Data Interoperability in Pediatric Cardiopulmonary Exercise Testing:

From Israel to Irvine and back

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Irvine…

- One of the 8 Universities of California (UC system)
- Growing rapidly
- Great location (Southern CA.. Between LA and San Diego)
- Where the Pediatric Exercise and Genomic Research Center (PERC) is located

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13 EXERCISE AND LUNG FUNCTION IN CHILD HEALTH AND DISEASE

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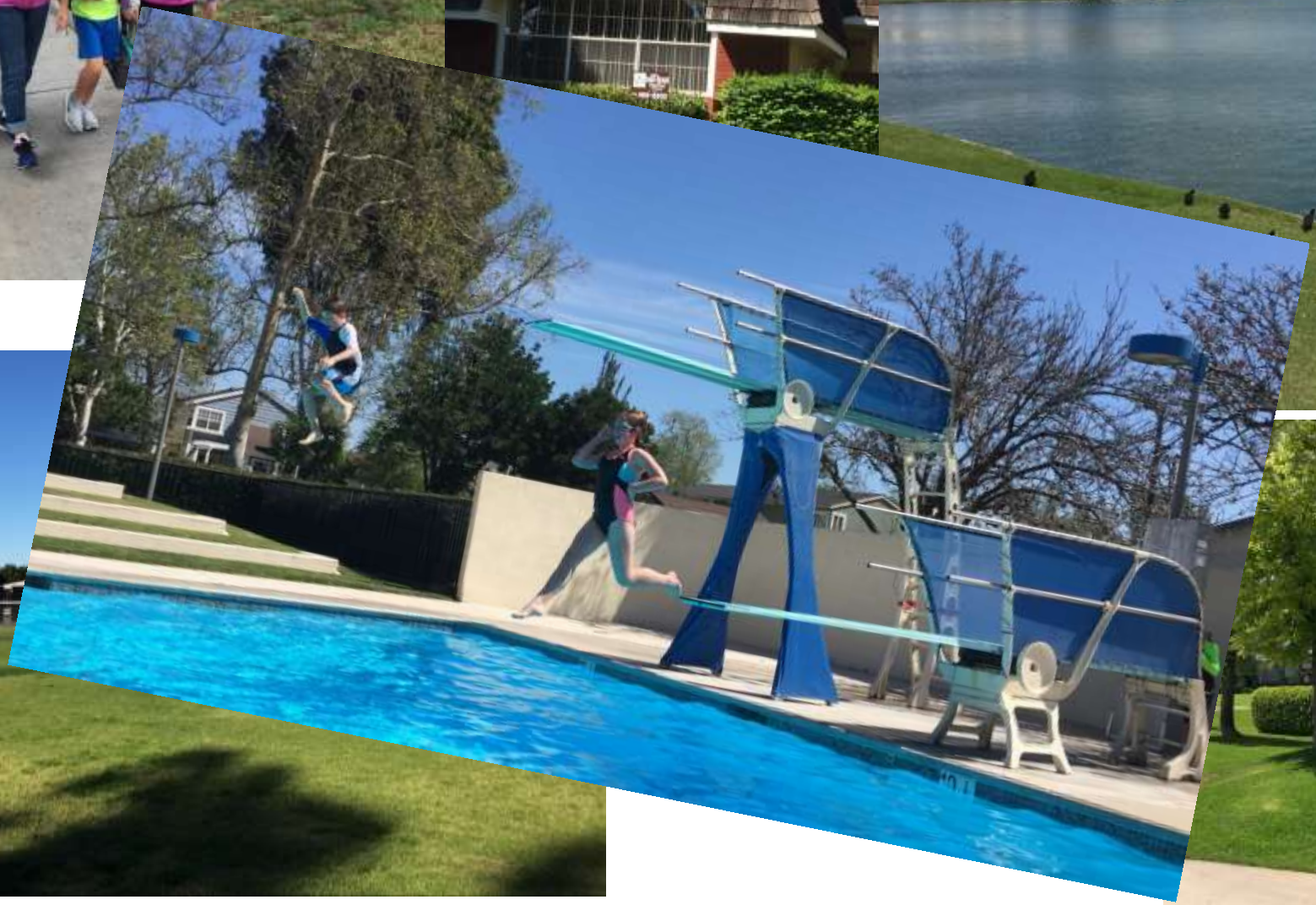
THE BIOLOGIC RELEVANCE OF EXERCISE IN THE GROWING CHILD

While the idea that "exercise is good for children" seems axiomatic, translating this vague notion into specific, biological mechanisms that actually could be used to influence health has proven difficult. Never before has the need for such research been so great. We find ourselves in the midst of an emerging epidemic of pediatric obesity, type 2 diabetes, and the metabolic syndrome, all, in large measure, ominous consequences of unprecedented levels of physical *inactivity* in children.[114,168] The parallel epidemic of childhood asthma seems equally intractable, disproportionately affects lower socioeconomic strata children,[228] and is itself linked to physical inactivity and obesity.[124,178,244,264] At the same time, therapeutic advances result in increasing numbers of childhood sur-

(Fig. 13-1). We now know that exercise can lead to a substantial perturbation of cellular homeostasis including a profound metabolic acidosis, markedly altered oxygen, and substrate flux in tissue and mitochondria, and, on occasion, frank tissue injury. Even in healthy adults and children, exercise results in what appears to be a "danger" type activation of innate immune responses[58,147,175,214] that involves increased levels of circulating cytokines (e.g., interleukin-6 [IL-6]), leukocytosis, alterations in both gene expression and epigenetic control elements in circulating leukocytes (Fig.13-2),[189–192] and leukocyte adhesion molecules that have been associated with lung diseases such as asthma and CF.[66,222] An intriguing question is: Given the profound inflammatory response that occurs with exercise, why doesn't everyone wheeze with physical activity?



Pediatric Exercise and Genomics Research Center - PERC

- The dream of Shlomit Radom-Aizik and Dan Cooper
- Focus on translational science in the exercise field
- The effect of exercise in health and disease conditions
- Maturation effects
- Children (preterms, infants, pre/post pubertal) and young adults

My project

- **Goals:**
  - To compare treadmill and cycle ergometer modalities
  - To study the response to low/moderate/high exercise Intervals
  - To repeat the NHANES study with gas exchange parameters

  in children and young adults

- Graduate students:
  - Muscle responses to exercise (NIRS)
  - New device to measure body composition

Study design

- 6 Study visits:

1. Cycle ergometer (CE) ramp test (Body composition, Questionnaires, Consent)

randomized

2. Treadmill (TM) ramp test
3. Low intensity (40% of peak WR) interval exercise – 30 min (2 min of exercise and 1 min of rest)
4. Moderate intensity (60% of peak WR) interval exercise – 30 min
5. High intensity (80% of peak WR) interval exercise – 30 min
6. NHANES protocol on TM

De facto…

- 95 healthy children (7-18 y/o) and 19 young adults (19-35 y/o) recruited
- > 650 Lab visits
- Huge data base…
- Very intense 6 month…

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NHANES - National Health and Nutrition Examination Survey

- National level
- Thousands of children
- Data on physical activity and fitness levels
- Interviews and fitness tests

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HR, Speed, Incline, Anthropometrics

