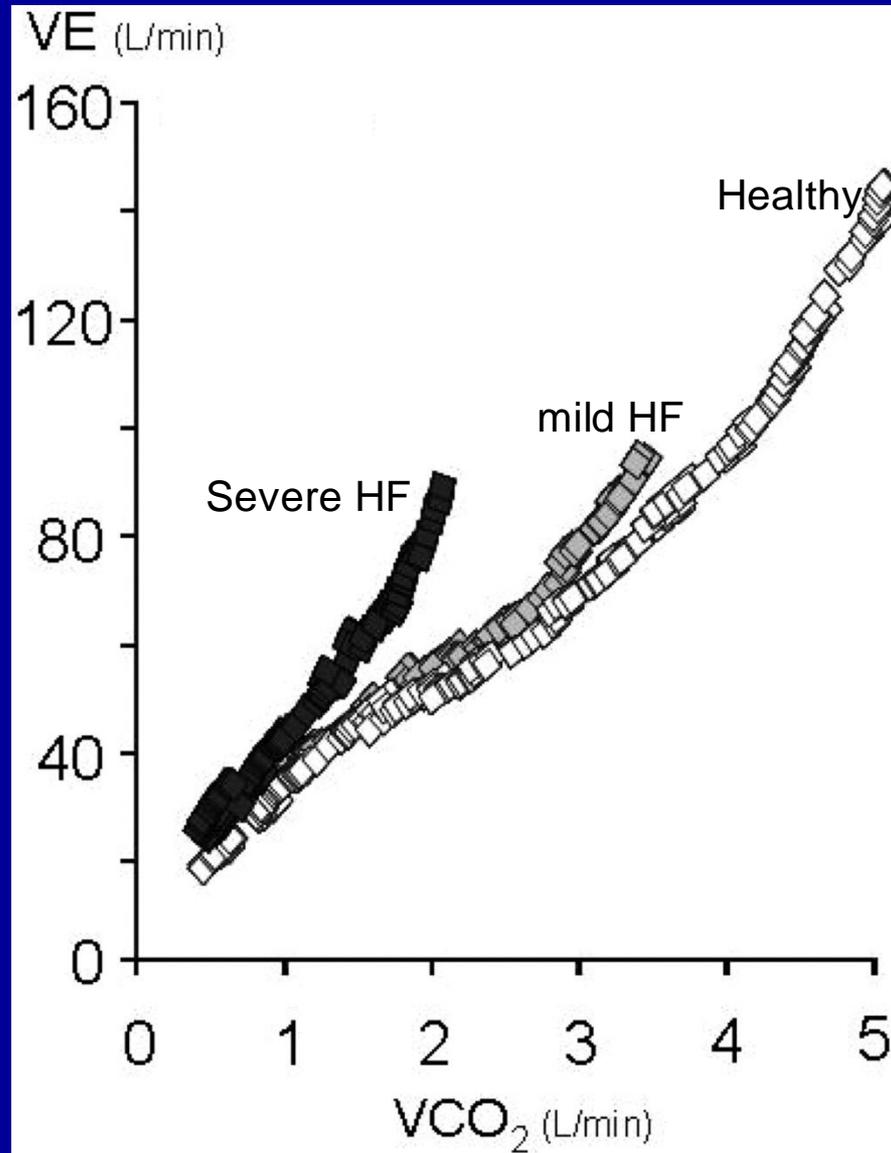
Rhythmic Handgrip Exercise + Transient Hypoxia ($F_{I}O_2 \sim 1.0$)

(Stickland et al., 2008)



