

Whole Body Periodic Acceleration (WBPA)

History 1996-

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Acceleration Therapeutics: How it Really Happened

● September 1996

- NIMS manufactures apnea monitors for NIH multicenter trial of babies at risk to SIDS
 - **Since parents shake babies to wake them during apnea or near SIDS, we wondered whether an automated shaker be attached to crib as a new therapeutic device.**

● December 1996

- Breathing in babies in NICU (MSMC) monitored with RespiTrace
 - Small deflections on breath waveforms every second (2 babies).
 - Eureka moment
 - **Deflections due to air expulsion as baby was patted on buttocks by caregiver because diaphragm.**
 - **Deflections were ~10% -15% of babies' natural breath volume.**
 - **Considered that such action might be basis for a non-invasive ventilator.**
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Automated Patented Backside Patting Device but Dangerous if Baby Moves.



Baby-Patting Machine

Pediatric theories come and go, but certain time-honored practices continue to bring guaranteed results. Patting baby to sleep, for instance. A device that paid tribute to this ancient practice, aided and abetted by modern technology, was patented by Thomas V. Zelenka in 1971. The mechanism, which attached to the side of the crib, operated a mechanical arm which swung a well-padded glove regularly against the baby's rump. Designed to take over a tiresome and time consuming task, the device obviously required some parental vigilance, lest the baby change position and get paddled on the head by mistake.



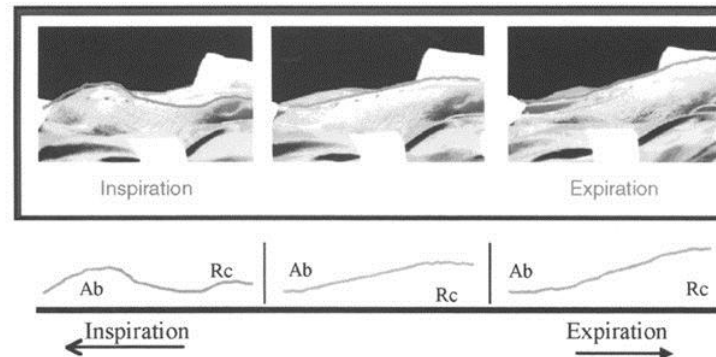
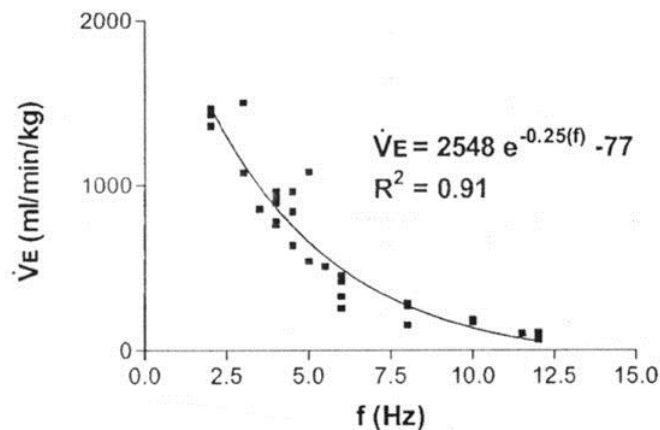
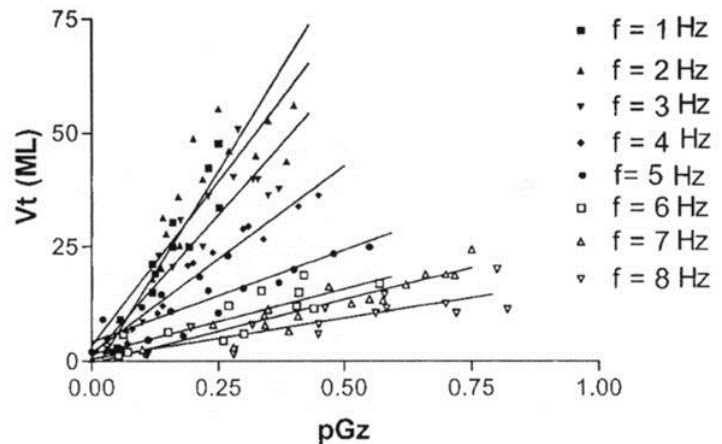
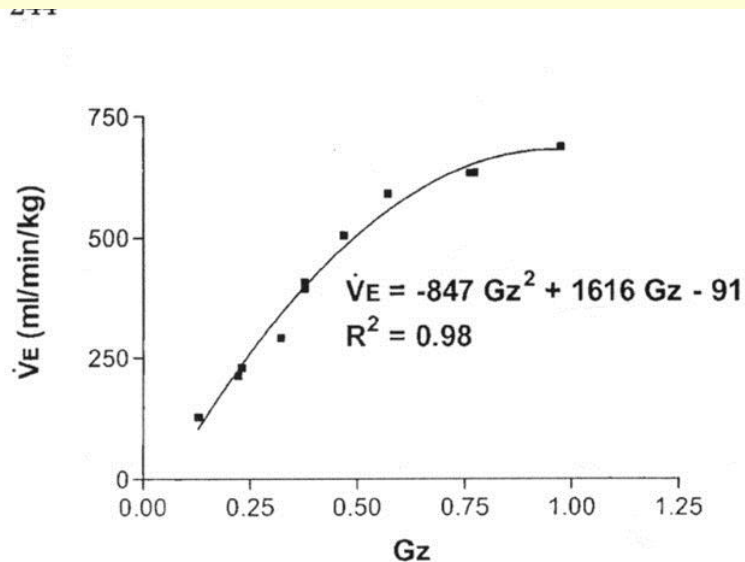
Non-Invasive Motion Ventilation

Hypothesis

- Up and down movements of diaphragm produce ventilation.
 - Buttock patting: diaphragm moves upward to expel air.
 - Hand released: passive recoil causes diaphragmatic descent and inspiration.
- **Eureka moment**
 - Rapid repetitive shifting body head to foot might be used to wake up baby with near SIDS or throw diaphragm into motion to achieve ventilation.
 - Such motion is termed **PERIODIC ACCELERATION (pGz) or NON-INVASIVE MOTION VENTILATION.(NIMV)**



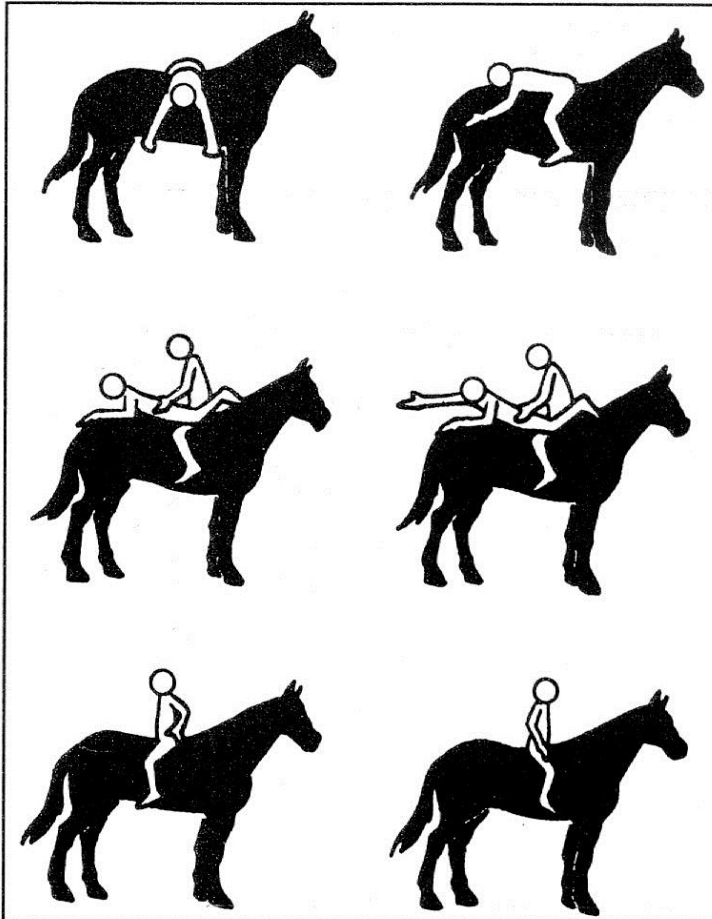
Non-Invasive Motion Ventilation in Anesthetized Paralyzed Pigs



