A genetic disease of the hypoxia-inducible factor pathway alters skeletal muscle metabolism in humans

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The hypoxia-inducible factor (HIF) pathway

(very simplified)

Wang and Semenza,
J Biol Chem 1995

Salceda and Caro,
J Biol Chem 1997

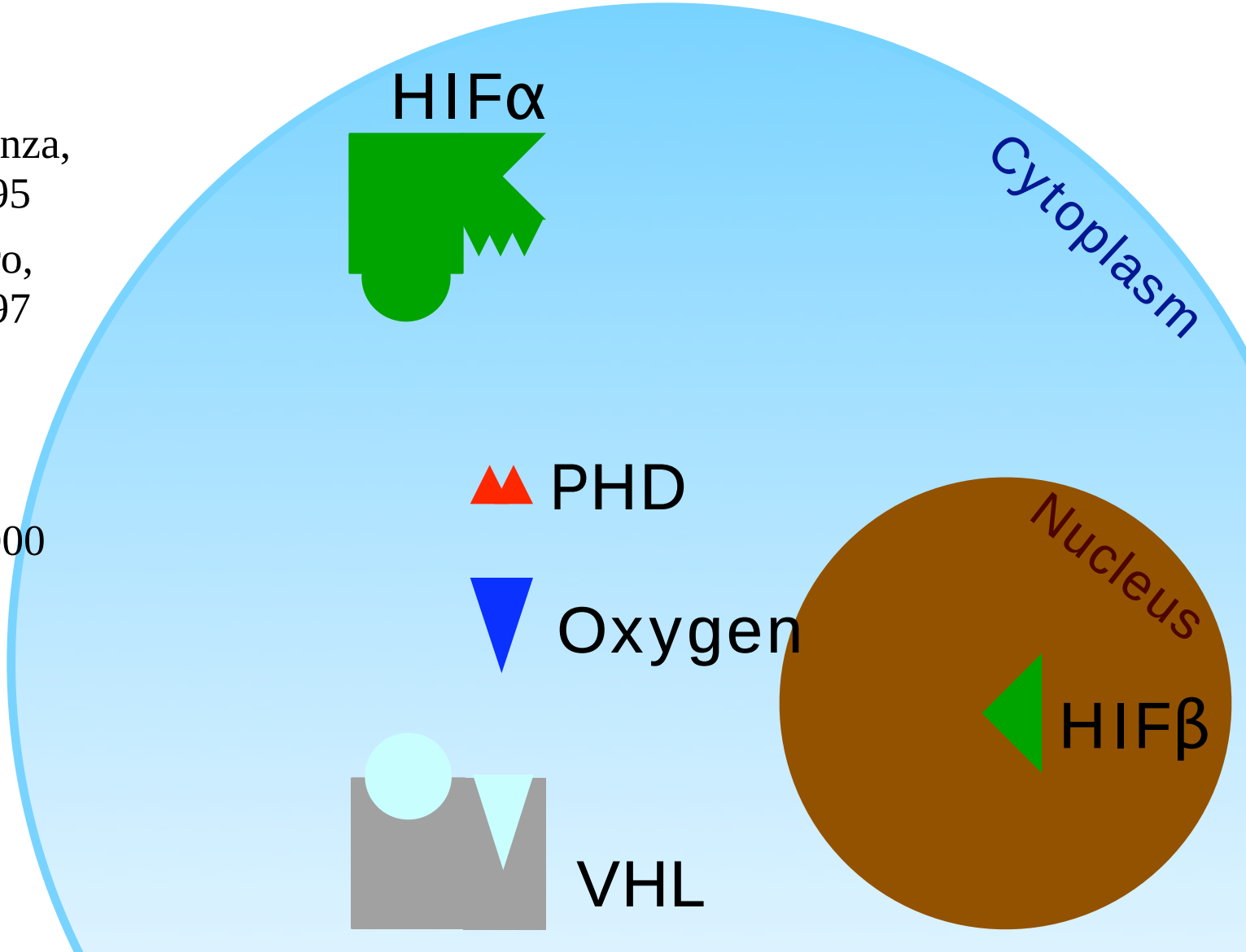
Maxwell et al,
Nature 1999

Ohh et al,
Nat Cell Biol 2000

Jaakkola et al,
Science 2001

Ivan et al,
Science 2001

Epstein et al,
Cell 2001



What does HIF do in hypoxia?