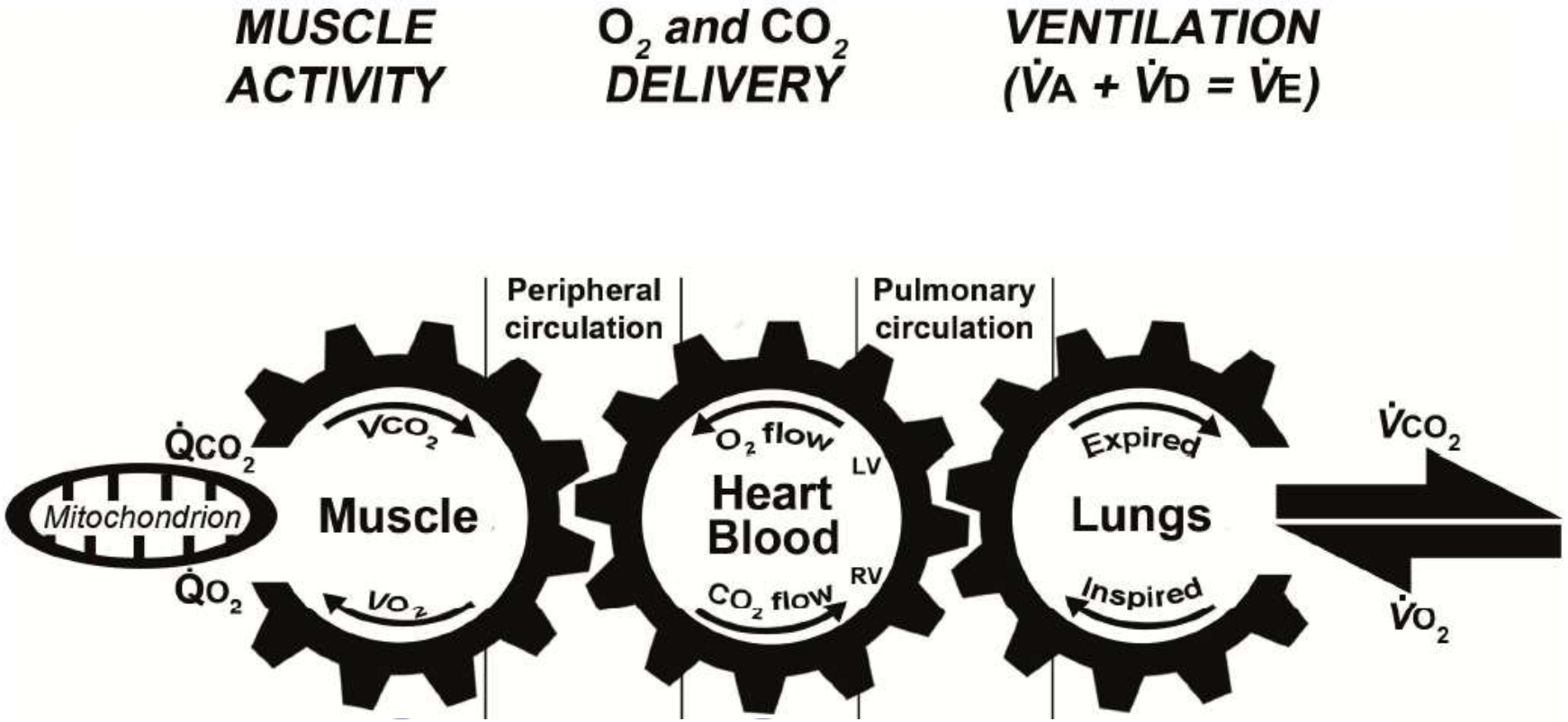
↓

Estimation of VO_2 max

↓

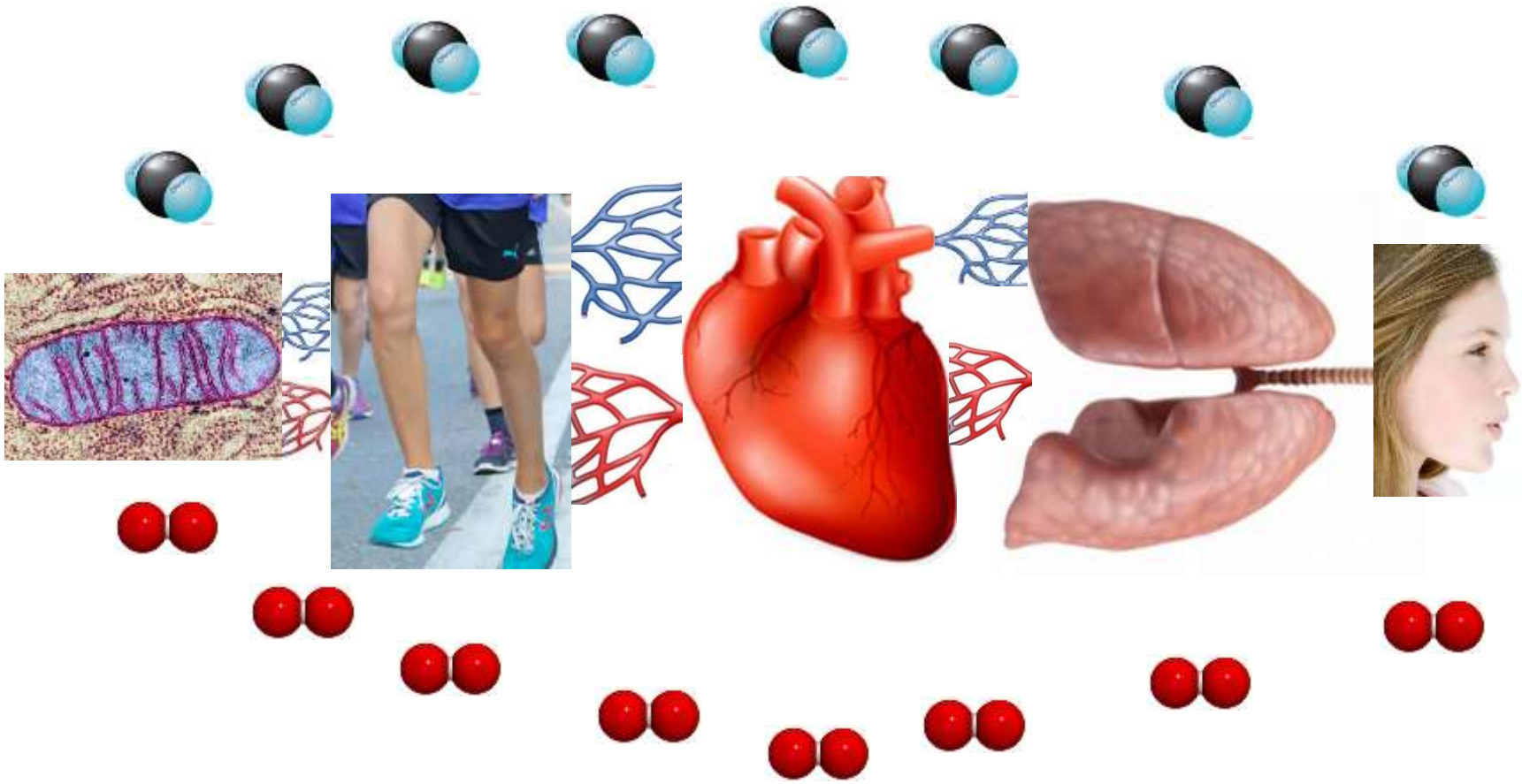
Fitness levels

Wasserman gears

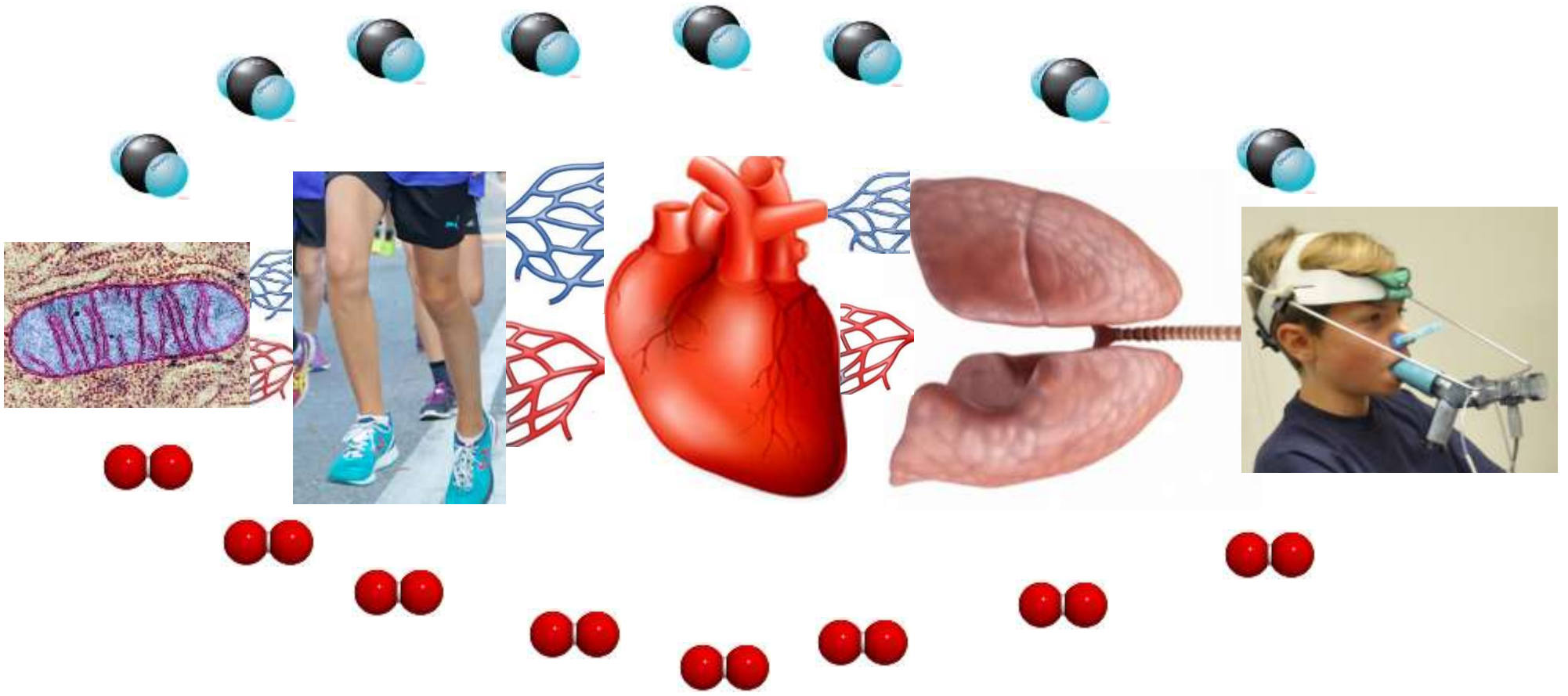


Mayo Clinic Proceedings 2006 81, 1603-1611DOI: (10.4065/81.12.1603)