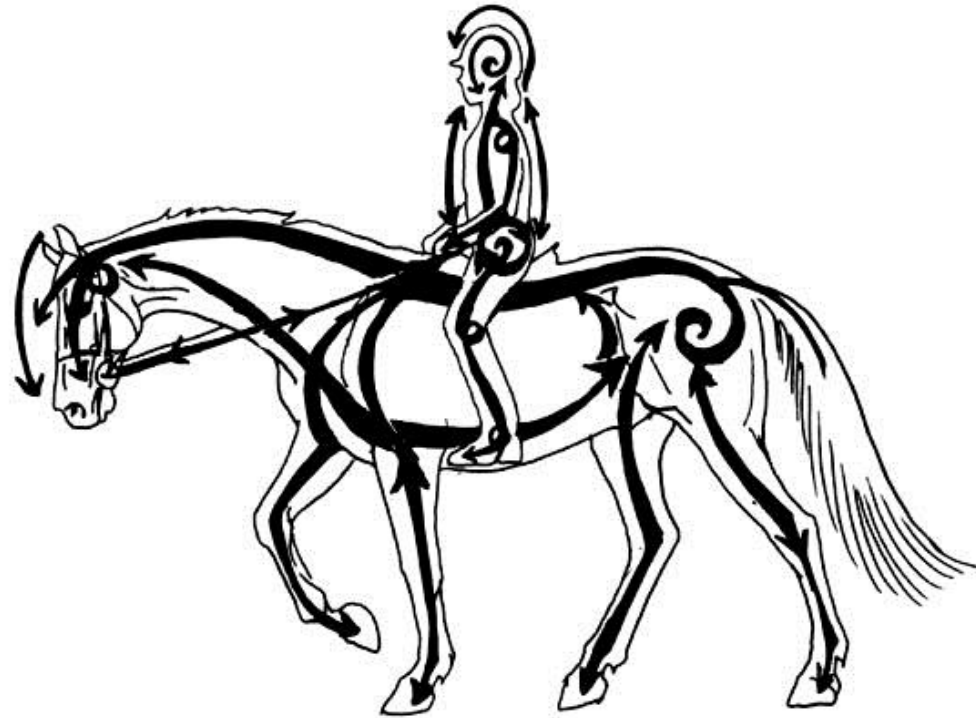
Paradoxical motion between Rc & Ab produces adequate ventilation in animal species with highly compliant Rc. This is not the case in human adults where only a maximum of 50 ml per acceleration-deceleration has been observed.

Horseback Riding Produces WBPA

Hippotherapy for Treatment of Spasticity in Cerebral Palsy Form of WBPA



Basis for Hippotherapy



Movement of horse produces movement in rider's body

Harris. Horse Gaits, Howell Book House, Hoboken NJ, 1993, page 161

Note: Median strides per minute for trotting horse is ~140 & for jogging humans is ~140.




Building a Motion Platform

● Proof of concept 1997-1999

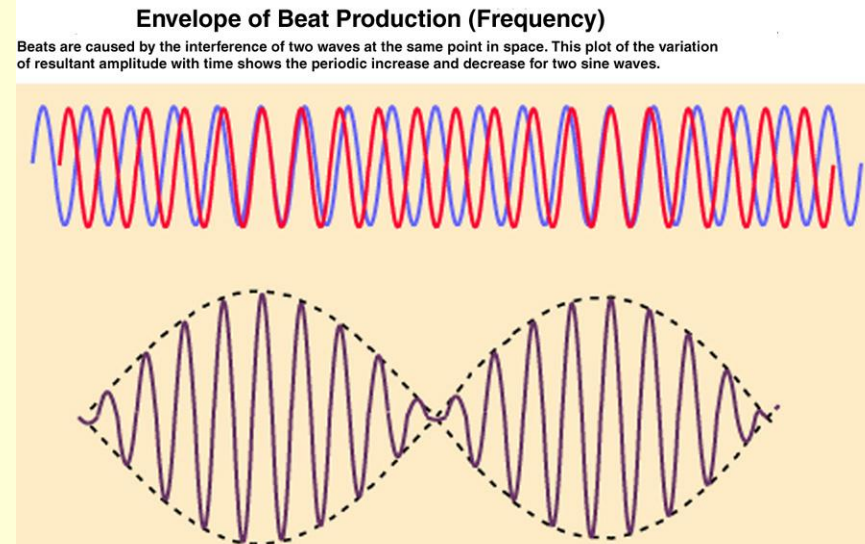
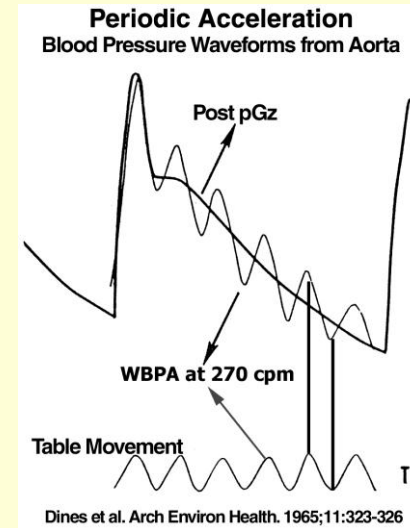
- Drive mechanisms for motion platform to achieve ventilation in anesthetized, paralyzed pigs depends upon adequate g forces.
- Valve drive systems such as solenoids, hydraulic & pneumatic fail because of insufficient $\pm g$
- Linear DC motor, amplifier and controller powering motion platform
 - 2-4 Hz with horizontal travel to produce pGz of $\sim \pm 0.3$ provided excellent ventilation in healthy pigs.
 - Initially called Non-Invasive Motion Ventilation [NIMV].
- As more applications recognized, technology was designated periodic acceleration (pGz) or whole body periodic acceleration (WBPA)

● Adult motion platform 2000-2009

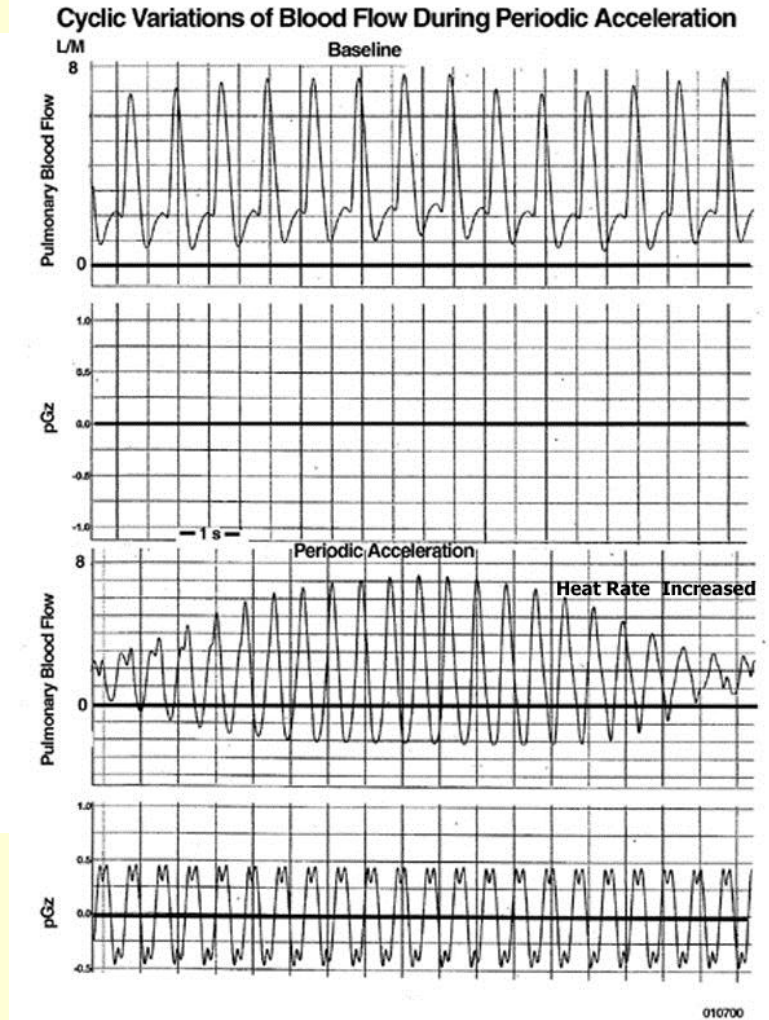
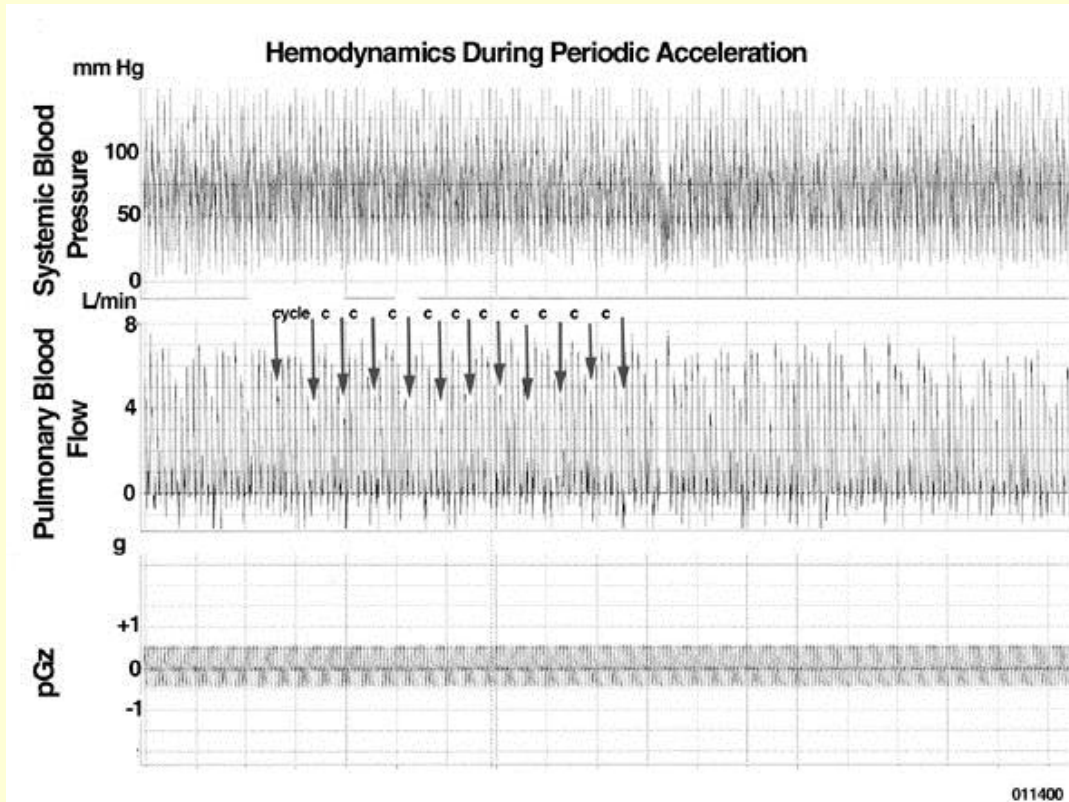
- No off-the-shelf motor and controller with remote variable travel & variable speed to meet specifications.
 - 2000: Single flywheel drive with bicycle wheel but too much side to side motion.
 - 2000 – 2002 Double flywheel drive to control travel distance along with another motor to control speed; noisy & expensive to manufacture.
 - 2008-2009 Most recent motion platform designed and fabricated using a digitally controlled DC brushless motor with a wireless hand controller to regulate time, speed & travel distance.
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Added Pulsations Observed in Blood Pressure Recordings during NIMV in Pigs