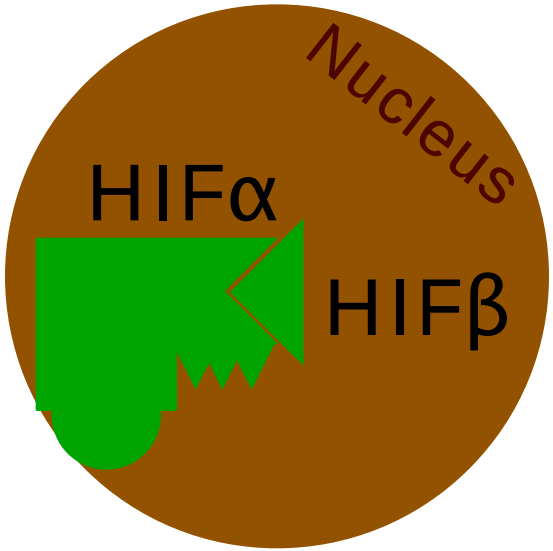
Up-regulation of hypoxia-responsive genes

Hormonal regulation

Angiogenesis

Energy metabolism

...and hundreds more!

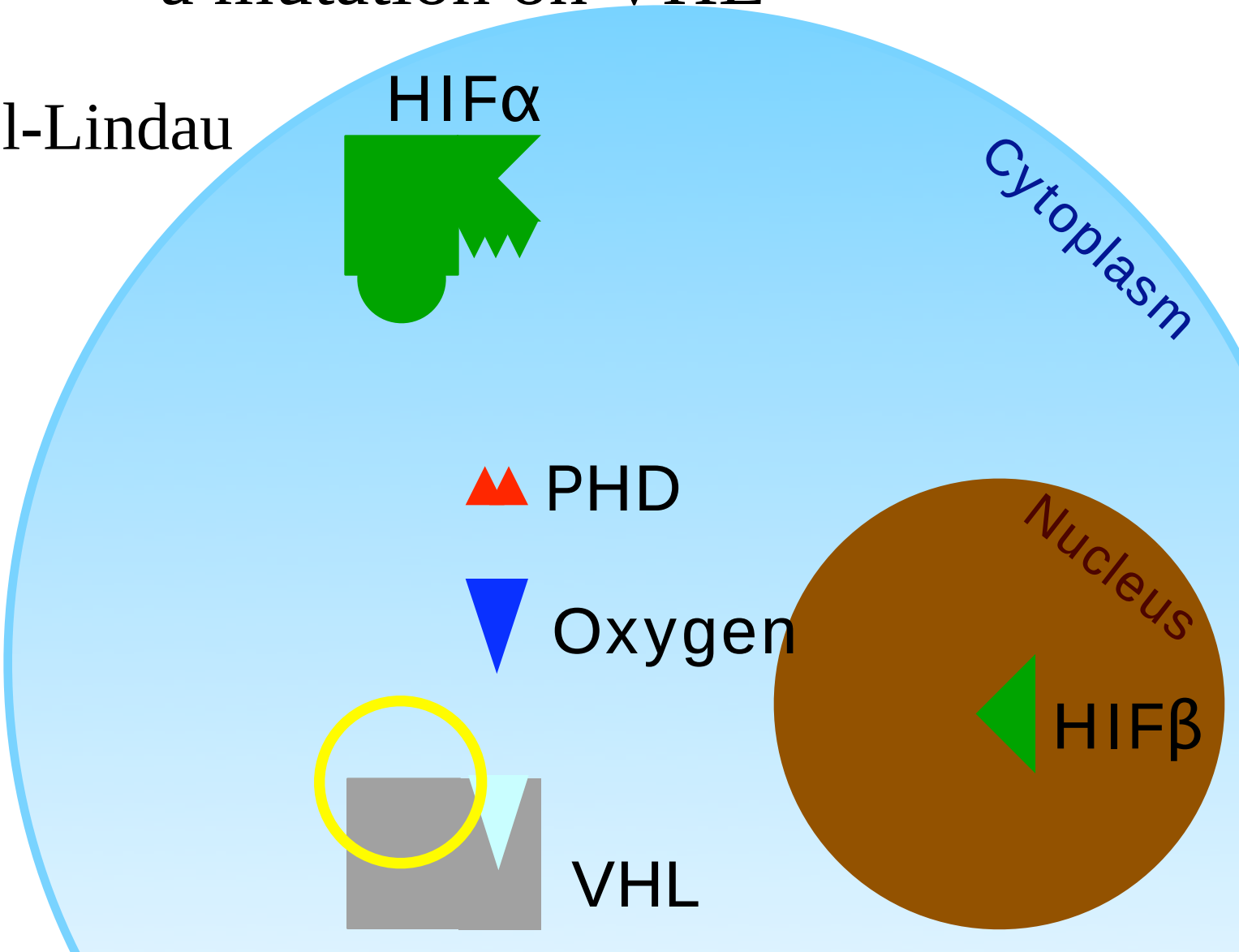


Reviews: Semenza, *Biochem J* 2007; Schofield and Ratcliffe, *Nat Rev Mol Cell Biol* 2004