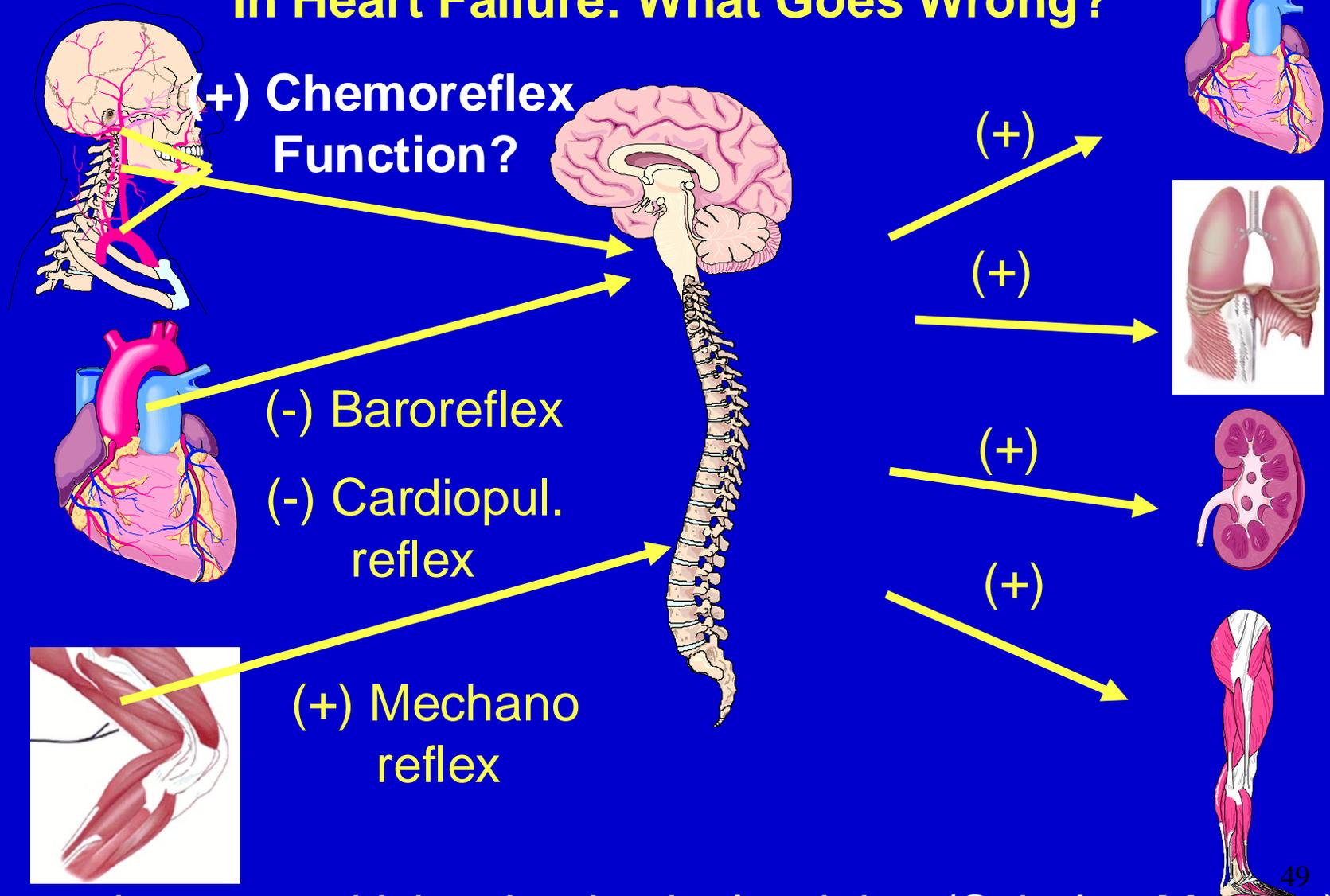
MSNA latency to $\downarrow P_{AO_2} \sim 15 - 20$ sec.

Exercise Hyperventilation in Human CHF



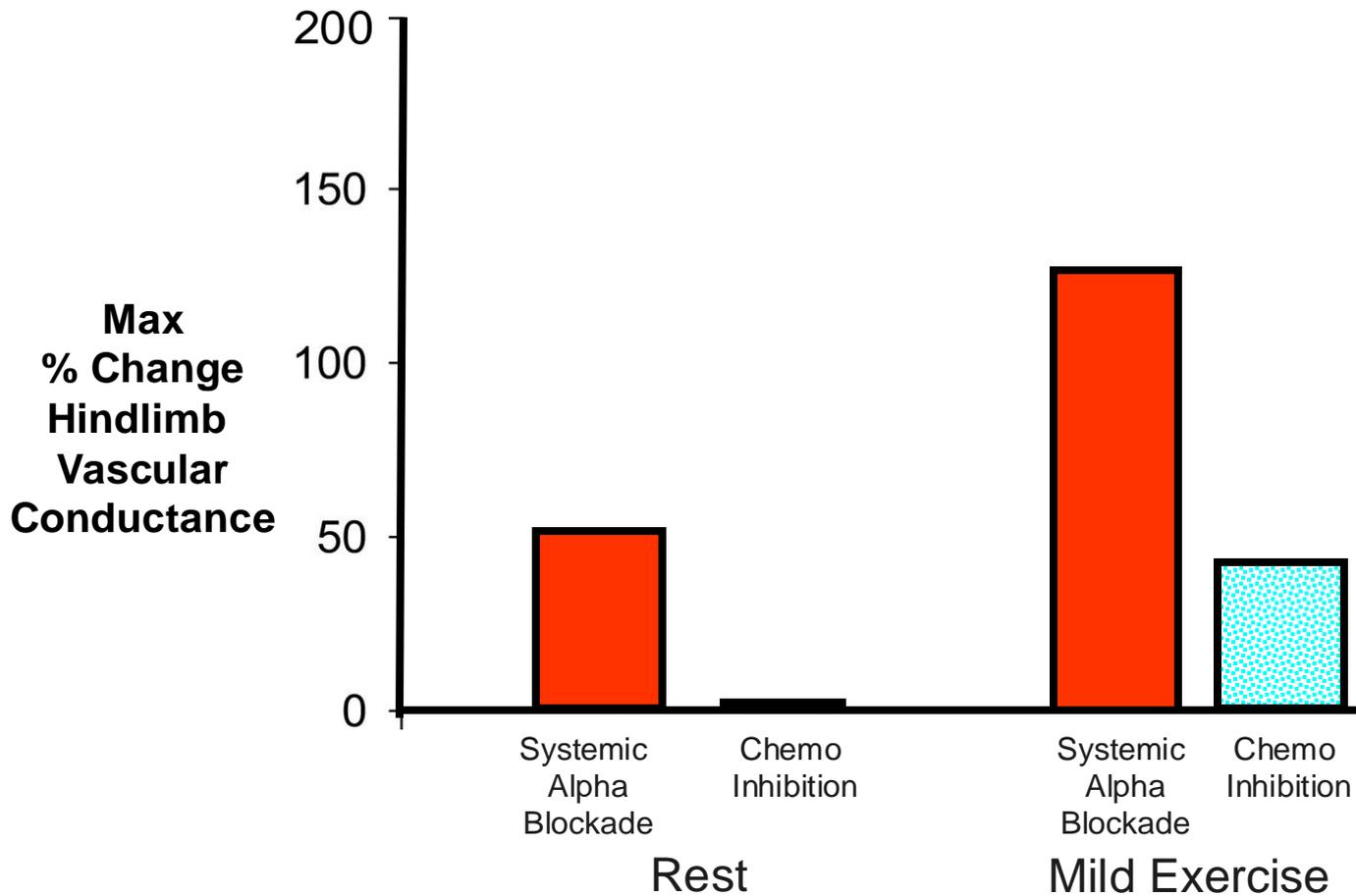
- ↑ Sensitivity of muscle afferents, carotid chemos
- ↑ Pul. cap. pressures
- ↑ V_d/V_t
- Inhibitory effects of hyperoxia/muscle afferent blockade (Olson 2013)