Modified “Wasserman gears”…

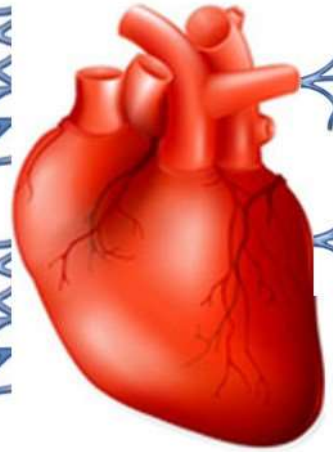


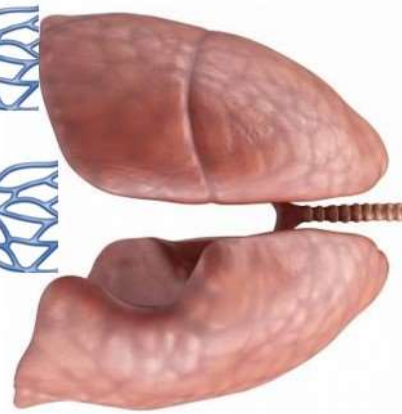
Modified “Wasserman gears”…



Peripheral circulation

Pulmonary circulation





- Mitochondrial disorders

- Obesity
- Myopathy
- Chronic Muscle disorder

- Occlusion
- Hypertension
- Vasoregulatory asthenia

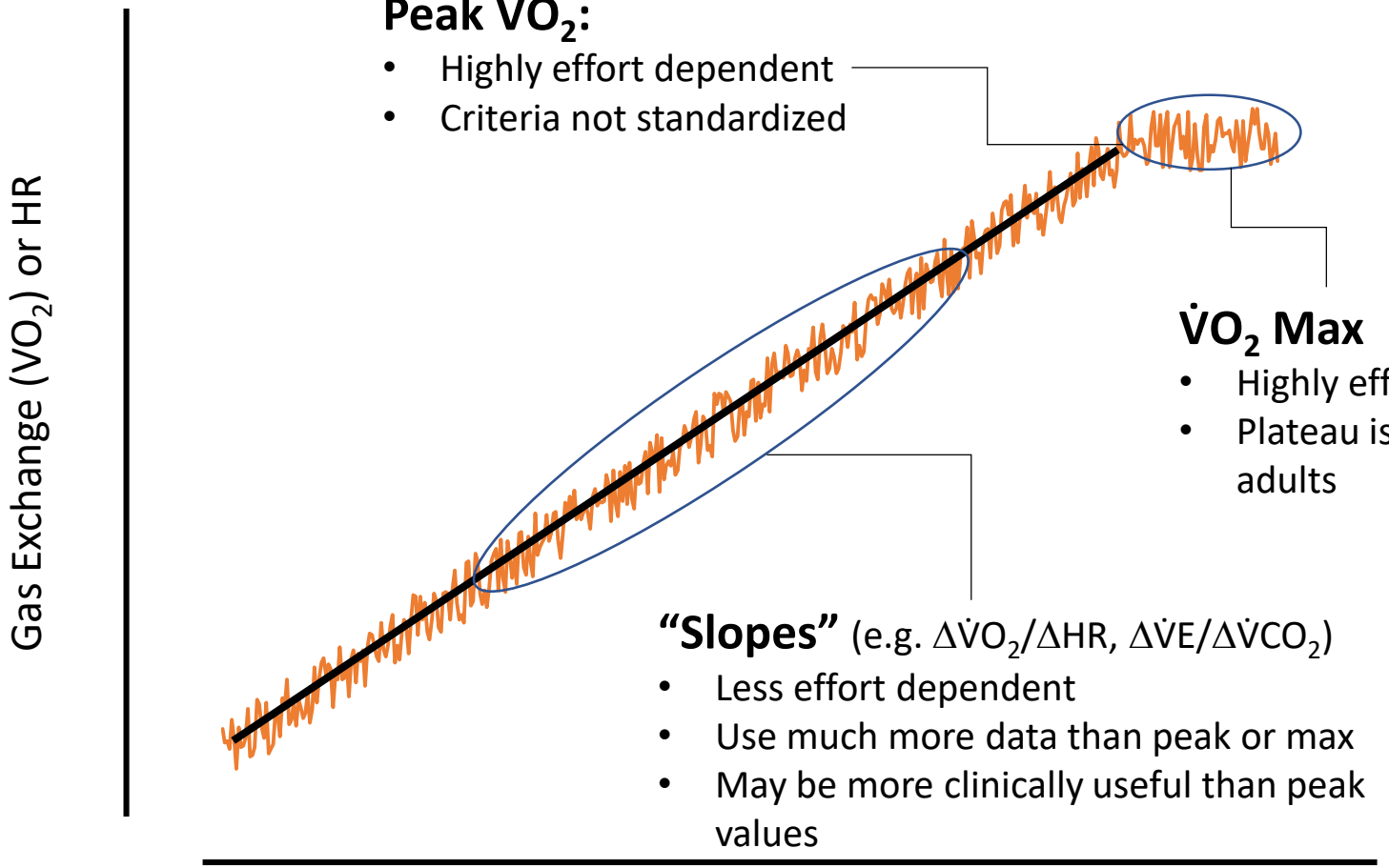
- Heart disease
  - Coronary
  - Myocardial
  - Valvular
- Anemia

- Thromboemboli
- Vasculitis
- Pulmonary hypertension

- Obstruction
- Restriction
- Chestwall
- Infiltrative

Airway → Lower / Upper

Cardiopulmonary testing



Peak $\dot{V}O_2$:

- Highly effort dependent
- Criteria not standardized

$\dot{V}O_2$ Max

- Highly effort dependent
- Plateau is uncommon in children and adults

"Slopes" (e.g. $\Delta\dot{V}O_2/\Delta HR$, $\Delta\dot{V}E/\Delta\dot{V}CO_2$)

- Less effort dependent
- Use much more data than peak or max
- May be more clinically useful than peak values

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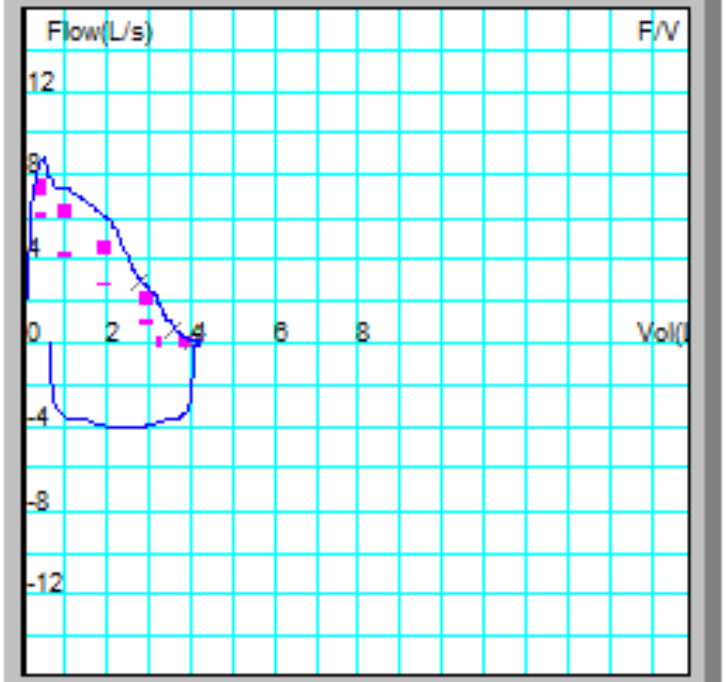
Results

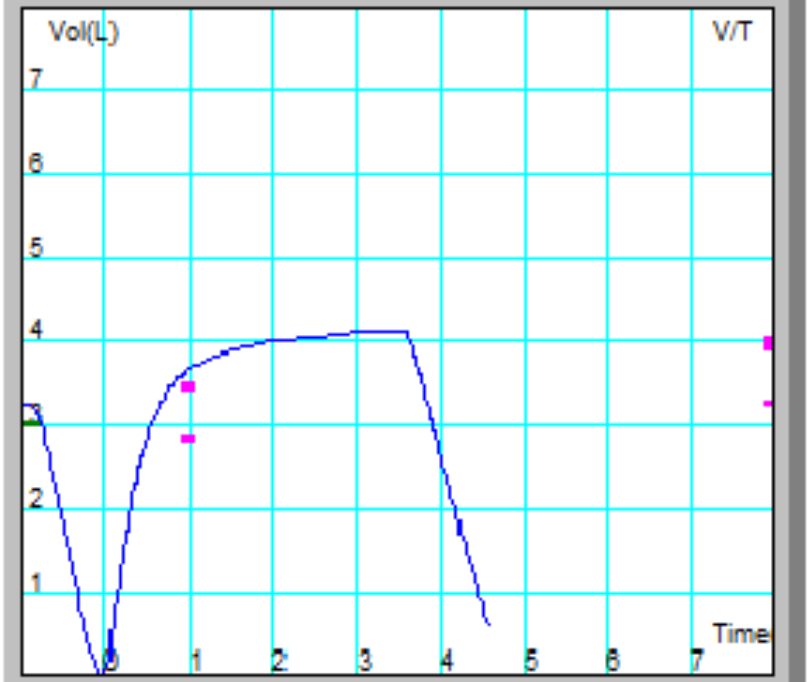
Result	Pred	Best	%Prd	2nd	%Prd	3rd	%Prd
FVC (L)	3.95	4.13	105%	4.14	105%	3.99	101%
FEV1 (L)	3.44	3.67	107%	3.62	105%	3.60	105%
FEV1/FVC	0.82	0.89	108%	0.87	106%	0.90	110%
FEF25-75% (L/s)	3.93	4.74	121%	4.31	110%	4.64	118%
PEFR (L/s)	7.47	8.81	118%	8.64	116%	8.67	116%
Vext %	---	1.19	---	1.38	---	1.32	---

Usability cautions:
Acceptability cautions: Time Time Time
Reproducibility cautions:

FVC Flow vs. Volume



FVC Volume vs. Time



Data Interoperability in exercise tests

- Many Ergometers
- Many protocols

Introduction

- Different ergometers can produce different physiological responses (e.g., VO_2 max)
- Cardiopulmonary exercise testing **(CPET)** data must be **scaled** to the magnitude of the metabolic perturbation (**WR**)
- The two most commonly used CPET devices are **cycle ergometer** and **treadmill**

Cycle ergometer

Advantages

- **Accurate external WR**
- Stability of the upper torso
- Gait/balance/obesity/orthopedic

Disadvantages

- Less common activity
- Cooperation dependent (rpm)

Treadmill

Advantages:

- Commonly used
- Walking/running are more typical activity

Disadvantages:

- **No accurate external WR**

CPET interoperability

- No standardized approach to ensure data interoperability between different CPET ergometers

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Directly measured
(both modalities)
- $\dot{V}O_2$peak
- $\Delta\dot{V}E/\Delta VCO_2$
- $\Delta\dot{V}O_2/\Delta HR$
- Recovery kinetics