- During NIMV, pulsations corresponding to frequency of the motion platform were superimposed upon the innate pressure pulse.
- Beat frequency noted.
- Terms chosen to encompass vascular phenomenon: pGz or Whole Body Periodic Acceleration (WBPA).



WBPA Produces Beat Frequency in Instantaneous Pulmonary Blood Flow





Non-Invasive Motion Ventilation in Stiff Lungs


- Is NIMV effective in abnormal lungs?
 - Instilled human meconium (first sterile feces of newborn) in trachea of paralyzed pigs as model of lung damage.
- Procedure
 - Compare standard mechanical ventilation to NIMV.
 - ***Standard mechanical ventilation:*** pulmonary and systemic arterial pressures rose & cardiac output fell; pulmonary & systemic vascular resistance rose – expected result.
 - ***NIMV:*** pulmonary and systemic arterial pressures fell and cardiac output rose; pulmonary & systemic vascular resistance fell – unexpected result.

Adams et al. J Appl Physiol 2000;89:2447






Super Eureka Moment

- NIMV, which is whole body periodic acceleration (WBPA), relieved pulmonary hypertension associated with meconium aspiration.
 - Postulate: Beneficial effects were due to nitric oxide (NO) released into circulation from added pulses brought about by WBPA that stimulated eNOS activity through increased pulsatile shear stress.
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Goals for Fabricating Human WBPA Commercial Device

- Increase NO delivery from eNOS into circulation.
 - Apply WBPA in horizontal posture with motion platform
 - Repetitively move subject in fixed axis, head to foot, to avoid motion sickness.
 - Establish platform settings for adults.
 - pGz a function of a combination of travel & frequency
 - Travel in mm
 - Frequency in cycles per min (cpm)
 - Duration of treatment in min
 - Measure effectiveness of NO delivery into circulation.
 - Ascertain frequency and duration of treatments.
 - Keep g forces within safety vibration limits of ISO 2601.
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Rocking Soothes Infants: Settings Based Upon Frequency & Travel

Influence of Amplitude & Frequency of Rocking on Activity of Two-Month Old Infants

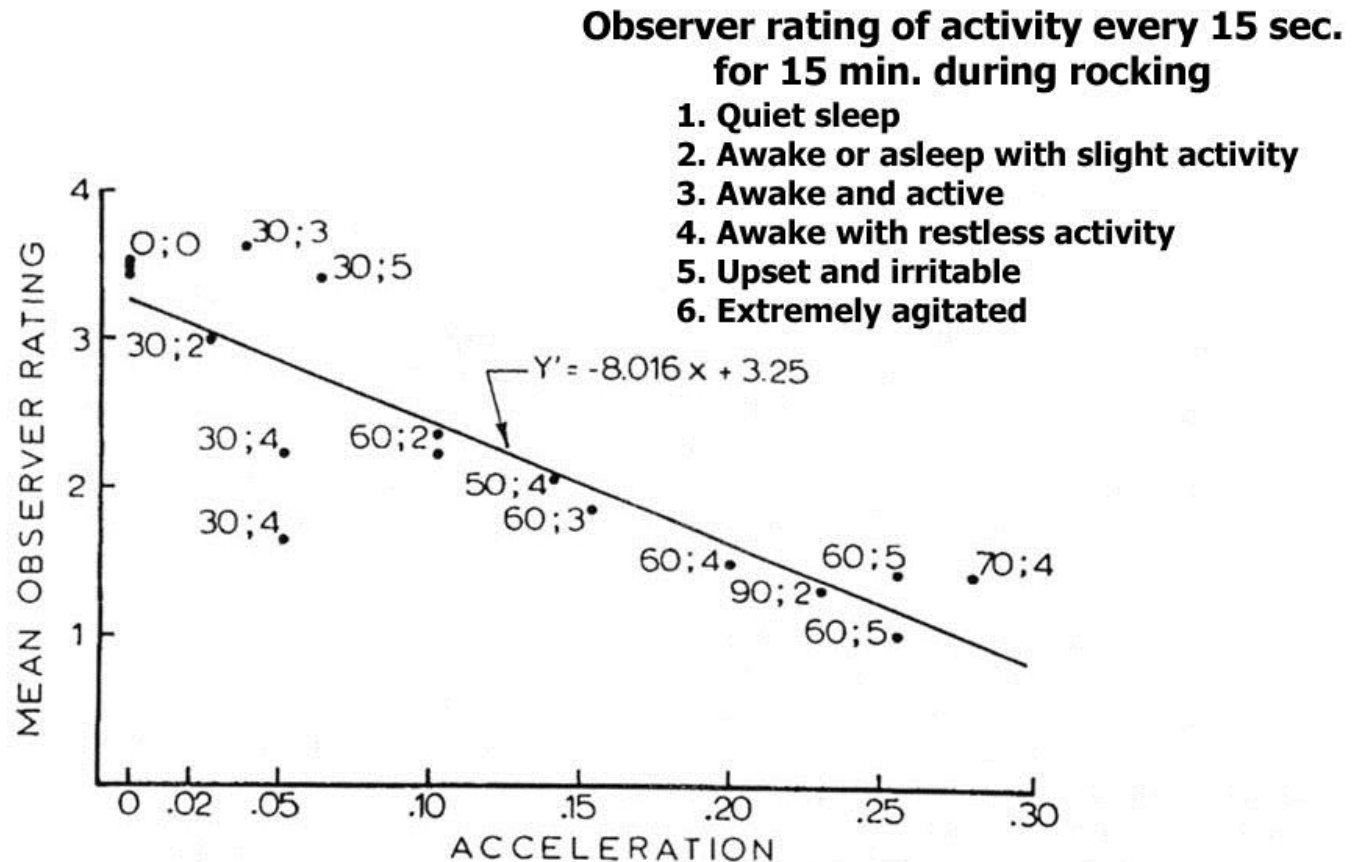
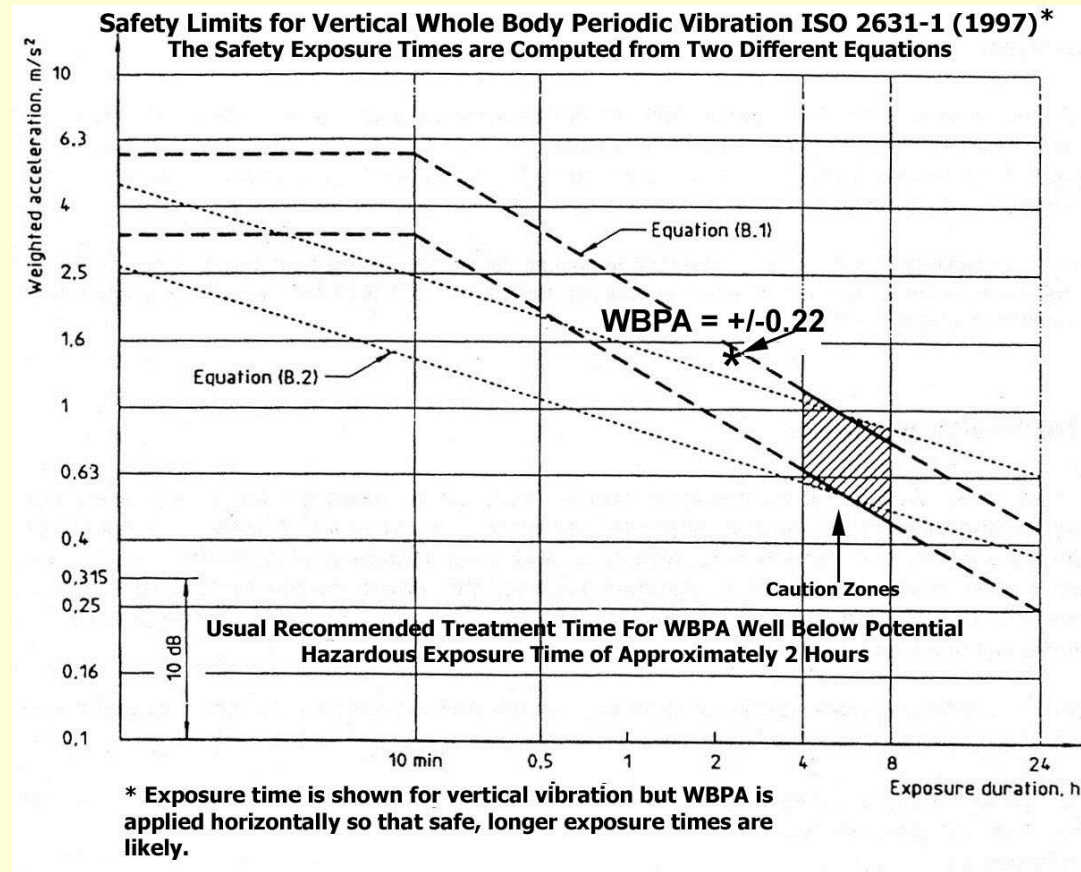