Feedback Control Of “Excessive” Sympathetic Outflow and Hyperventilation In Heart Failure: What Goes Wrong?



...↓ chemosensitivity via physical training (Schultz, Marcus)

SYMPATHETIC TONE: Effects of α Blockade / Chemoreceptor Inhibition: HEALTHY CANINE (EF 55%)



(Stickland 2008)

Inhibiting Carotid Chemoreceptor Tonic Activity During (Normoxic) Exercise in Healthy Humans



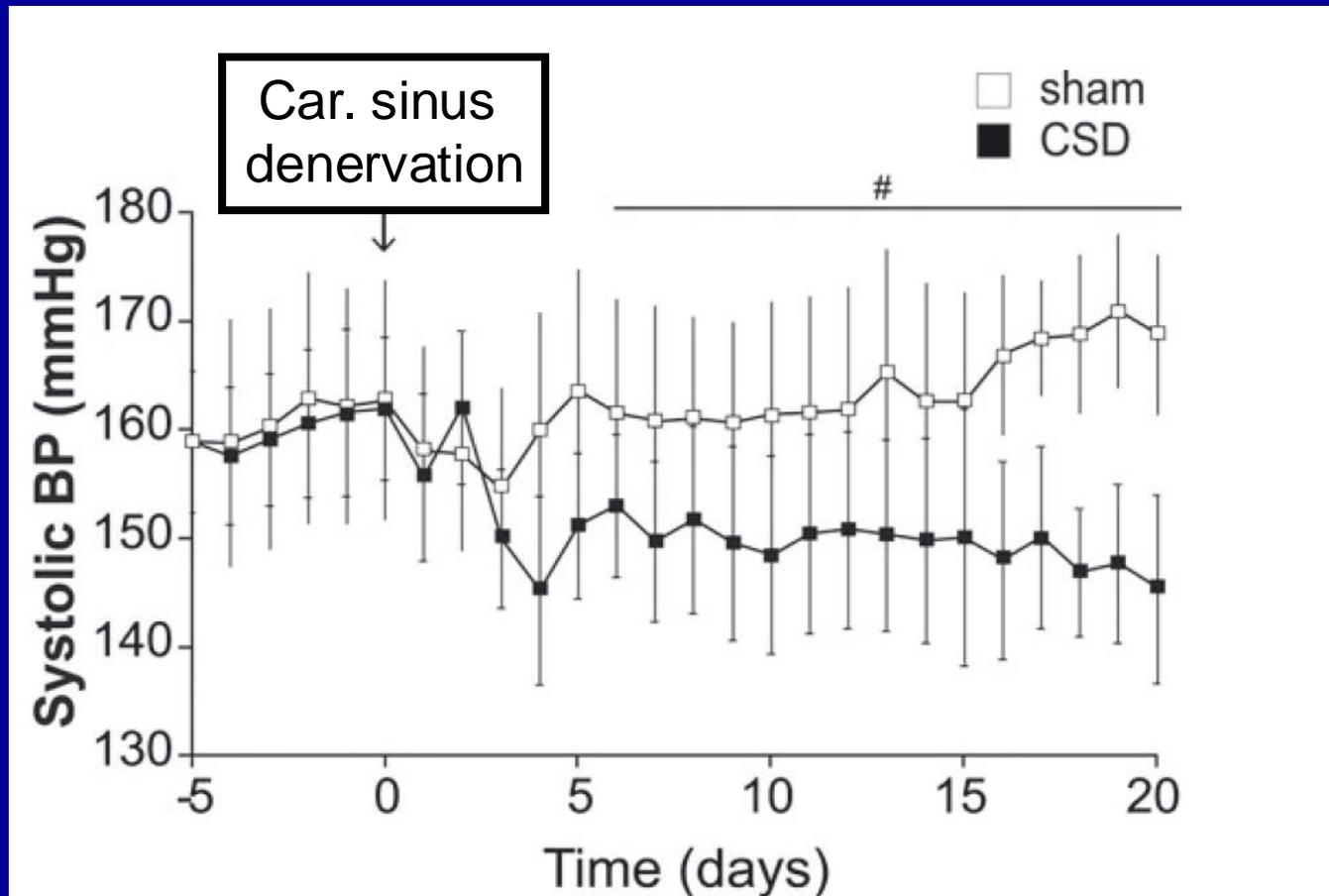
- ↓ VE, MSNA, MAP
- ↑ Limb vascular conductance, blood flow
- Hyperadditive interactive effects of Carotid chemoreflex + muscle afferent input on SNA mediated vasoconstriction /VE