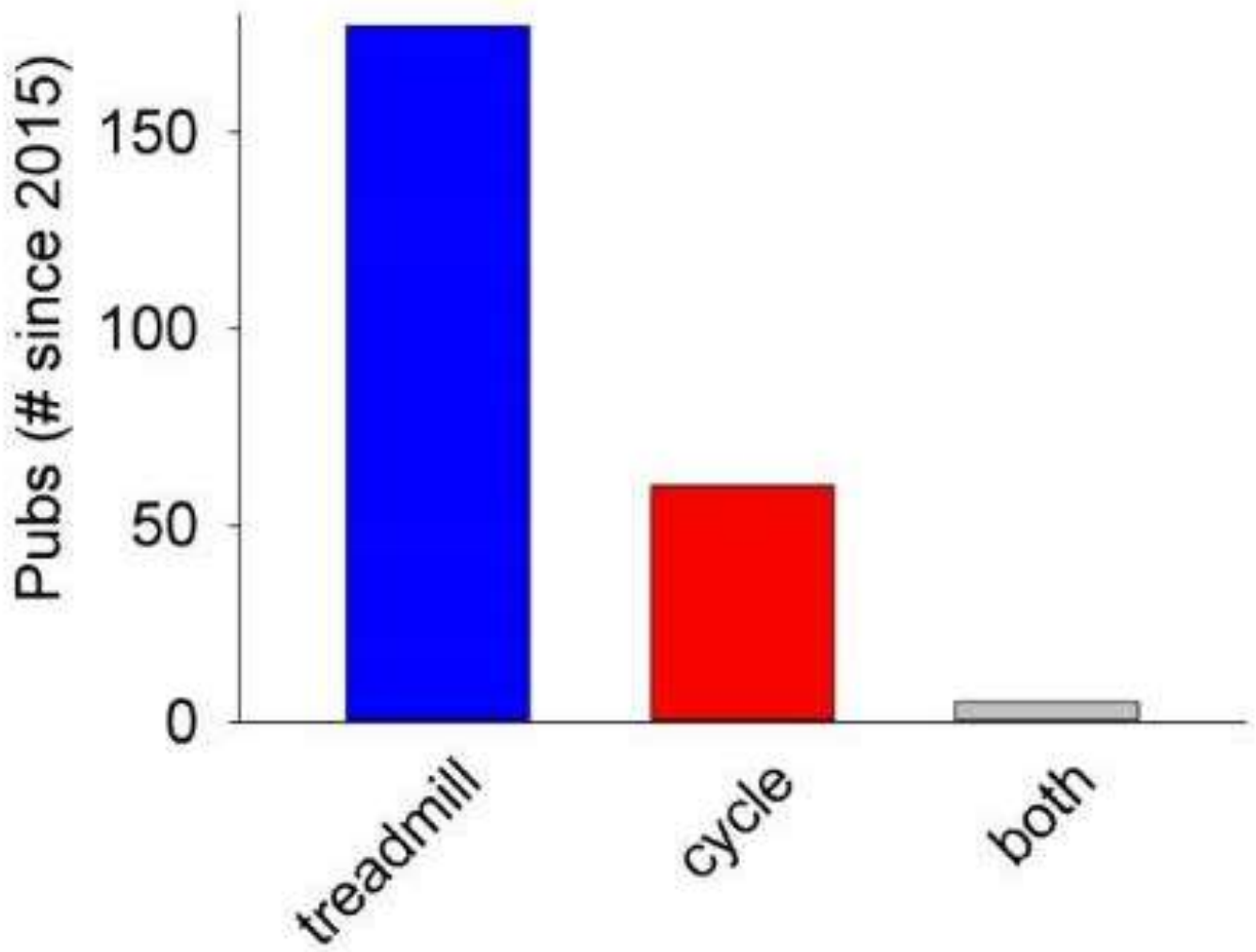
Cycle Ergometer

Treadmill

Directly measured
(cycle ergometer)
- $\Delta\dot{V}O_{2CE}/\Delta WR_{CE}$
- $\Delta HR_{CE}/\Delta WR_{CE}$

Indirectly measured
(estimated from V•I•m)
- $\Delta\dot{V}O_{2TM}/\Delta WR'_{TM}$
- $\Delta HR_{TM}/\Delta WR'_{TM}$

PubMED search: CPET and Modality in Children and Adolescents



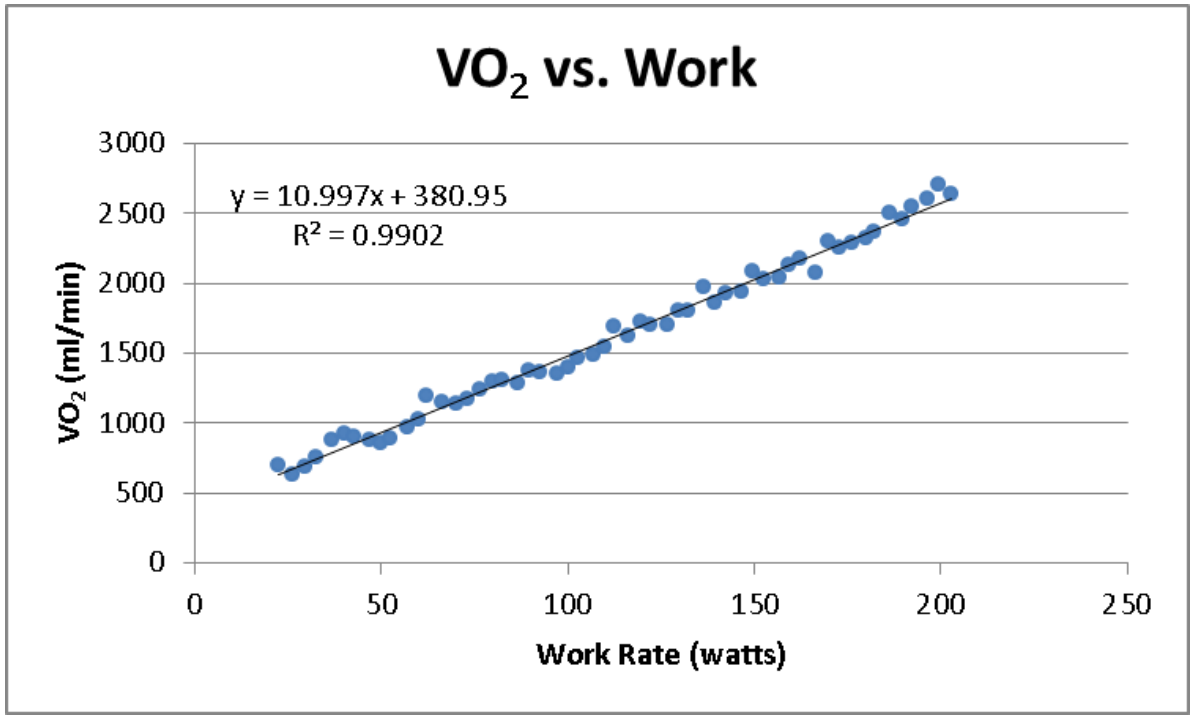
Goal

- To compare CE and TM exercise data
- To estimate WR_{TM} (WR') associated with TM exercise* in early and late pubertal children

* **VIM** = Velocity ,Incline ,Body Mass

Our strategy

Step 1: Cycle ergometer to solve the linear equation $\dot{V}O_2 = a \cdot WR + b$ for each participant



13 y/o boy

Step 2: Back calculate treadmill work (WR')

Assuming the same relationship (VO_2/WR) for TM

$$VO_2 = a \cdot WR + b$$

$$WR' = (VO_2' - b)/a$$

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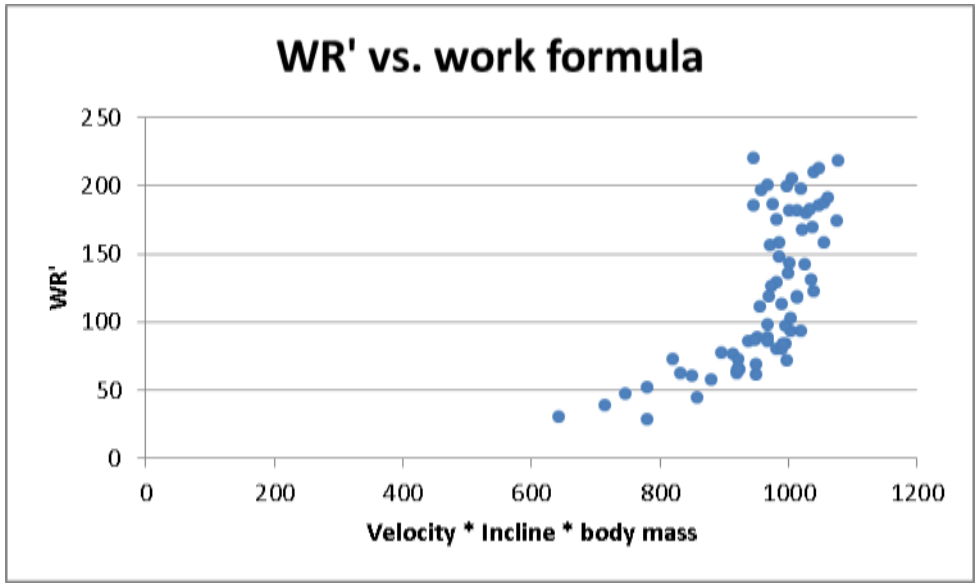
WR=(f)VIM

(Velocity, Incline, Body Mass)