FIG. 4.—Mean observer ratings during the last 5 minutes of rocking as a function of maximum acceleration. (The first number in each pair is the frequency in cycles per minute, and the second number is the amplitude in inches.)

Pederson & Ter Vrugt. *Child Dev* 1973;44:122-128


pGz When Rocking Infants & ISO 2631-1 Safety Standard for Vertically Positioned Adults

- 10 infants 1–3 months, weight 3 - 5 Kg
- Mothers asked to move strollers with infants in “usual fashion.”
- Frequency – 60 to 90 cpm
- WBPA in non-vigorously crying baby $\pm 0.2 - \pm 0.3g$; vigorously crying baby $\pm 0.9g$ up to 5 seconds.
- Rib cage and abdomen moved paradoxically






Establishing Settings for Human WBPA

- To increase pulsatile shear stress, g must be appropriate
 - Rocking soothes babies at $\pm 0.20g$ to $\pm 0.30g$.
 - Treatment duration
 - 45 minutes daily chosen as best guess estimate
 - Level of serum nitrite with WBPA equivalent to level with moderate aerobic exercise
 - Therefore, duration time of 30 to 45 minutes deemed appropriate based upon AHA recommendation that moderate aerobic exercise be carried out at least 30 minutes daily at least 5 days a week.
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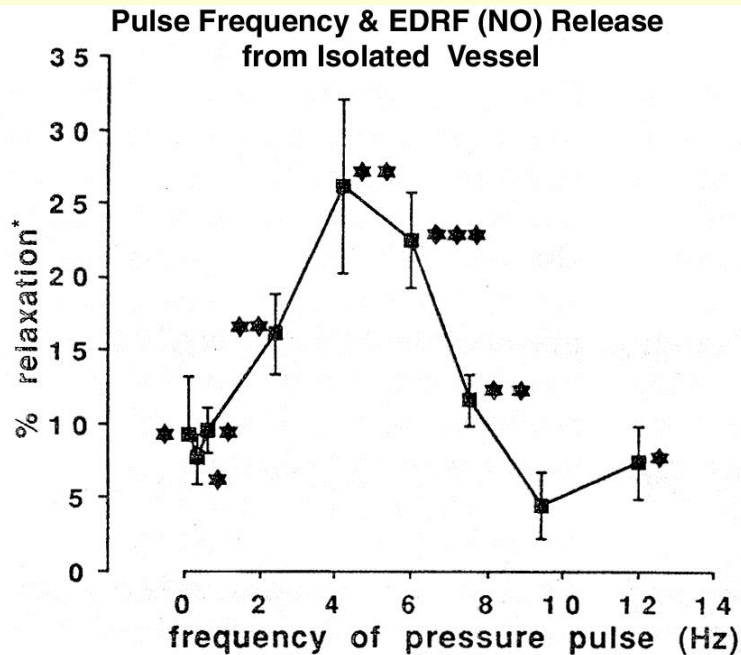


Technological & Human Interface Considerations for WBPA

- Safety & comfort for most adults with applied WBPA: $\pm 0.15g$ to $\pm 0.25g$, 120 to 180 cpm.
 - Such specification limits travel to $< \sim 18mm$.
 - Longer travel with lower speeds (rocking infants) to achieve adequate WBPA from a motion platform would be expensive to build and subject to more mechanical breakdowns.
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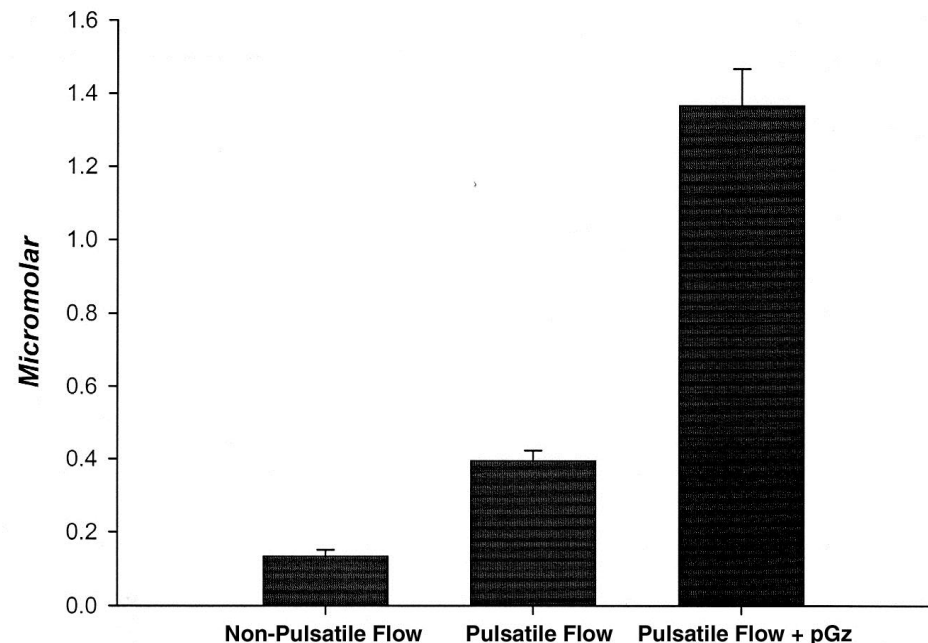


Increased Pulsatile Shear Stress to Perfused Blood Vessel Increases NO Release



*% relaxation signifies the recipient rabbit aorta response that had been pre-constricted with phenylephrine upon receiving the effluent from a donor rabbit aorta subjected to pulsatile amplitude of 2 mm Hg at a mean flow of 9 ml/min (Hutcheson & Griffith: Am.J.Physiol.1991;261:H257).

Perfusate Nitrite (NO Electrode) from Isolated Perfused Porcine Aorta




Mean pressure was 39 mmHg & mean flow 307 ml/min for non-pulsatile flow, 62 mmHg & 444 ml/min for pulsatile flow, and 63 mm Hg & 426 ml/min for pulsatile flow + pGz, respectively. Pulsatile pump frequency was 1 Hz and pGz was 3 Hz with g +/- .7.

Adams et al. Ann Biomed Engineer 2003;31:1337




NO Released by Action of Nitric Oxide Synthases

- NOSs ↑NO but amount, site, & duration of action differ.
 - eNOS
 - Present in vascular endothelium and cardiomyocytes.
 - Exercise & WBPA activate eNOS to periodically release NO in nMol/L through increased shear stress.
 - Here NO: “Less is more.” – beneficial.
 - iNOS
 - Present in monocytes, neutrophils, macrophages, etc.
 - Activated by NF- κ B, inflammatory cytokines and endotoxin – NO released in μMol/L quantities for hours and days.
 - Aids host defense but its unregulated release is harmful.
 - nNOS
 - Present in nervous system, cardiomyocytes, skeletal muscle.
 - Released at nerve endings and acts as neurotransmitter.
 - Exercise & WBPA activate nNOS in cardiomyocytes to release NO – here may be anti-arrhythmogenic.
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Measurement of Endothelial Derived Nitric Oxide (eNO)

- NO is metabolized in blood within 4 sec.
 - Plasma nitrite is semi-quantitative estimate of NO
 - Accurate measurements of acute changes involve a technically difficult research technique.
 - Values may be altered by dietary ingestion of nitrite/nitrate and protein.
 - May be reduced in presence of ↑oxidative stress.
 - Currently, an impractical clinical practice measurement.
 - Changes of dicrotic notch position of finger pulse reflect physiological activity of NO released into circulation.
 - Currently, data processing during WBPA too labor intensive for clinical practice.
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Nitric Oxide & Reflected Pulse Wave (1)