(Stickland, Morgan, Wan, Amann)

Systemic Hypertension and Carotid Chemoreceptors

- Chemoreceptor glomus cell proliferation
- Imbalance of CB HIF iso-forms, neuromodulators
- ↑ Ang II receptors in chemos
- Bilateral CBX in hypertensive humans = ↓ MAP

Hypertension is significantly dependent on the carotid body input in the spontaneously hypertensive rat.
(Abdala et al., 2012)

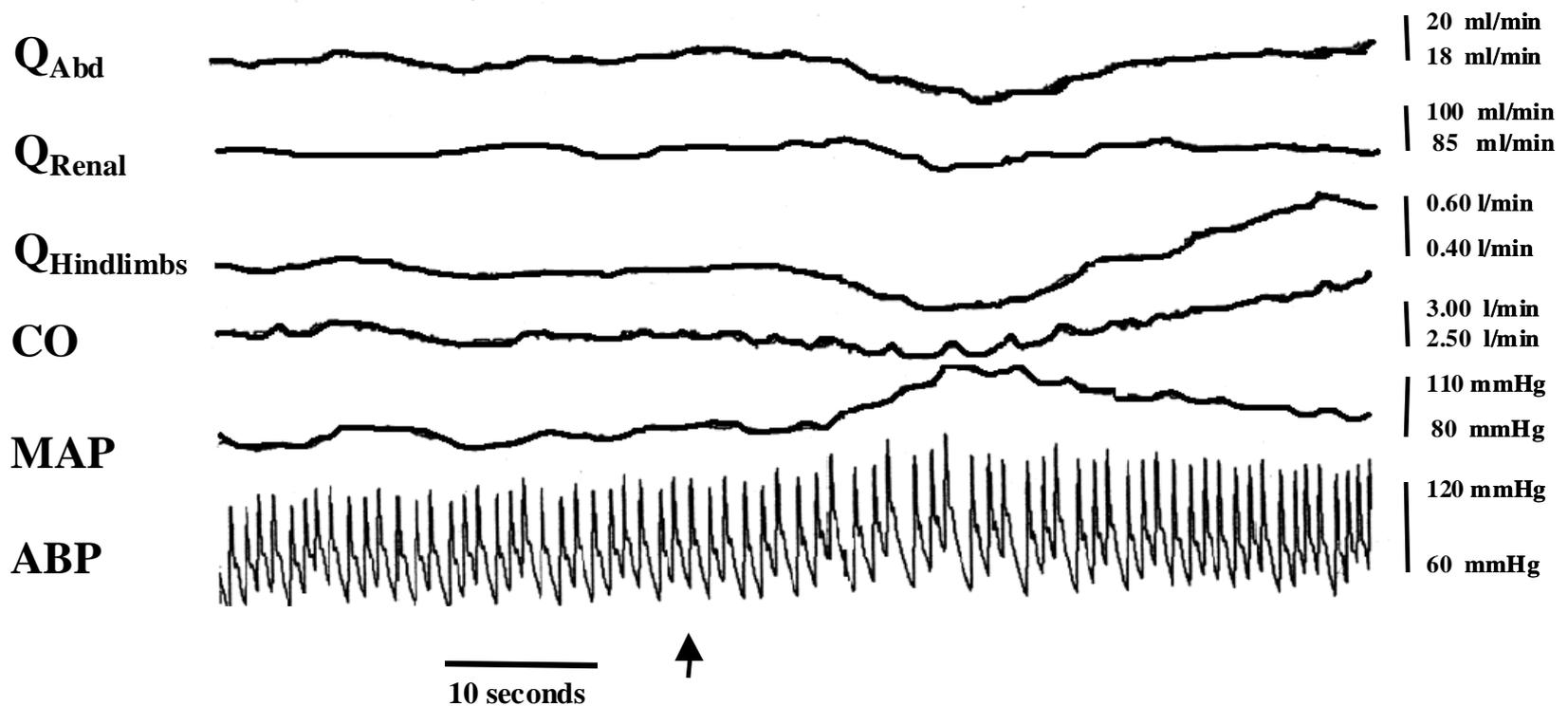


...role for (selective) CBX in drug resistant hypertension??