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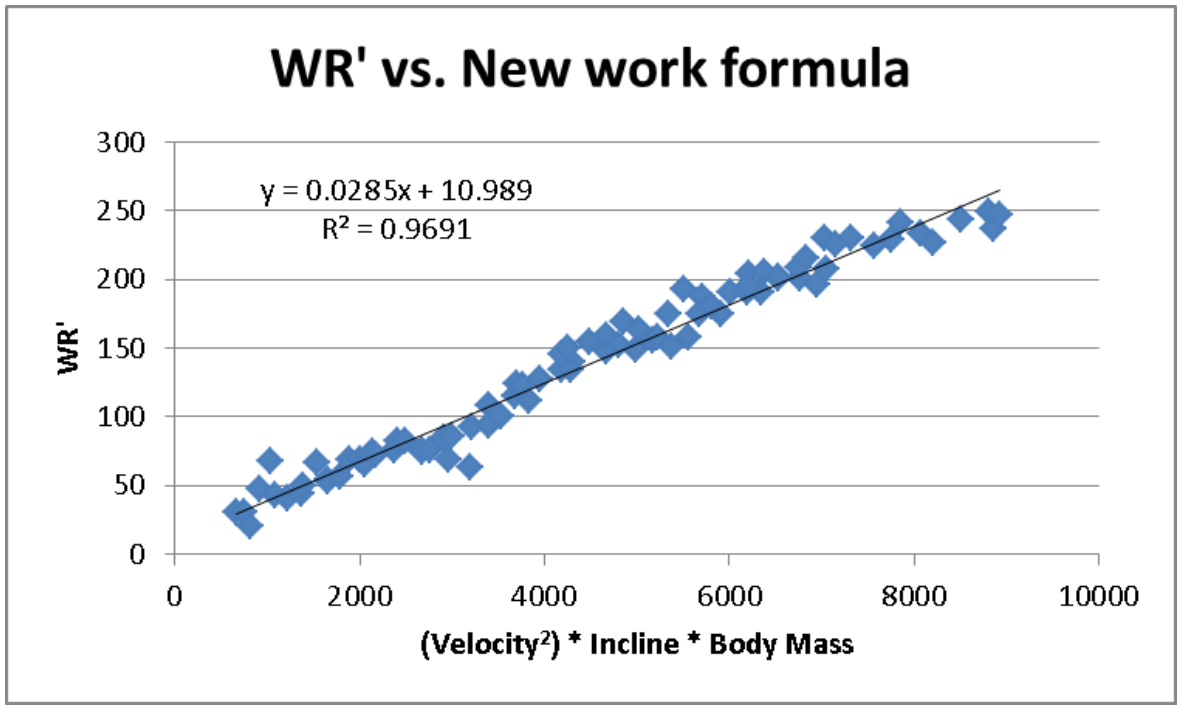
$WR' = (f)V^2IM$

$\frac{1}{2} MV^2$



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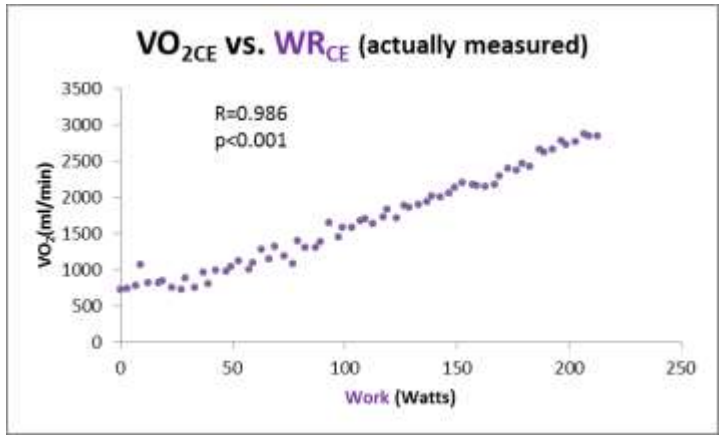
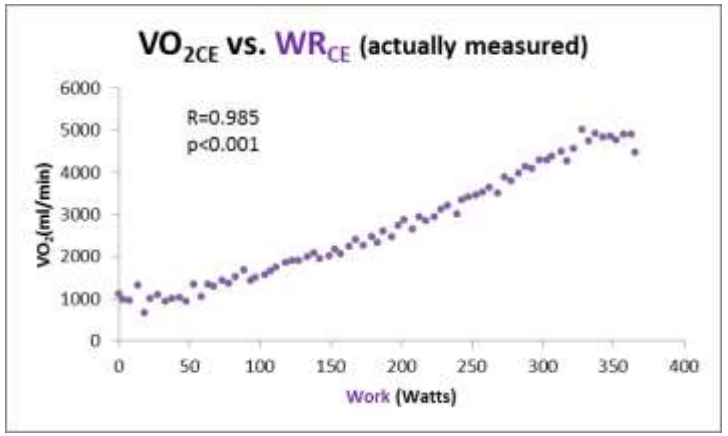
12 y/o Boy