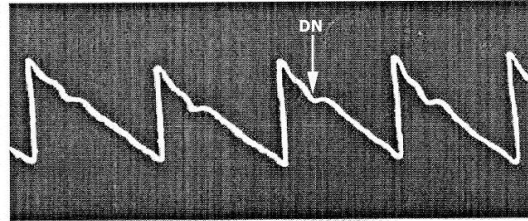
- Dicrotic notch of finger pulse (photoelectric-plethysmography)
 - Reflected arterial wave (position on pulse waveform is function of time of travel to and time to return from resistance site).
 - Vasodilatation: longer distance to resistance site & return to pulse - dicrotic notch moves downward on diastolic limb of finger pulse & may even move into next finger pulse.
 - Vasoconstriction: shorter distance to resistance site and return to pulse - dicrotic notch moves upward on diastolic limb of finger pulse.
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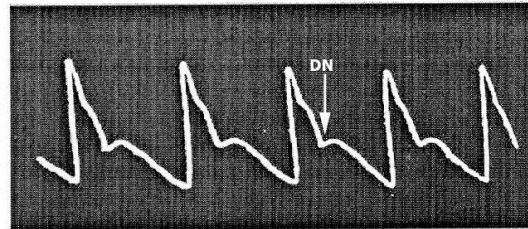
Nitric Oxide & Reflected Pulse Wave (2)

- Downward descent of dicrotic notch
 - NO donor drugs, e.g. nitroglycerin, nitroprusside.
 - Aerobic exercise [eNOS pathway].
 - Whole Body Periodic Acceleration [eNOS pathway].
 - Beta-adrenergic agonists (salbutamol) [eNOS pathway].
 - Alcohol [eNOS pathway].
 - Indomethecin [eNOS pathway]
 - Upward ascent of dicrotic notch
 - L-NAME [blocks eNOS pathway]
 - Dicrotic notch positional changes are specific to eNOS pathway and reflect physiological activity of endothelial derived NO [Nier et al. Exp Physiol 2008;93:503]
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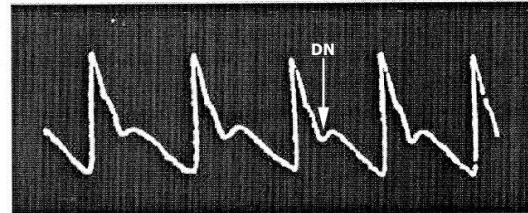
**First Demonstration that Nitric Oxide Causes
Descent of Dicrotic Notch (DN) of Pulse (1879)**



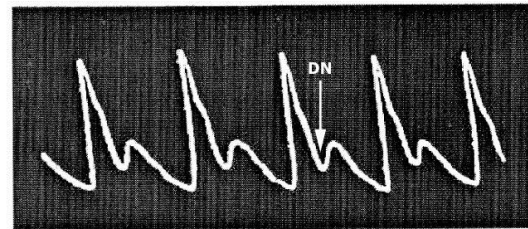
1 Before dose



2 2 min after dose



3 8 min after dose

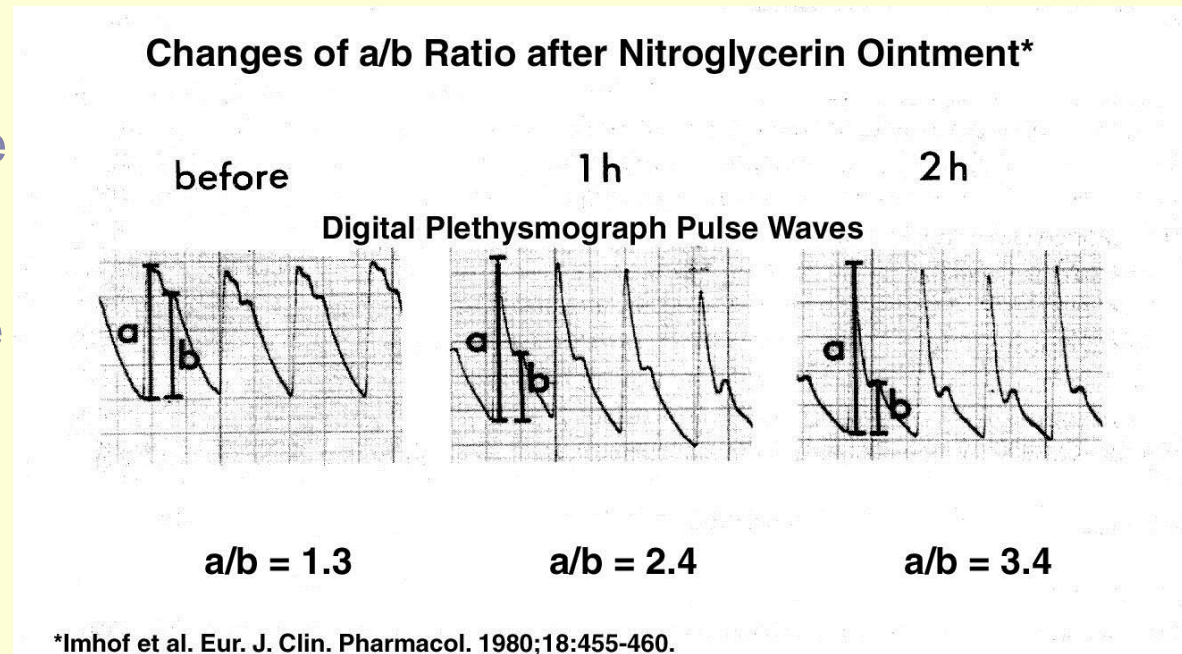


4 9 min after dose

**Radial artery sphygmographs after NTG reproduced
by O'Rourke et al Brit J Pharmacol 2001;51:507-522
after Murrell: Nitroglycerin as a remedy for angina
pectoris. Lancet 1879;80:80-81,113-115,151-152,225-227**

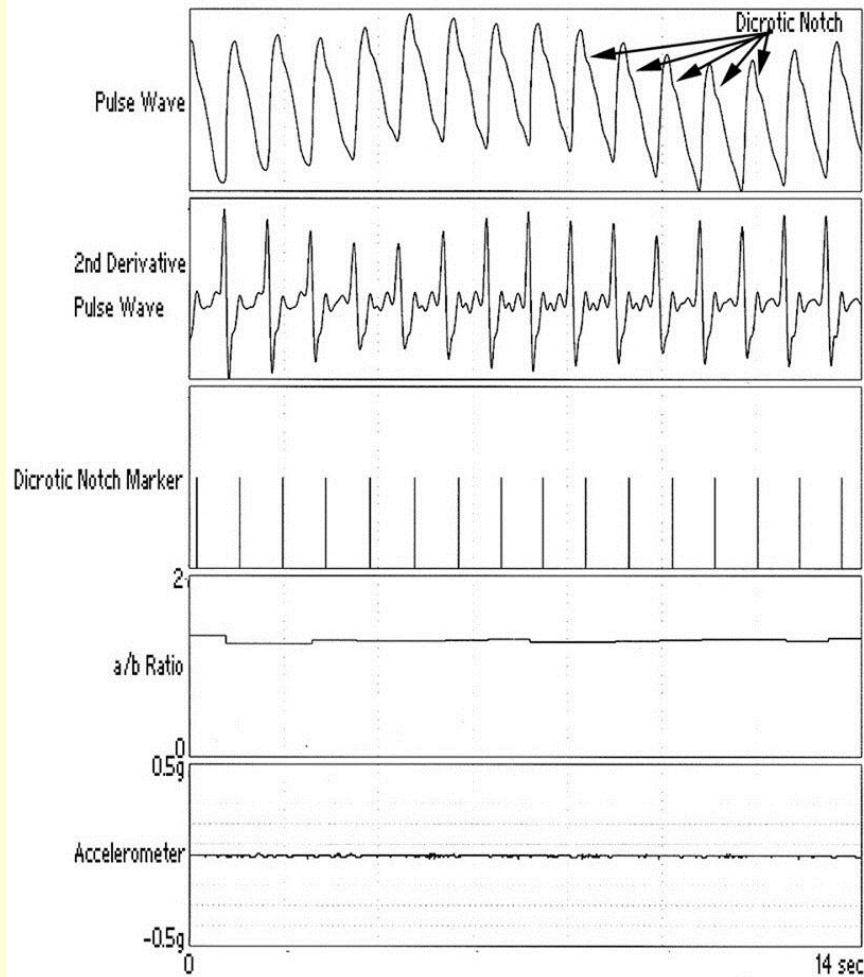
Quantitation of Dicrotic Notch Descent of Digital Pulse

- Measured with a/b ratio
 - a = amplitude of pulse
 - b = height of dicrotic notch above end-diastolic level of pulse
- Recommended by FDA in 1970s to determine whether nitroglycerin in skin patches effectively reaches circulation.