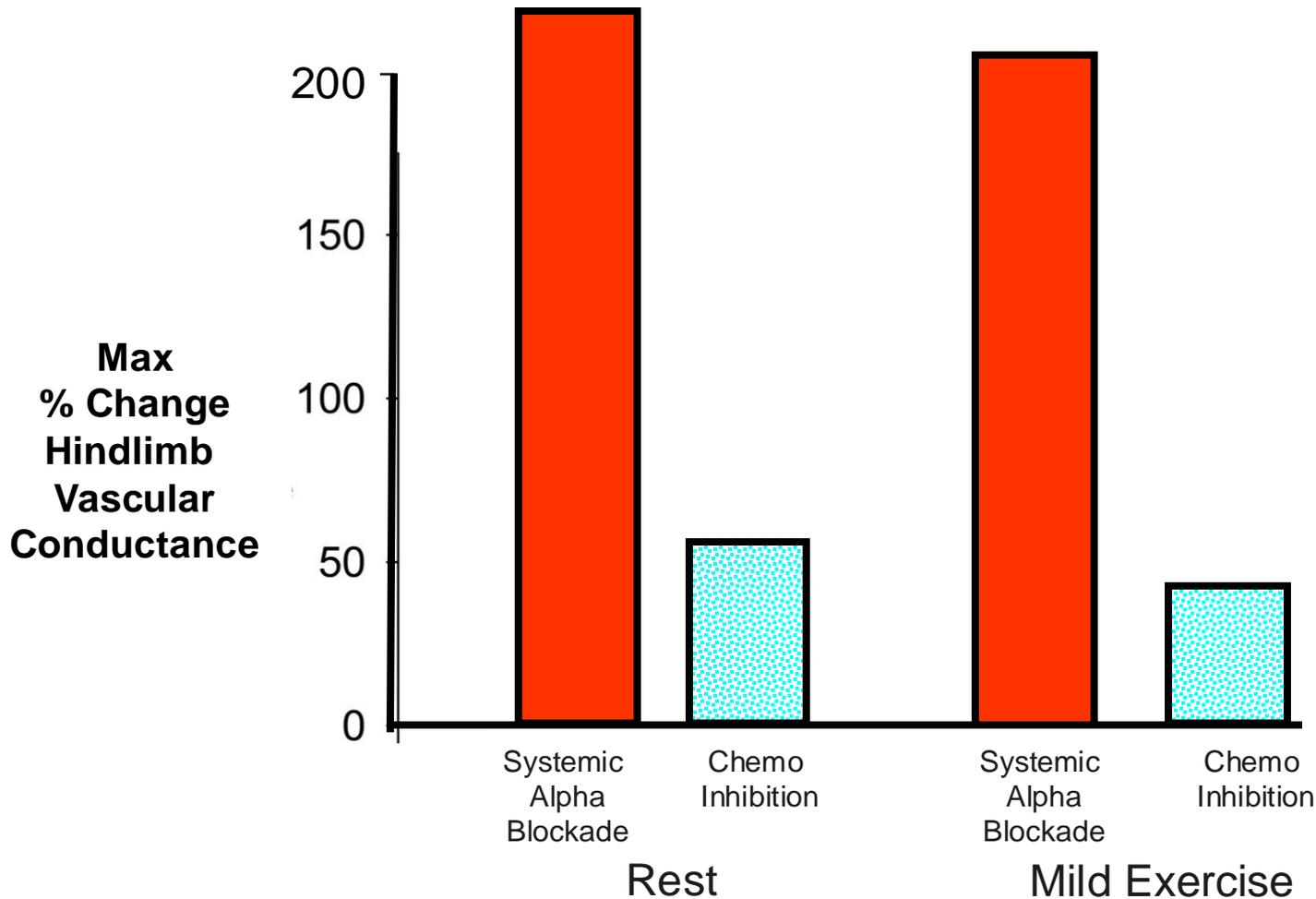
Summary: Critical Roles for Carotid Chemoreceptor in Health and Disease

- Multiple stimuli - CV / resp. / metabolic effects
- Extended chemoreceptor pathway / peripheral chemoreceptor hyperadditive effects on central CO₂ responses
- Chemoreceptor contributions in health to eupnea, sympathetic control of vascular resistance
- Adaptive / Maladaptive chemoreceptor sensitization in hypoxic acclimatization
- Role in sleep apnea pathogenesis / treatment
- Role of chemo / muscle afferents in CHF, hypertension