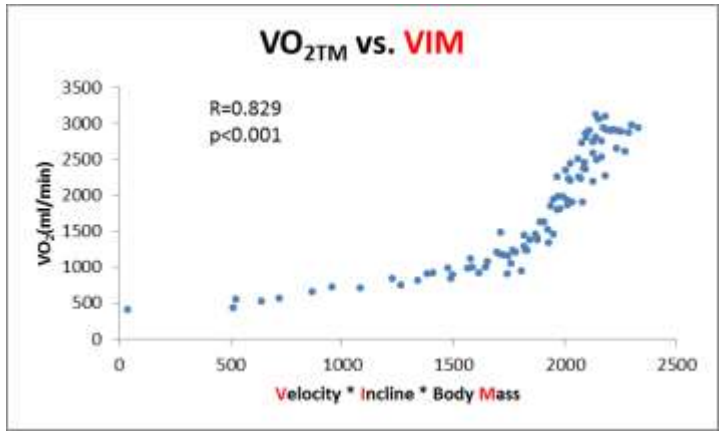
17 y/o Boy

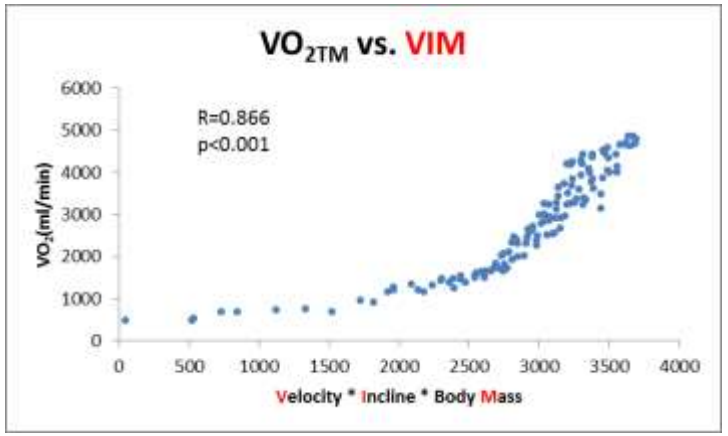
CE



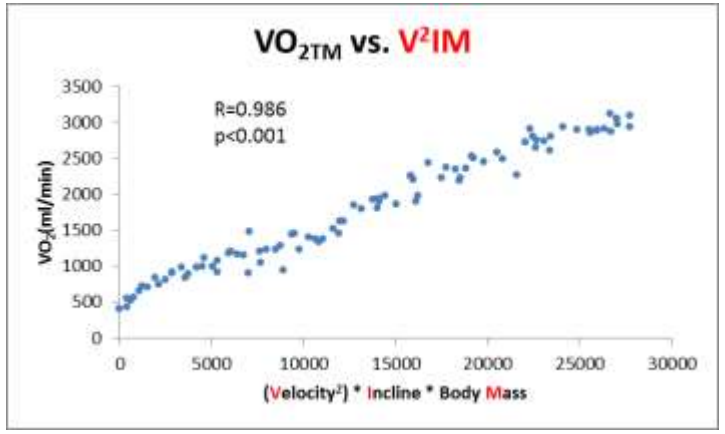


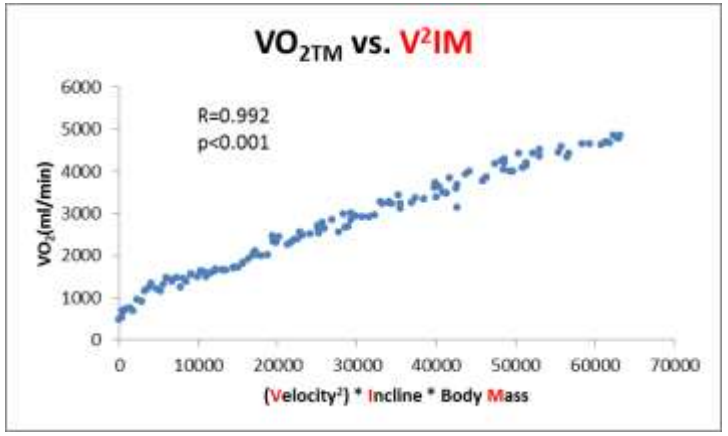
TM





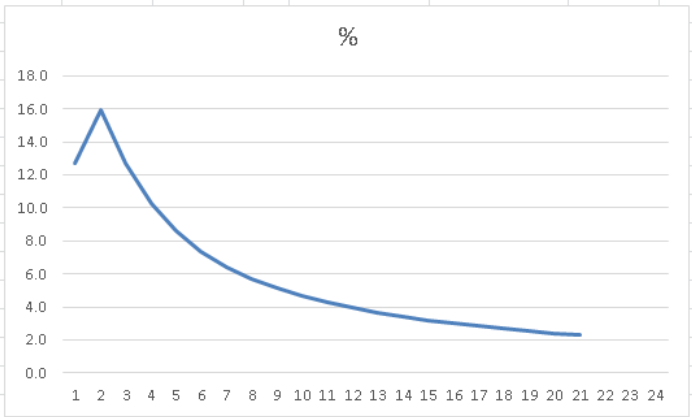
TM

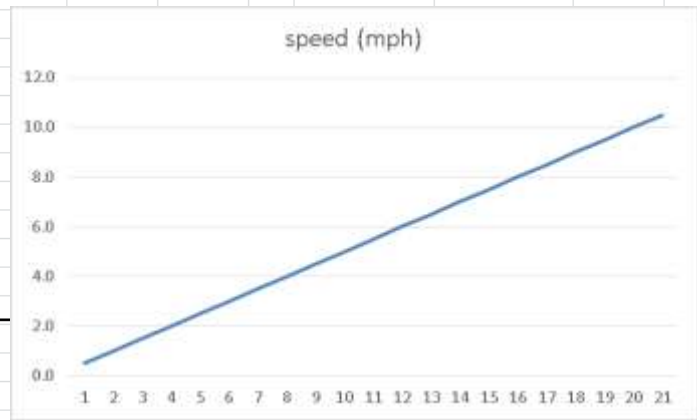




Personalize protocol

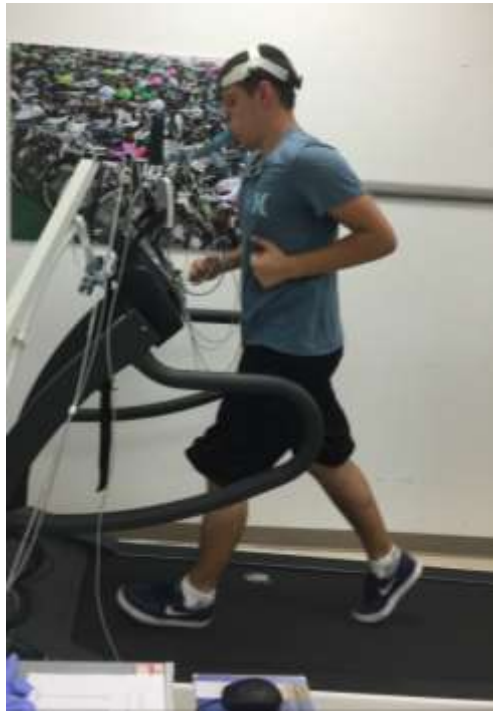
	A	B	C	D	E	F	G	H	I
1			Step #	Watt	%	speed (m/sec)	speed (mph)	alpha(rads)	speed (km/h)
2	start speed	0.5	0	5	12.7	0.22	0.5	0.2211884	0.8
3	end speed	10.5	1	25	15.9	0.45	1.0	0.2777957	1.6
4	step-size	0.5	2	45	12.7	0.67	1.5	0.2211884	2.4
5	weight	46.5	3	65	10.3	0.89	2.0	0.1792115	3.2
6	v exponent	2	4	85	8.6	1.12	2.5	0.1497437	4.0
7			5	105	7.4	1.34	3.0	0.1283290	4.8
8			6	125	6.4	1.56	3.5	0.1121683	5.6
9			7	145	5.7	1.79	4.0	0.0995752	6.4
10			8	165	5.1	2.01	4.5	0.0895002	7.2
11			9	185	4.7	2.24	5.0	0.0812634	8.0
12	GK-077-WiT		10	205	4.3	2.46	5.5	0.0744071	8.9
13			11	225	3.9	2.68	6.0	0.0686130	9.7
14			12	245	3.6	2.91	6.5	0.0636529	10.5
15			13	265	3.4	3.13	7.0	0.0593595	11.3
16			14	285	3.2	3.35	7.5	0.0556073	12.1
17			15	305	3.0	3.58	8.0	0.0523002	12.9
18			16	325	2.8	3.80	8.5	0.0493636	13.7
19			17	345	2.7	4.02	9.0	0.0467388	14.5
20			18	365	2.5	4.25	9.5	0.0443786	15.3
21			19	385	2.4	4.47	10.0	0.0422450	16.1
22			20	405	2.3	4.69	10.5	0.0403069	16.9
23									
24									
25									
26	Rest - 2 minutes								
27									
28	Warm up - 1 minute (0.5 mph)							**Jogging speed:** _____	
29									
30	Exercise - 20 w/min (as visit 1)								
31									
32	Recovery - 2 minutes (2 mph)							**Date of visit:** _____	
33									
34									
35									





Step 3

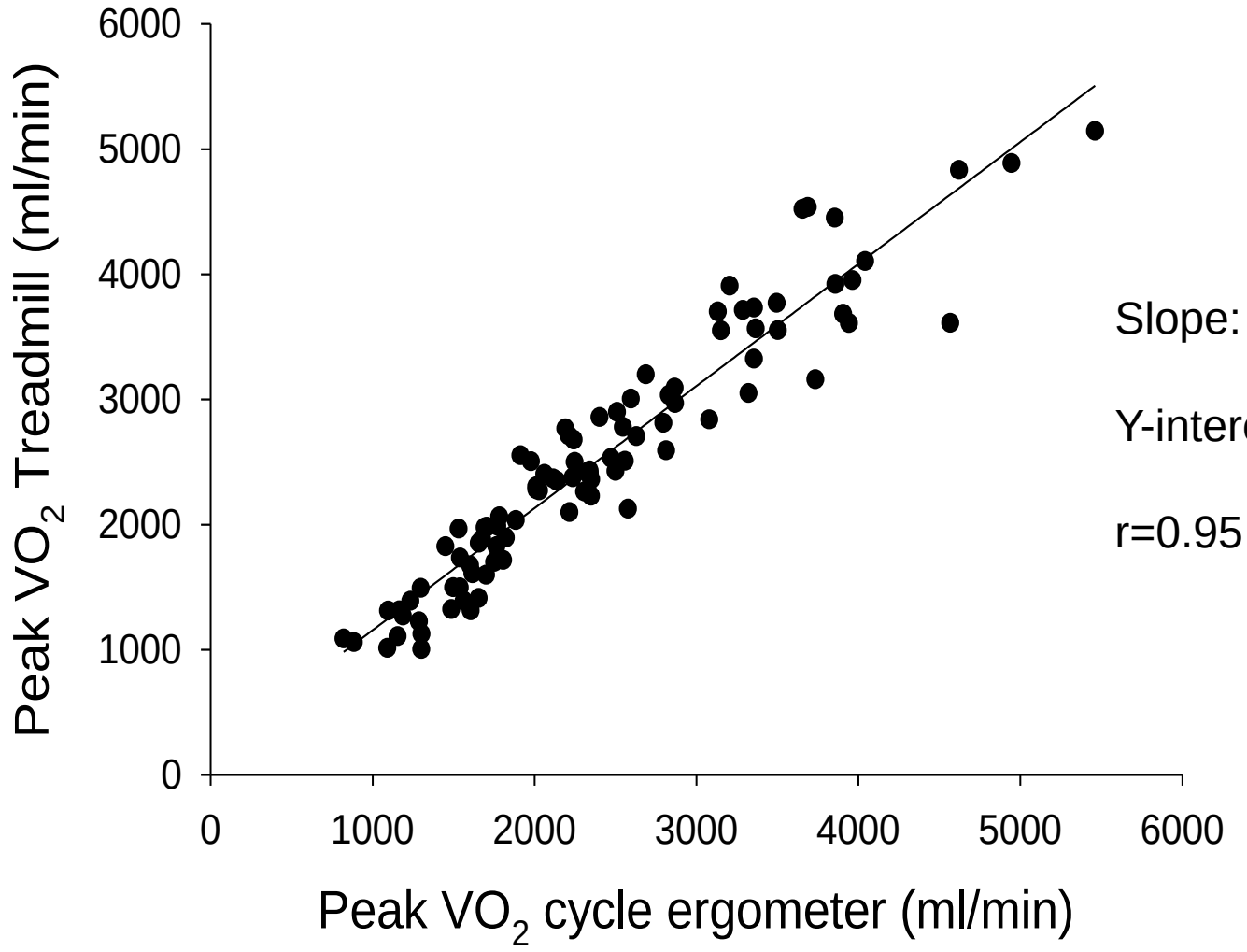
- Explore differences between early pubertal (tanner 1-3) and late pubertal children (tanner 4-5)



Results

	Total n=94	Early boys n=18	Early girls n=16	Late boys n=18	Late girls n=23	Male adults n=8	Female adults n=11
Age (yr) (Mean±SD)	16.1±6.8	10.8±1.7	8.8±1.1	16.9±1.4	15.5±1.8	29.0±2.3	26.3±4.6
Tanner score (Q) (Mean±SD)	N/A	1.4±0.5	1.3±0.4	4.4±0.5	4.3±0.5	N/A	N/A
Height (cm) (Mean±SD)	156.7±17.3	144.0±11.8	132.1±9.4	172.4±7.0	161.4±6.0	178.8±9.0	161.8±4.8
Total body mass (kg) (Mean±SD)	51.1±17.3	37.4±12.0	29.7±8.0	62.4±9.4	54.8±8.4	79.5±8.3	58.1±7.6
Lean body mass (kg) (Mean±SD)	35.3±13.2	25.2±6.5	19.0±3.8	47.3±6.5	35.4±4.6	59.5±7.0	38.4±5.0
% Body fat (Mean±SD)	28.7±6.9	29.0±5.9	32.6±5.6	21.3±5.0	32.6±5.2	22.5±5.2	31.2±4.3
BMI (Mean±SD)	20.0±3.5	17.5±3.0	16.7±2.4	17.2±3.3	20.9±2.2	24.9±1.9	22.1±2.3
BMI% (Mean±SD)	N/A	47.3±30.7	49.4±29.0	49.9±29.4	43.1±23.5	N/A	N/A
Ethnicity (Hispanic or Latino)	4/100	0/ 18	1/16	1/18	2/23	0/8	0/11
Race (White/Asian/African-American)	65/26/3	16/1/1	13/2/1	8/10/0	16/7/0	5/3/0	7/3/1