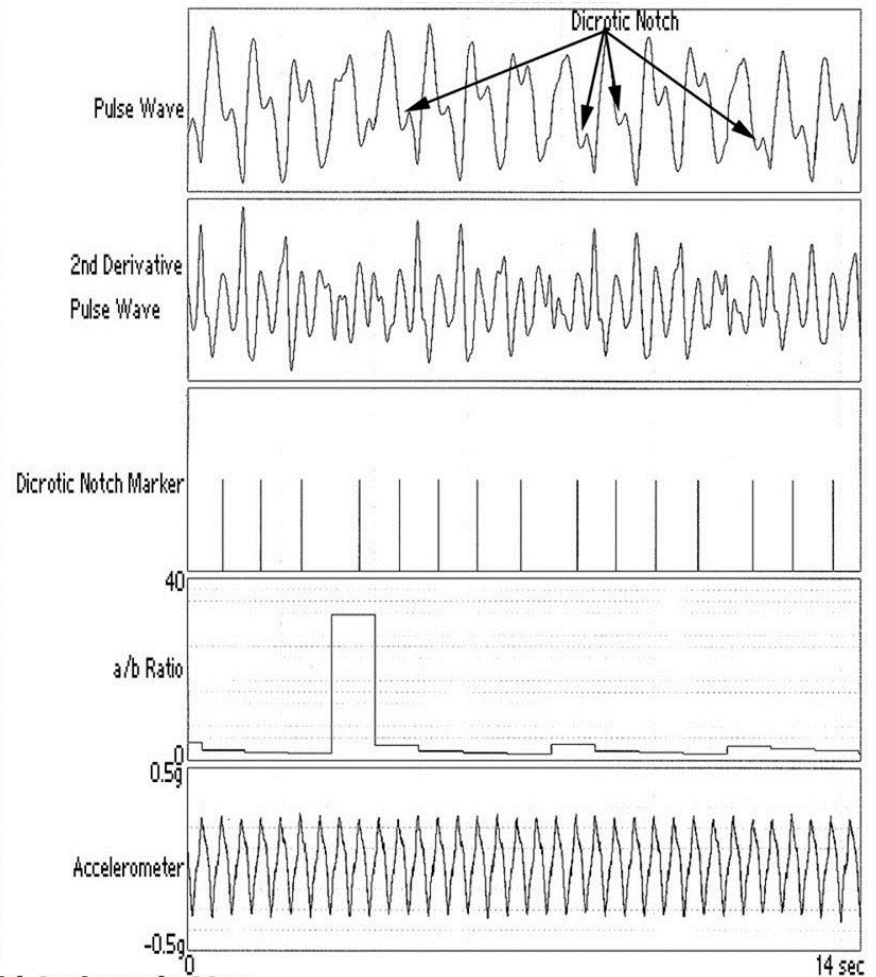


Effects of WBPA on Dicrotic Notch Position

Baseline



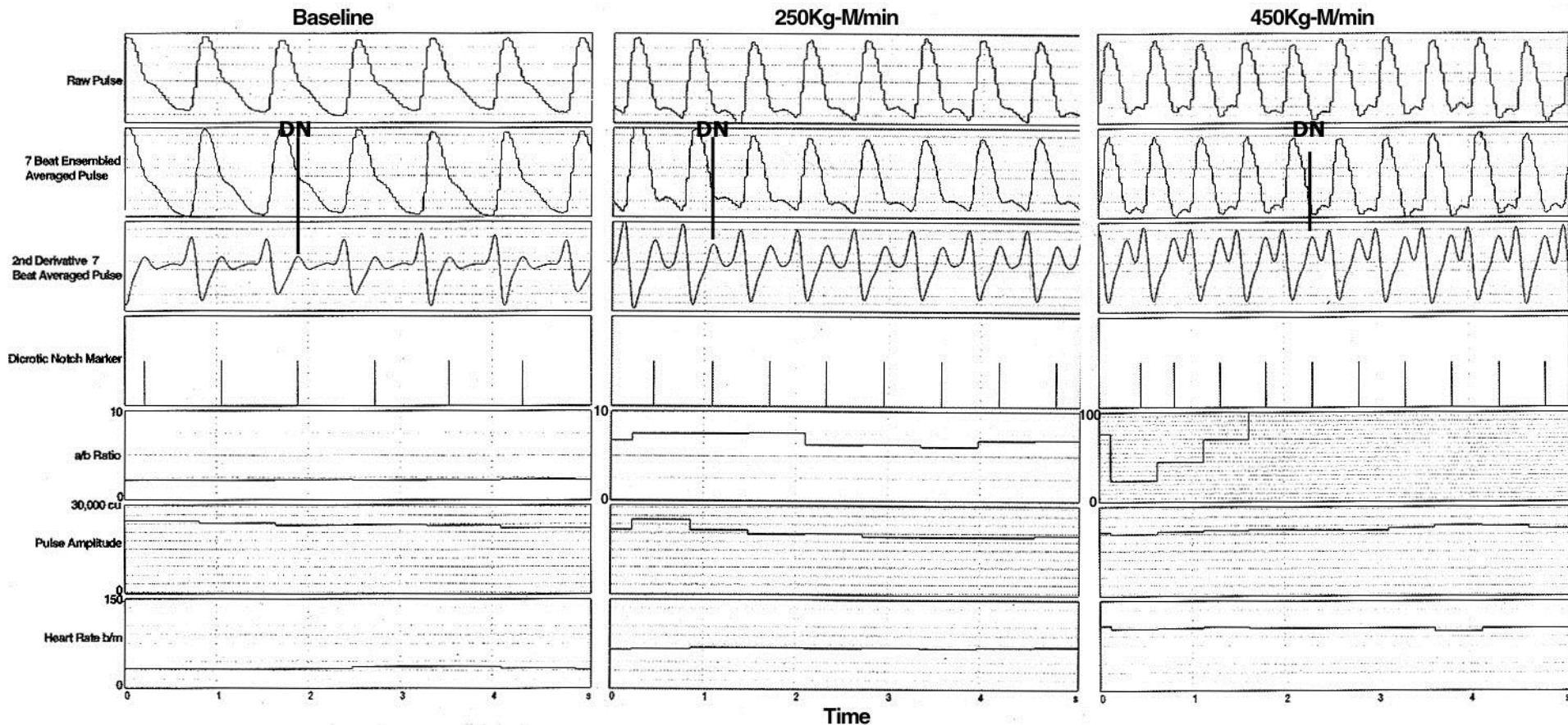
Whole Body Periodic Acceleration



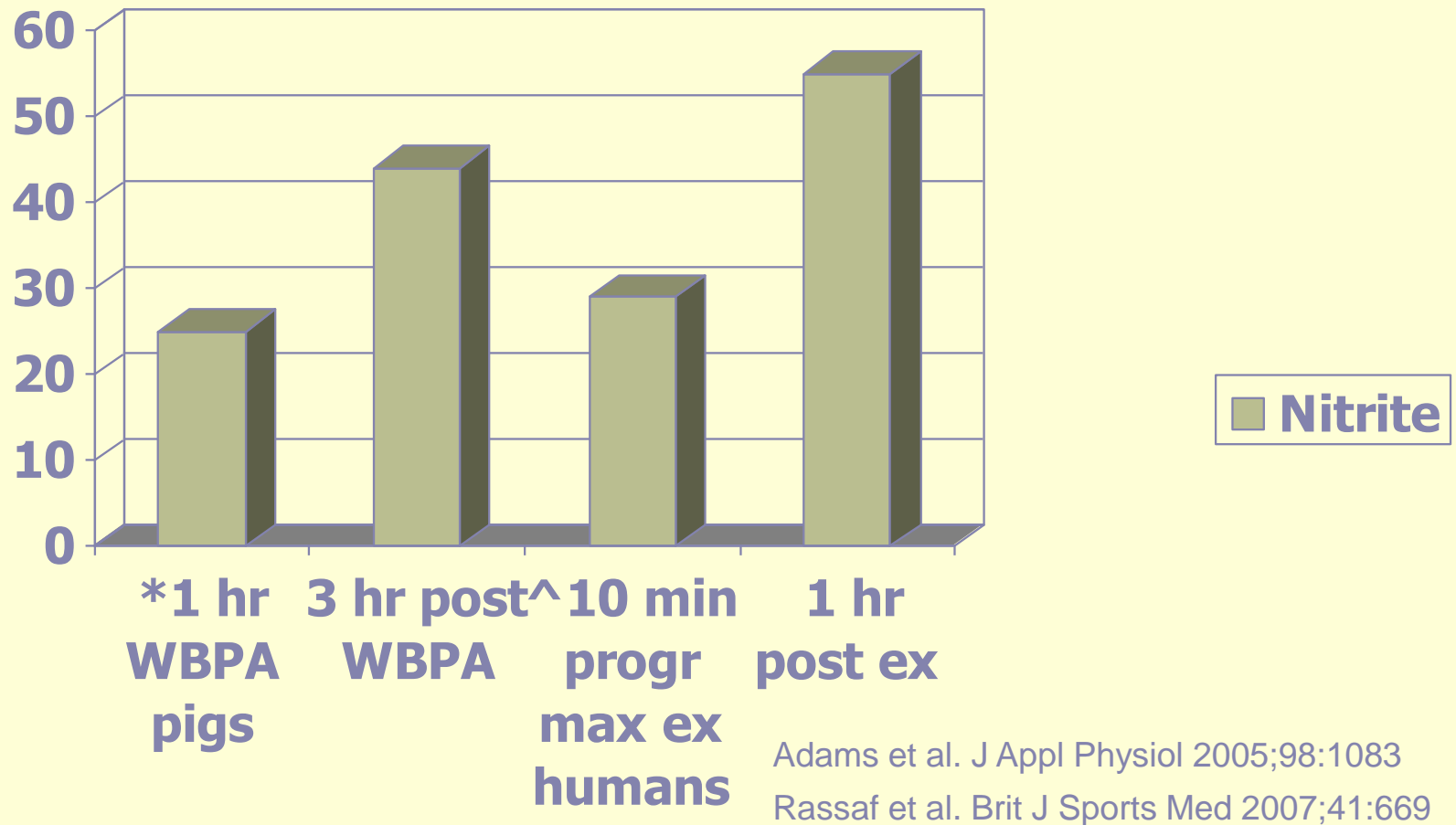
60 yr old Asthmatic Man

Exercise: Dicrotic Notch Detection from Wave on 2nd Derivative of Pulse

Effect of Supine Cycle Ergometry on Dicrotic Notch Position