Phrenic Artery Lactic Acid Bolus: Resting Dog



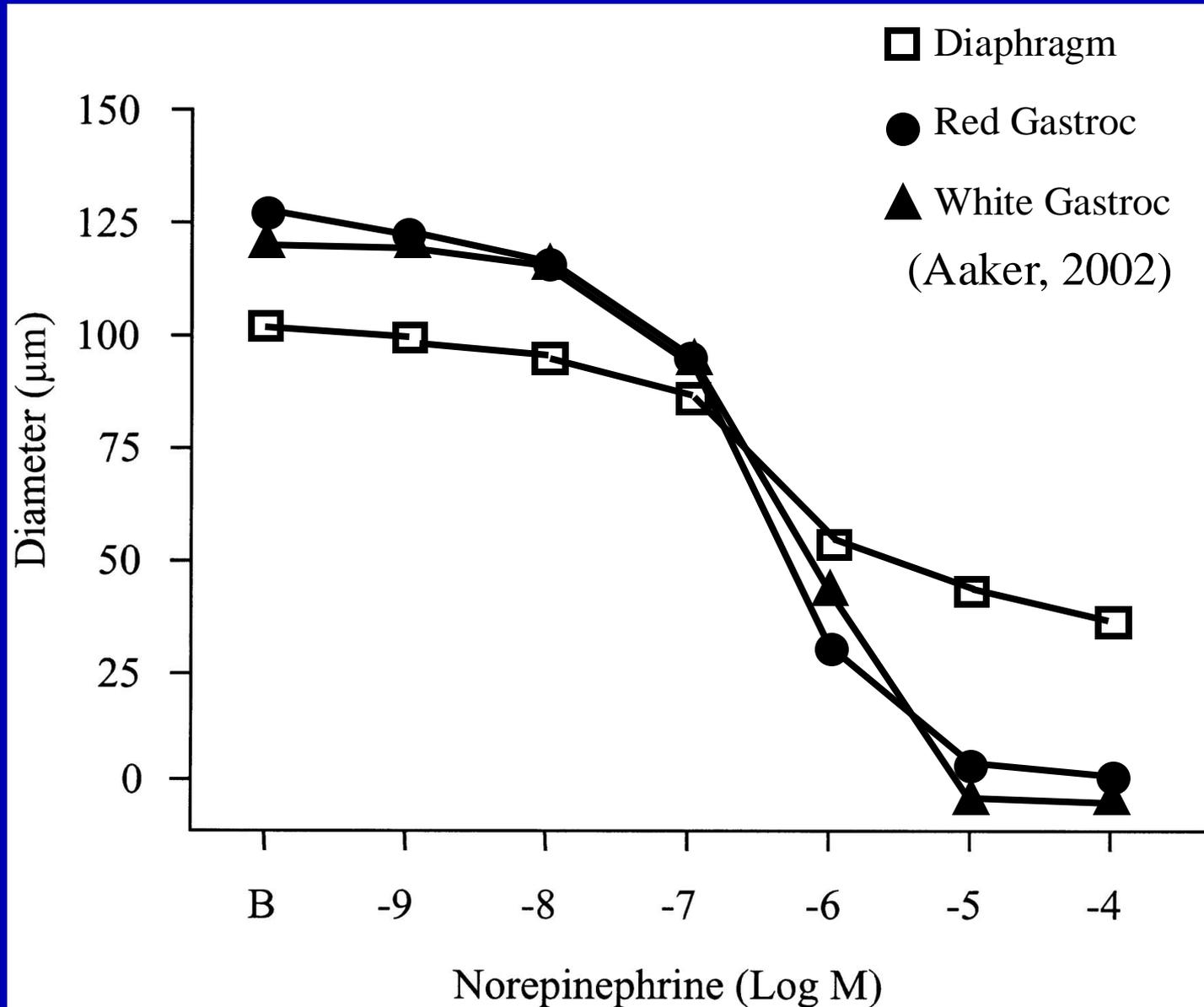
SYMPATHETIC TONE: Effects of α Blockade vs Chemoreceptor Inhibition: CHF CANINE (EF 18%, \uparrow Hypoxic Vent. Response)