Peak VO_2 values

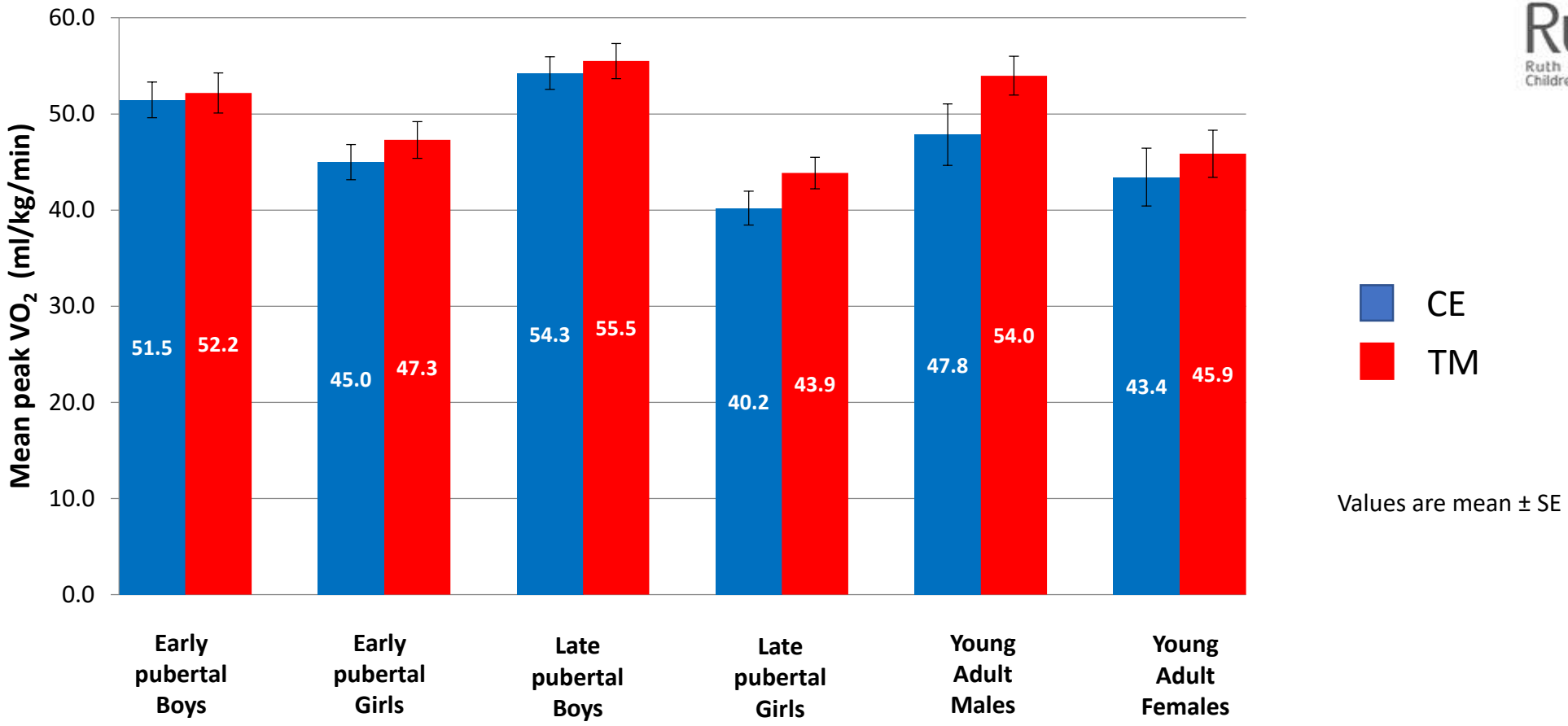


Slope: 0.975±0.0316, p<0.0001

Y-intercept, 182.81±81.87 ml O_2/min, p=0.028

r=0.95

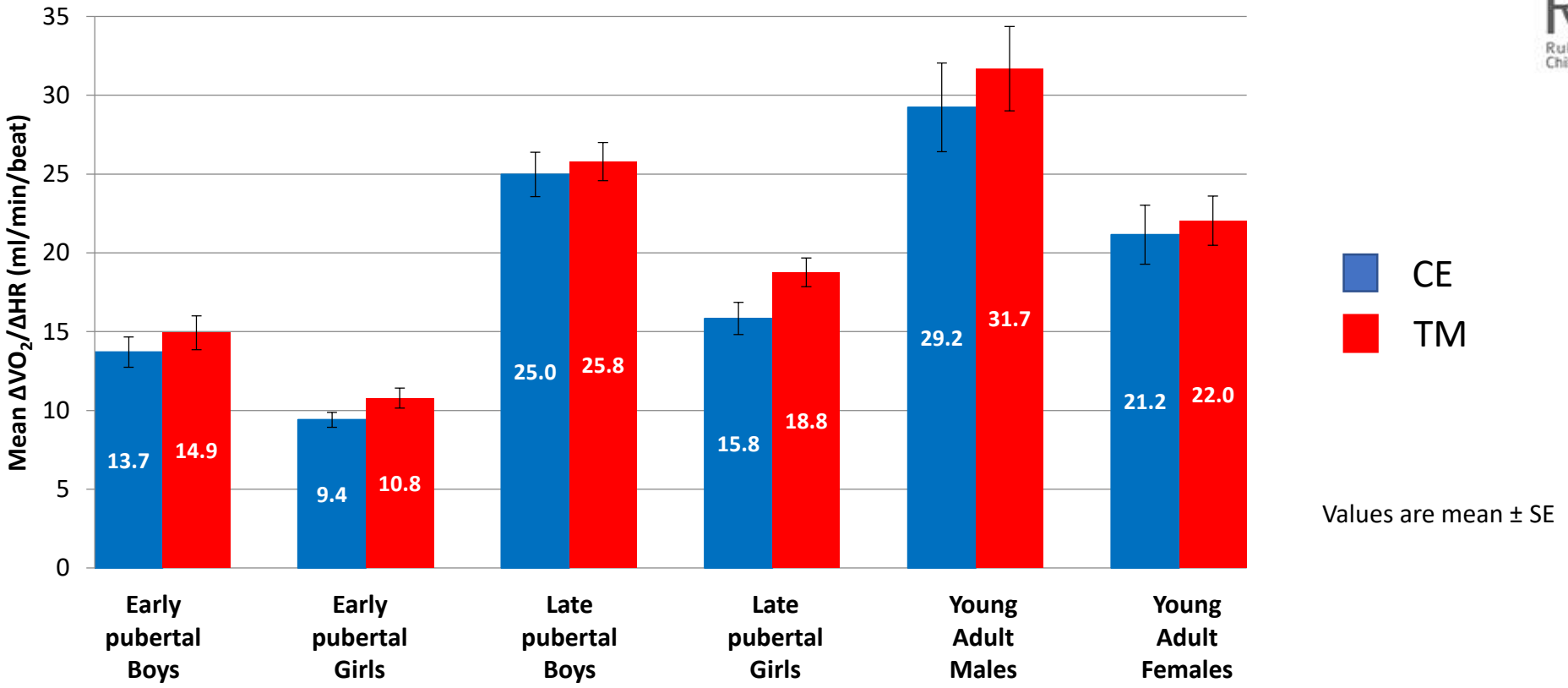
Mean peak VO_2 CE vs. Peak VO_2 TM



Values are mean ± SE

- Overall, a small but significant higher mean peak VO_2 difference (2.77±1.23 ml/kg/min) was found in TM vs. CE (p=0.0266)
- Within the subgroups there was no significant difference between CE and TM
- Males had higher peak VO_2 than females at all puberty levels
- Late pubertal females had the lowest mean values, statistically significant only from early puberty group