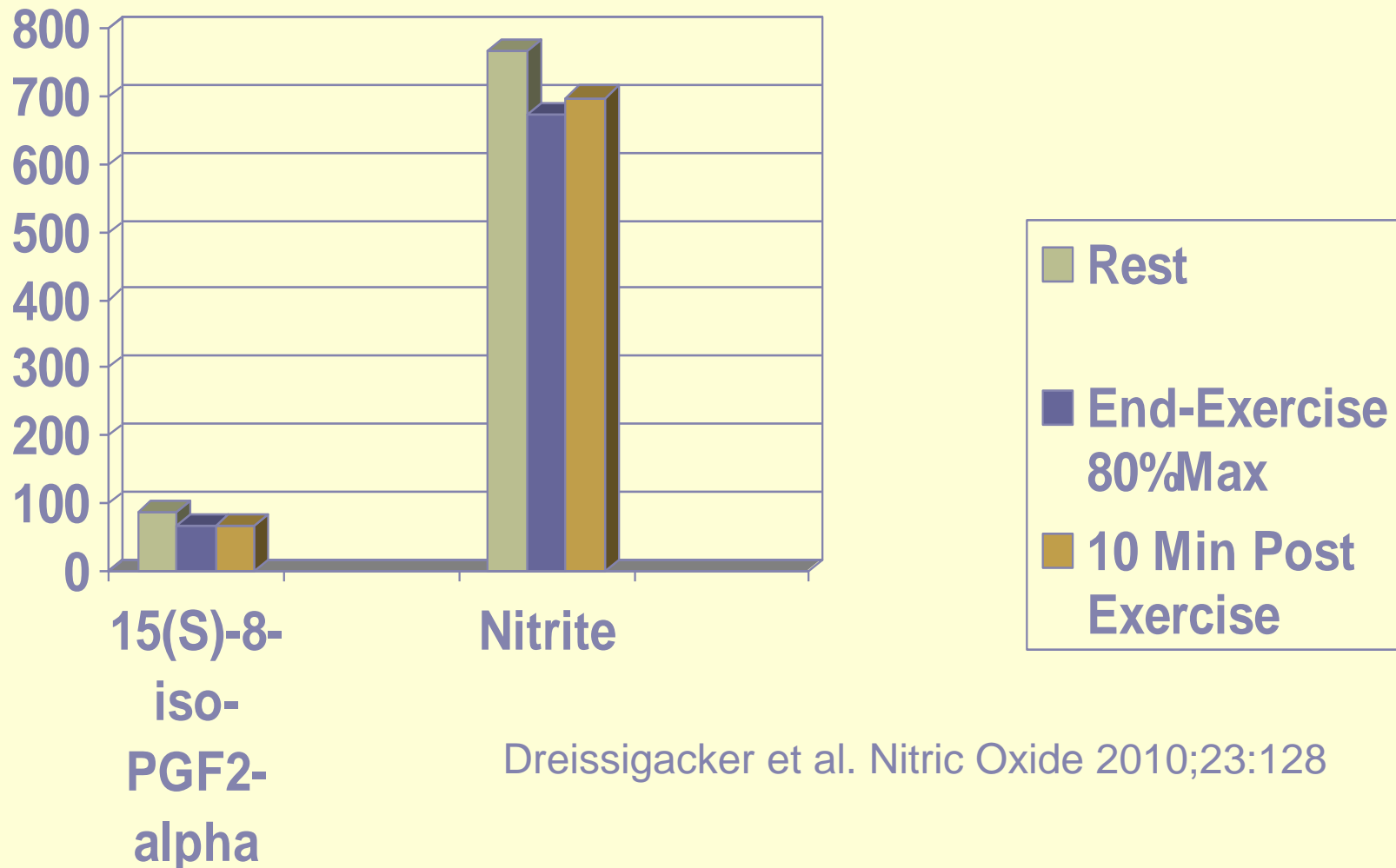
% Changes of Plasma Nitrite After WBPA or Exercise



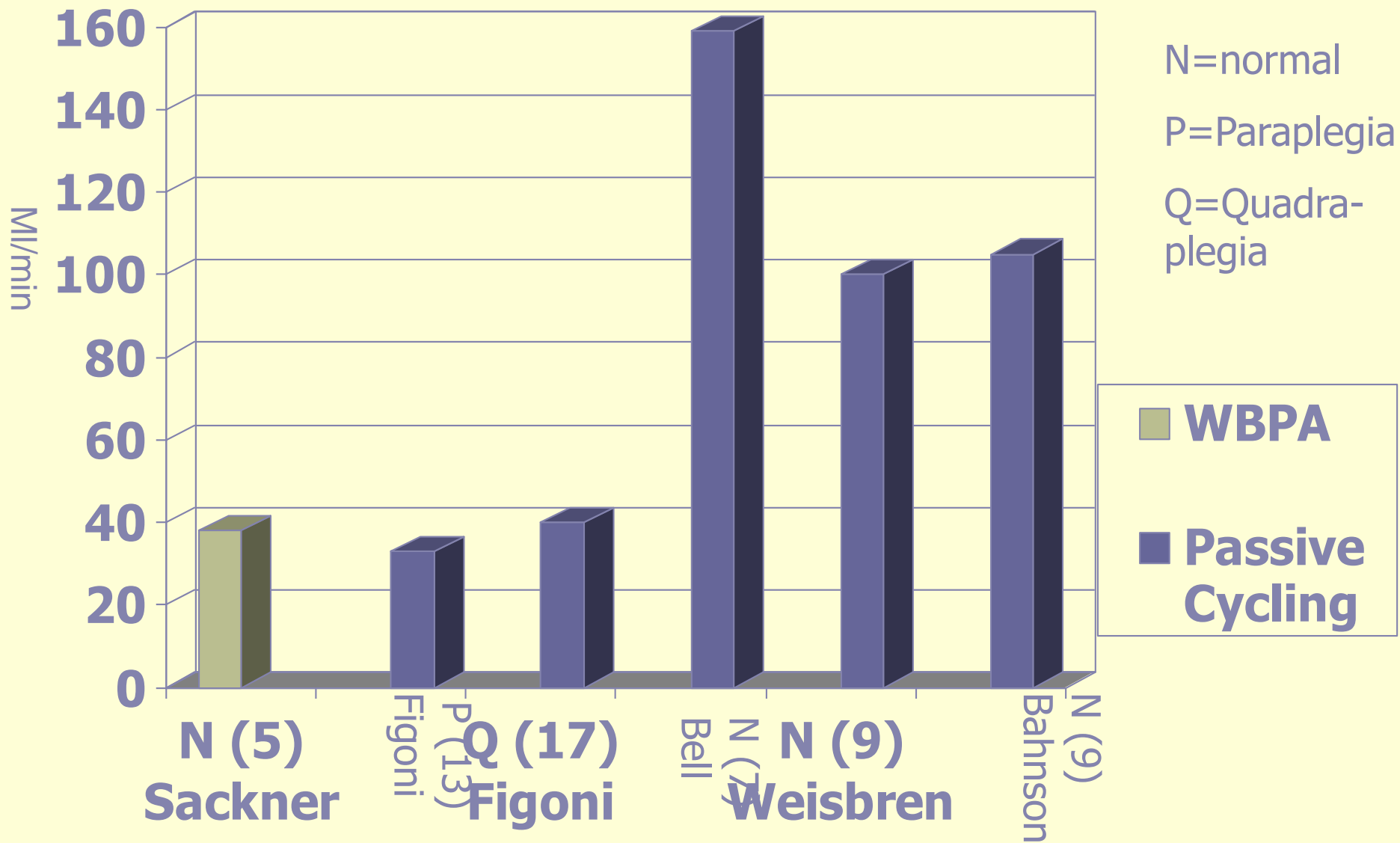
NO metabolized within 4 seconds; slow NO release after WBPA or exercise originates from nitrosylated proteins

Dicrotic Notch Descent: Better Marker for Stimulation of eNOS than Plasma Nitrite?