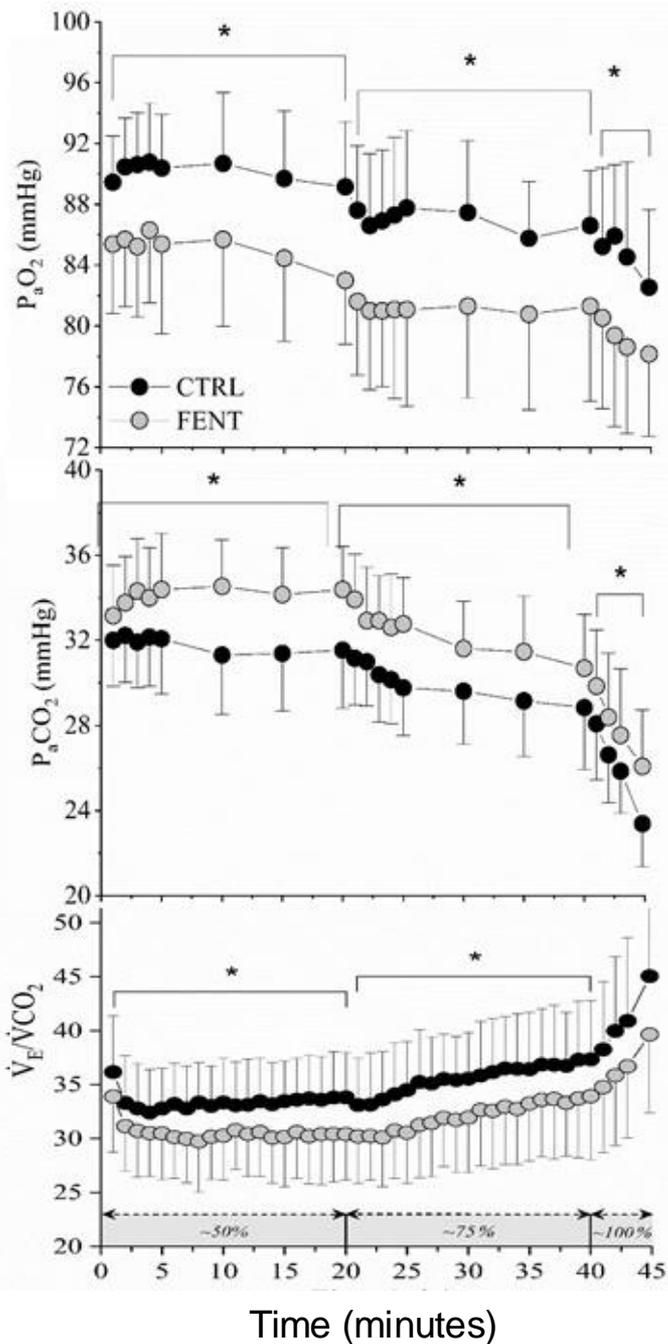


...also in human CHF/hypertensive patients

(Stickland 2015; Sayegh 2024)

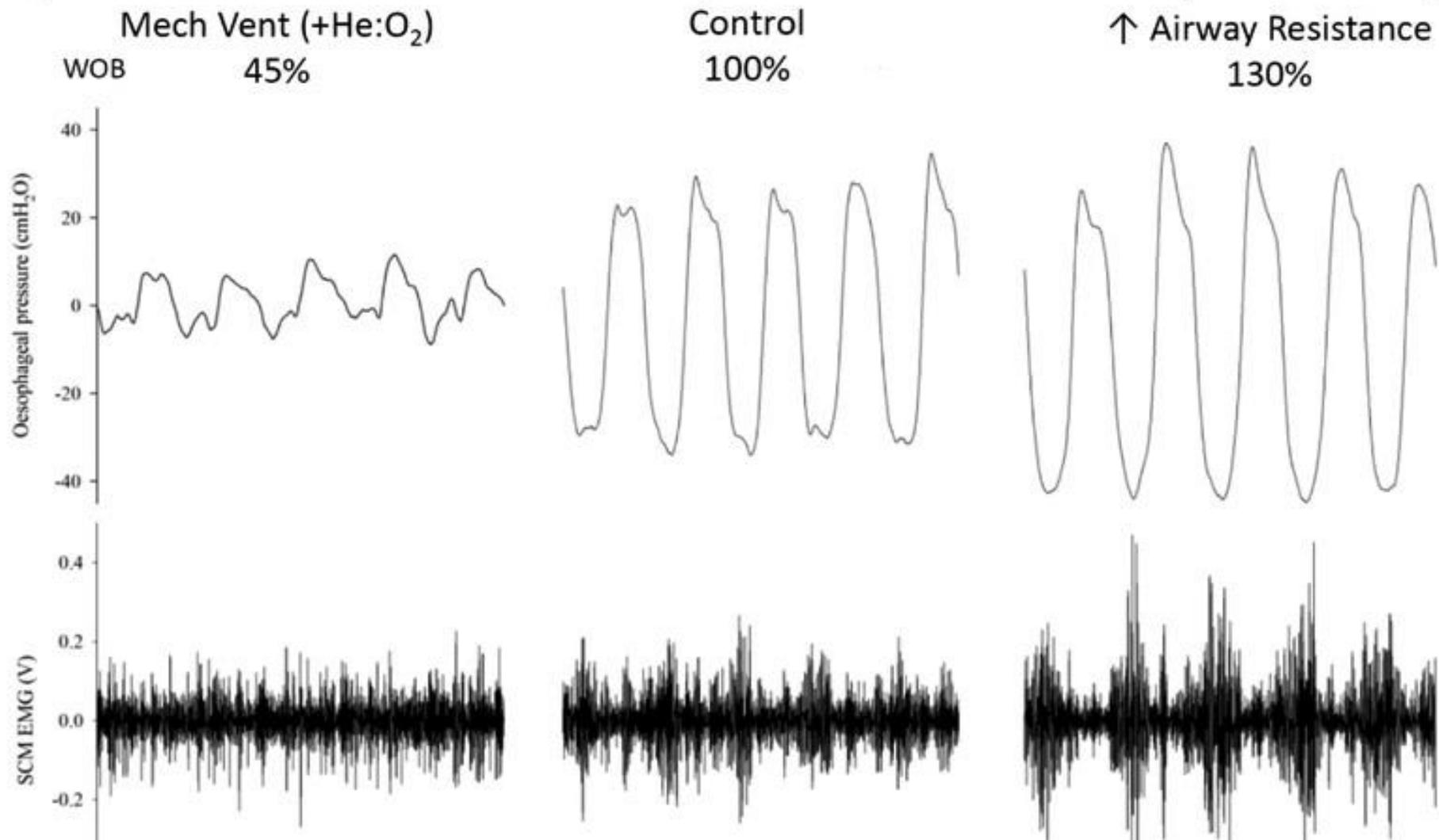
In Vitro Vascular Responsiveness





Muscle Afferent Effects on V_E , Gas Exchange in Prolonged Exercise (Iannetta, Amman, et al, 2024)