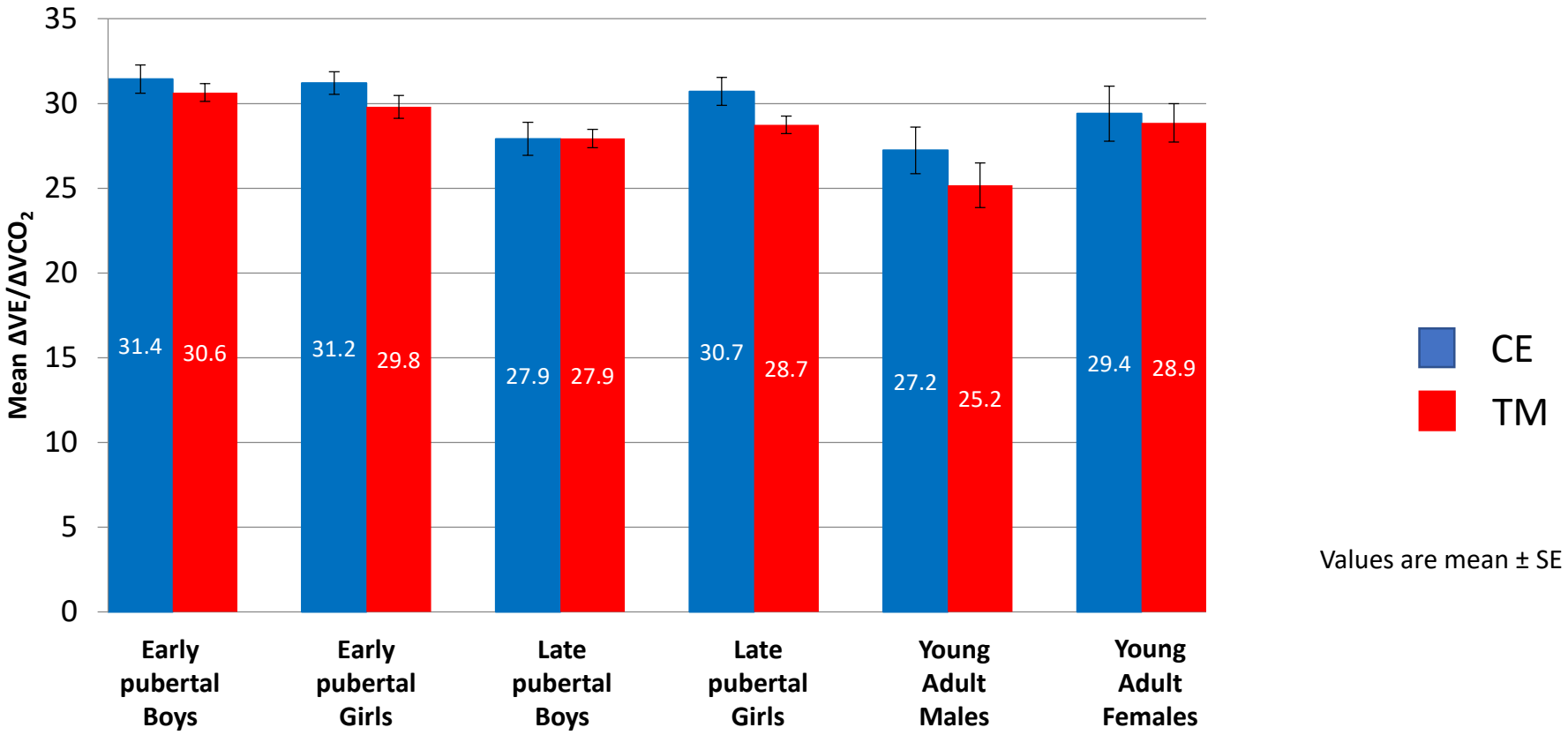
Mean $\Delta VO_2/\Delta HR$: CE vs TM



Values are mean ± SE

- Overall, a very small but significant higher mean peak $\Delta VO_2/\Delta HR$ difference (1.6 ml/min/beat) was found in TM vs. CE (p=0.04) (Figure 4).
- Highly significant maturation dependent differences in both boys and girls, as expected, mean $\Delta VO_2/\Delta HR$ increased with puberty

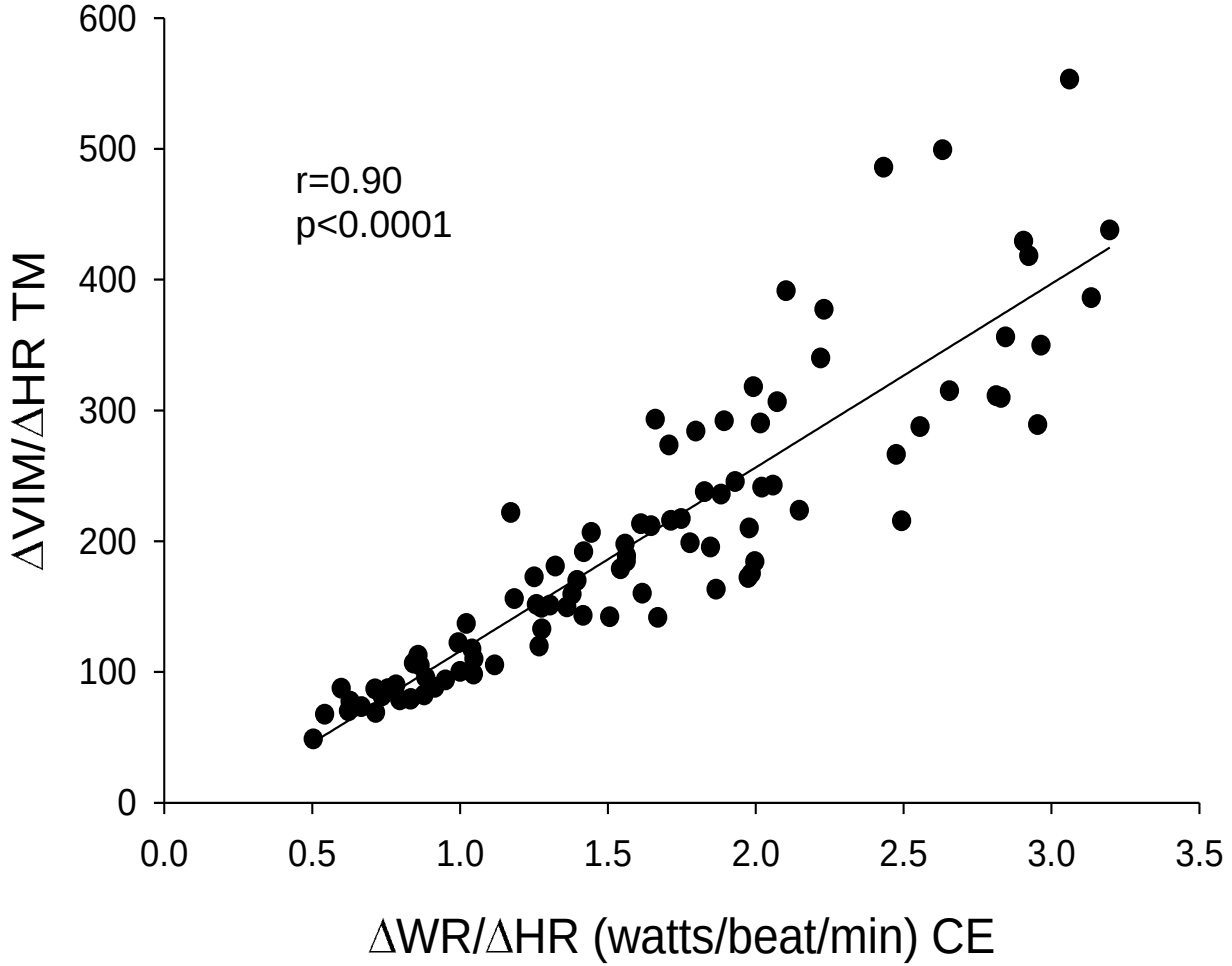
Mean $\Delta VE/\Delta VCO_2$: CE vs TM



Values are mean ± SE

- Overall, a small but significant higher mean $\Delta VE/\Delta VCO_2$ difference (1.151) was found in CE vs. TM (p=0.0317)
- In the boys, the values tend to be significantly grater in the younger compared to the older children

Interoperability of WR–HR slopes

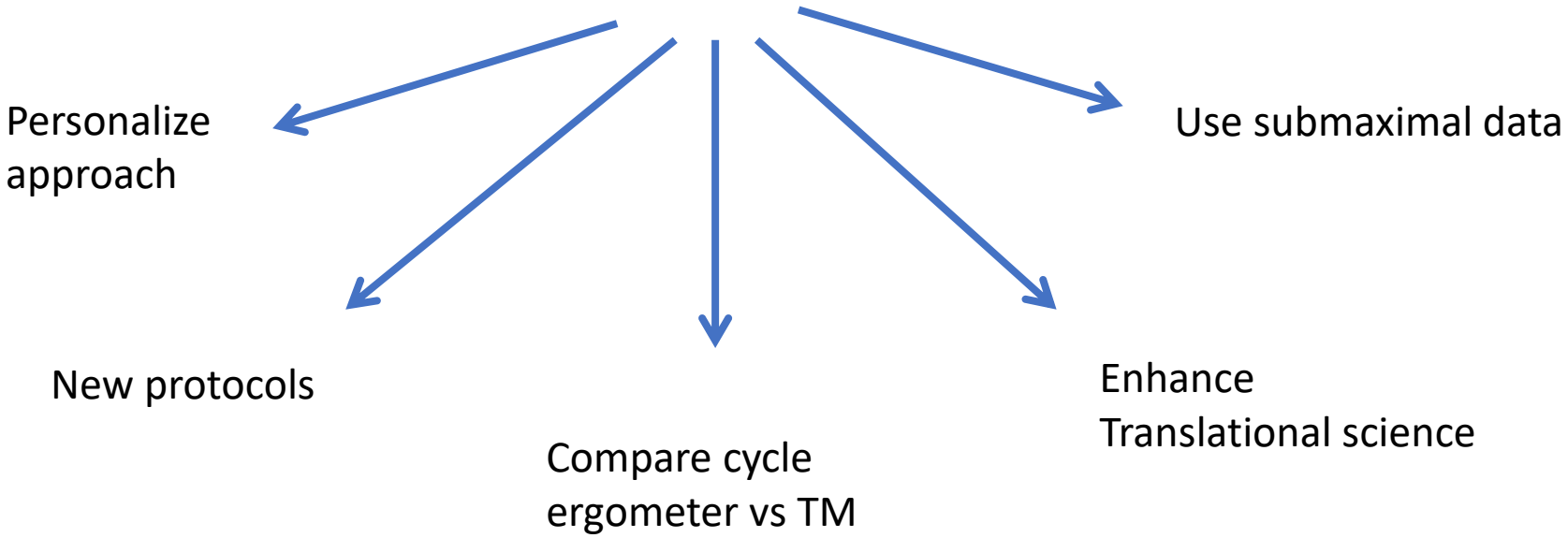


ΔVIM/ΔHR (TM) = 140.4 x ΔWR/ΔHR (CE) – 24.5

Discussion

Demand for assessment of physical fitness during childhood is increasing (e.g., childhood obesity, congenital heart disease, malignancy survivors, cystic fibrosis)

WR' knowledge



Discussion and Future Directions

- WR'_{TM} is a linear function of V^2, consistent with the standard equation for kinetic energy ($W=½MV^2$)
- Although significant, the difference between peak VO_2 TM vs. CE is small (no difference in the pre pubertal group)
- Submaximal gas exchange and heart ($\Delta VO_2/\Delta HR$, VE/VCO_2) differences were also very small
- In addition $\Delta VO_2/\Delta HR$ from both modalities reflected the expected maturational changes in almost identical ways
- Further analysis of our data might facilitate CPET data interoperability between TM and data obtained from other modalities and expand the use of exercise in clinical assessment and research

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Thank you!

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