Plasma Nitrite Reduced by ROS




Oxygen Consumption: WBPA (30 min) vs. Passive Cycling (5 min)





Pulsatile Shear Stress on Endothelium from WBPA Promotes Cardiovascular Protection

- Maintenance of vascular tone
 - \uparrow eNOS \rightarrow \uparrow NO*
 - \uparrow prostacyclin,* \uparrow adrenomedullin*
 - \downarrow endothelin-1*, \downarrow angiotensin II
 - \uparrow Kruppel-Like Factor-2 (KLF2)
 - \uparrow SIRT-1
 - Antithrombotic activity
 - \uparrow thrombomodulin
 - \uparrow heparin, \uparrow heparan, \uparrow tPA*
 - Increased of growth factors
 - \uparrow platelet-derived growth factor (PDGF), \uparrow transforming growth factor- β (TGF- β)
 - Mitigation of myocardial cell death
 - \uparrow NO* = \downarrow PARP-1 - \downarrow apoptotic death
 - \uparrow NO* = \downarrow Caspase 3 - \downarrow apoptotic death
 - \uparrow NO* = \downarrow mitochondrial permeability transition pore opening (MPTP) with C^{++} overload - \downarrow necrotic death
 - Mobilization EPCs
 - \uparrow NO*
 - Prevention of adhesive interactions with leukocytes
 - \downarrow VCAM-1
 - Reduction of oxidative stress
 - \uparrow SOD*
 - \downarrow NAPDH oxidase
 - Anti-inflammatory action
 - \uparrow NO* - \downarrow NF- κ B
 - Improved microvascular blood flow
 - \uparrow Myocardial blood flow (colored microspheres)*
 - \uparrow Coronary flow reserve*
 - Myocardial “suspended animation”
 - \uparrow NO* - \downarrow Myocardial oxygen consumption
 - Reduces ventricular arrhythmias post I-R
 - \uparrow Myocardial nNOS*
- *Documented with WBPA**
Modified from Ando & Yamamoto. Circ J 2009; Otto et al. AHA 2010; Adams 2001-2010; Fukuda Am Heart L 2010.
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Cystic Fibrosis Pathogenesis (1)

Cause

- Abnormality in the cystic fibrosis trans-membrane conductance regulator (CFTR)
 - Lungs are the organ system most severely affected.
 - Lung disease accounts for 95% of mortality.


Pathogenic features (early)

- Exact mechanism whereby CFTR mutant causes the following unclear
 - Obstruction of submucosal glands
 - Early on, mucus plugs become infected with *S. aureus* & *H. influenza*, then later with *P. aerogenosa*.
 - IL-8 & IL-6 are released into airway leading to a vigorous inflammatory response dominated by neutrophils.
 - Neutrophils release **elastase** onto airway surfaces that overwhelms anti-proteases.
- 



Cystic Fibrosis Pathogenesis (2)

● Pathogenic features (late)

- Due to abnormality in CFTR, mucus plaques become viscous which impedes bacterial phagocytosis.
 - CF lung disease
 - Impaired mucociliary clearance.
 - Loss of airway antimicrobial activity.
 - NO is constitutively released from iNOS in normal airway epithelial cells
 - Epithelial cells in CF have reduction of iNOS as an innate defect thereby impairing NO host defense.
 - Immune system fails to kill bacteria.
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Pathogenesis of Cystic Fibrosis & Role of WBPA (\uparrow eNO)

● \uparrow Neutrophil elastase

- Inflammation: \uparrow NF- κ B, IL-8, & iNOS activities
- Increased oxidative stress: \uparrow ROS & RNS
 - Sarcopenia (corticosteroids also a factor)
- Airway remodeling: \uparrow TGF- β 1
- CF-Related Diabetes: \uparrow oxidative stress & insulin resistance
- Bronchospasm in status asthmaticus
- \downarrow Mucociliary activity

● WBPA \uparrow eNO

- Anti-inflammatory \downarrow NF- κ B, IL-8, & iNOS activities
- Antioxidant: eNO & \downarrow NAPDH oxidase
 - Preserves muscle mass.
- Prevention airway remodeling: \downarrow TGF- β 1
- Anti-diabetogenic: \downarrow oxidative stress & insulin resistance
- \downarrow Mast cell degranulation in immediate reaction of allergic asthma & \downarrow late phase (\uparrow NF- κ B)
- \uparrow Tracheal mucus velocity

Manifestations of CFRD

Table 1. CFRD compared to type 1 and type 2 diabetes in the University of Minnesota CF population.

	CFRD	T1D	T2D
Prevalence in population	35%	0.2%*	11%*
Peak age of onset	20–24 years	Childhood, adolescence	Mid- to late-adulthood
Usual body habitus	Normal to underweight	Normal	Obese
Insulin deficiency	Severe but not complete	Complete	Partial, variable
Insulin resistance*	Usually modest, waxes and wanes with infection	Usually modest	Severe
Autoimmune etiology*	No	Yes	No
Ketones	Rare	Yes	Rare
HbA _{1c}	Unpredictable relation to mean blood glucose	Related to mean blood glucose	Related to mean blood glucose
Usual treatment	Insulin	Insulin	Oral agents, insulin
Microvascular complications*	Yes	Yes	Yes
Macrovascular complications*	No	Yes	Yes
Metabolic syndrome features*	No	No	Yes
Cause of death	Lung disease	Cardiovascular	Cardiovascular
Onset	Gradual	Acute	Gradual
Insulin secretion	Gradual deterioration	Eventually absent	Diminished
Insulin sensitivity*	Diminished (severely in acute exacerbations)	Variably decreased	Severely diminished

* WBPA complementary Rx

Laguna et al. Diabetes, Obesity Metabolism 2010;12:858; Rana et al. Nat Rev Endocrinol 2010;6:371

Oxidative Stress Theory for Development of CFRD

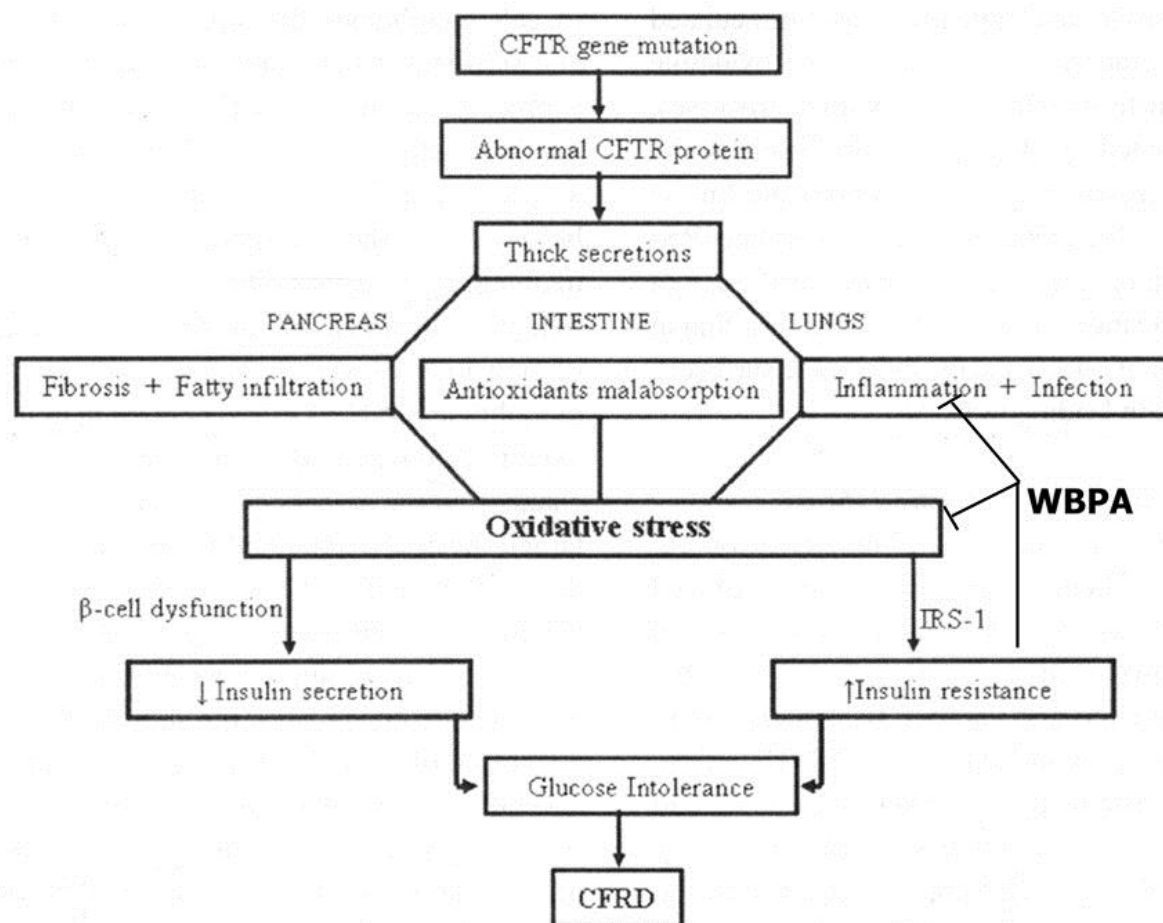



Figure 4. Possible links between CFTR dysfunction, oxidative stress and the occurrence of CFRD in CF. The multi-organ dysfunction of the CFTR protein is directly associated with an increase in oxidative stress which can alter glucose tolerance by reducing insulin secretion or inhibiting its signalling pathways then leading to CFRD.



Summary

- The discovery of the beneficial effects of whole body periodic acceleration (WBPA) was serendipitous with its initial impetus a result of clinical observations.
 - WBPA is a non-invasive, drug-free technology that can be employed in hospital, clinic or home for management of conditions/diseases marked by chronic inflammation and/or increased oxidative stress.
 - WBPA has potential to be a major alternative/ complementary therapy for management of chronic diseases.
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 - This research supported in part by grants from the Florida Heart Research Institute and the American Heart Association
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