↕ WORK OF BREATHING EFFECTS ON RESP / LIMB MUSCLE BLOOD FLOW (304W, 95% VO_{2max})



Blood flow (% control)

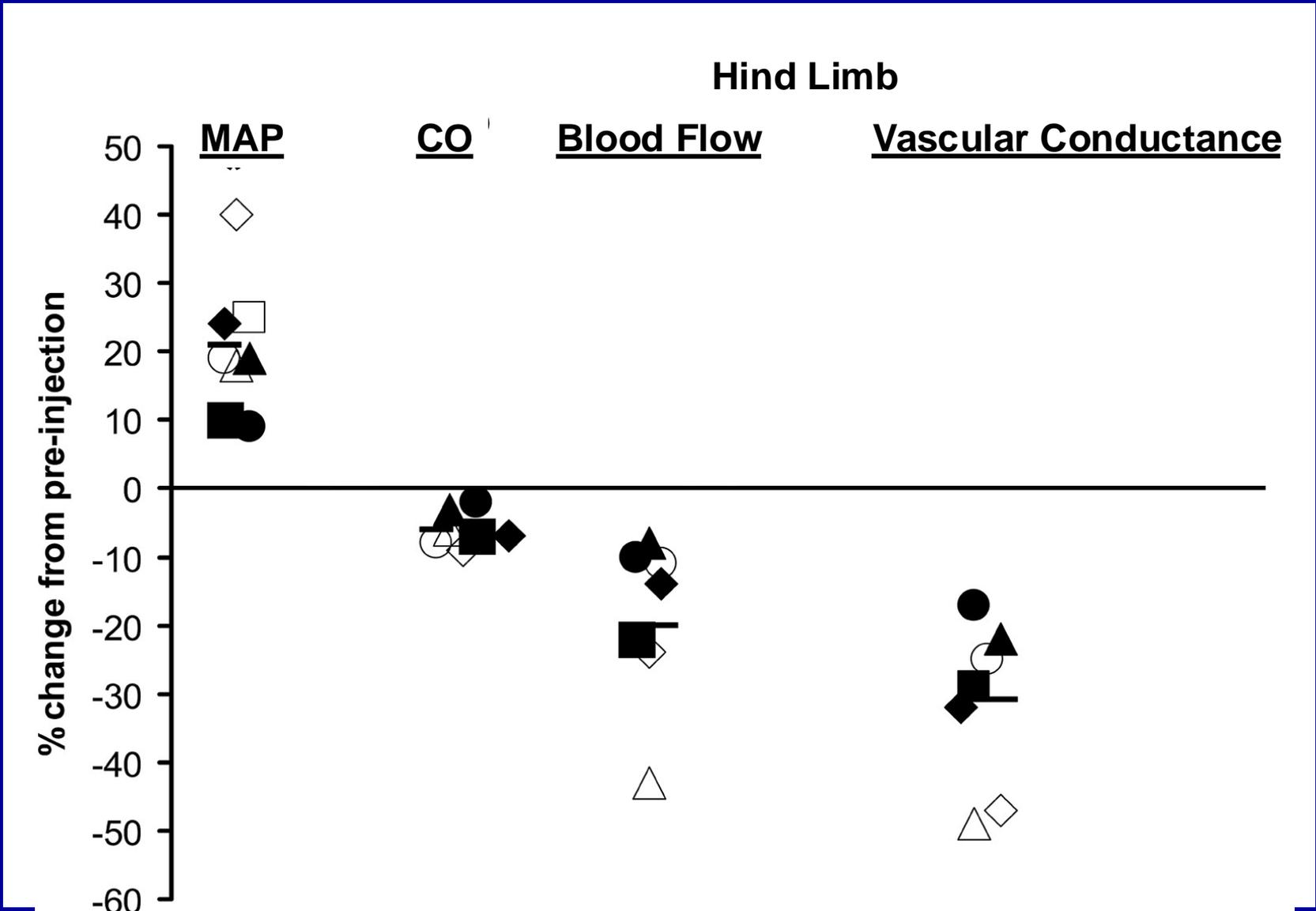
V. Medialis	115±15%	100%	95±12%
SCM	49±5%	100%	230±25%

(Dominelli et al., 2017)

Testing Diaphragm Metaboreceptor Effects on CV Response to Exercise in Canines

- Blood flow probes on ascending aorta, hind limb, abd muscle, renal feed arteries
- Moderate intensity treadmill exercise
- Lactic acid bolus delivered to diaphragm via phrenic artery catheter
- Pre- post-sympathetic blockade

Diaphragm Lactic Acid Bolus in Exercising Canine (n=8)



Symp block prevents CV response!

Effects in exercising humans??