Chuvash polycythaemia (CP)
a disease of the HIF pathway

Chuvash polycythaemia
a mutation on VHL

von Hippel-Lindau (VHL)



Ang et al,
Nat Genet 2002

Elevated HIF levels and abnormalities observed in CP patients

	CP Patients	Normal Range
Hb (g/dL)	21.8 ± 2.5	12 - 18
Hct (%)	76.5 ± 7.6	37 - 53
RBC ($x10^{-6}/\mu L$)	7.3 ± 0.8	3.8 - 5.9

(Values are average ± standard deviation)

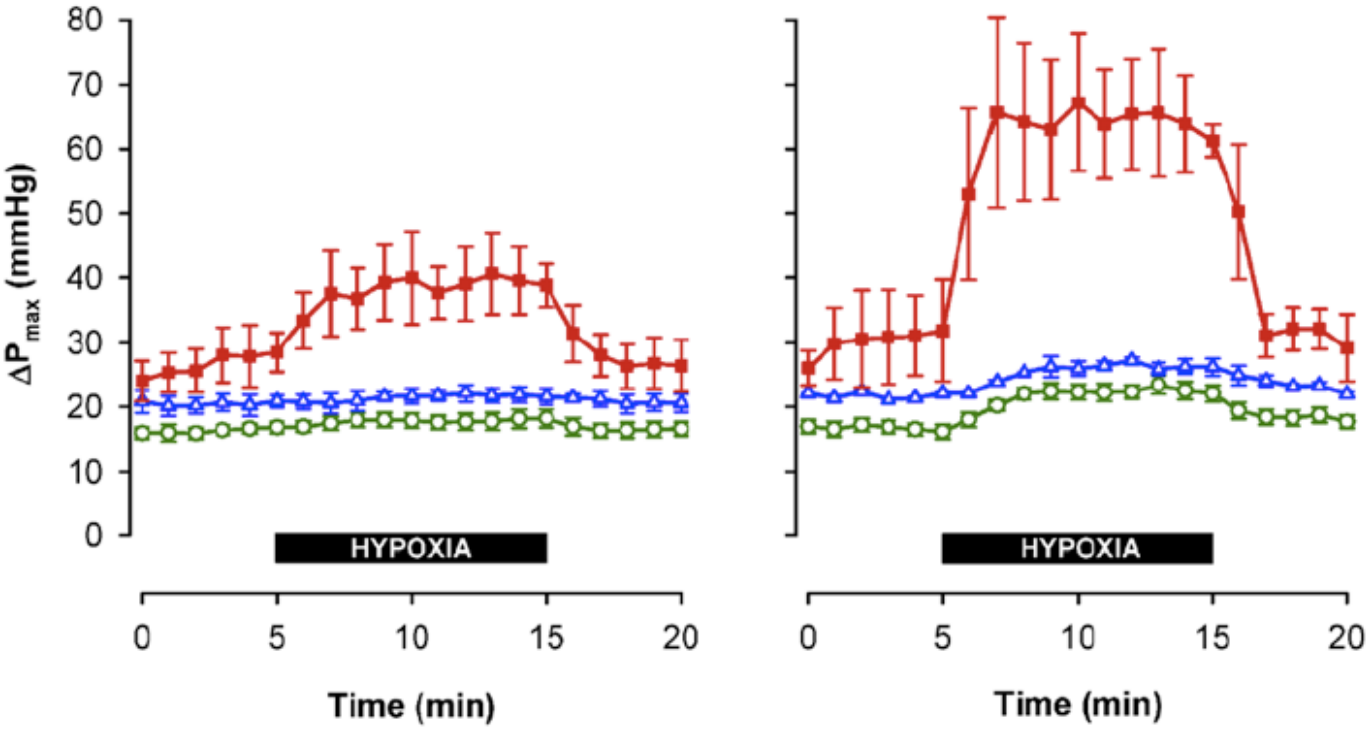
Sergeya et al., *Blood* 1997

Elevated HIF levels and abnormalities observed in CP patients

CP patients

Polyc. patients

Controls



Smith et al., *PLoS Medicine* 2006

Research question

Do mildly elevated levels of HIF, such as in Chuvash polycythaemia, alter:

- physical performance?

- skeletal muscle energy metabolism?

Participants

	CP patients (n = 5)*	Controls (n = 5)*
Age (y)	28 ± 8	32 ± 12
Height (m)	1.67 ± 0.10	1.74 ± 0.09
Weight (kg)	61 ± 6	72 ± 6
BMI (kg m^{-2})	22 ± 2	23 ± 2
Exercise per week (hours)	< 3	< 3

* 3 male and 2 female participants in each group

Skeletal muscle metabolism studied through

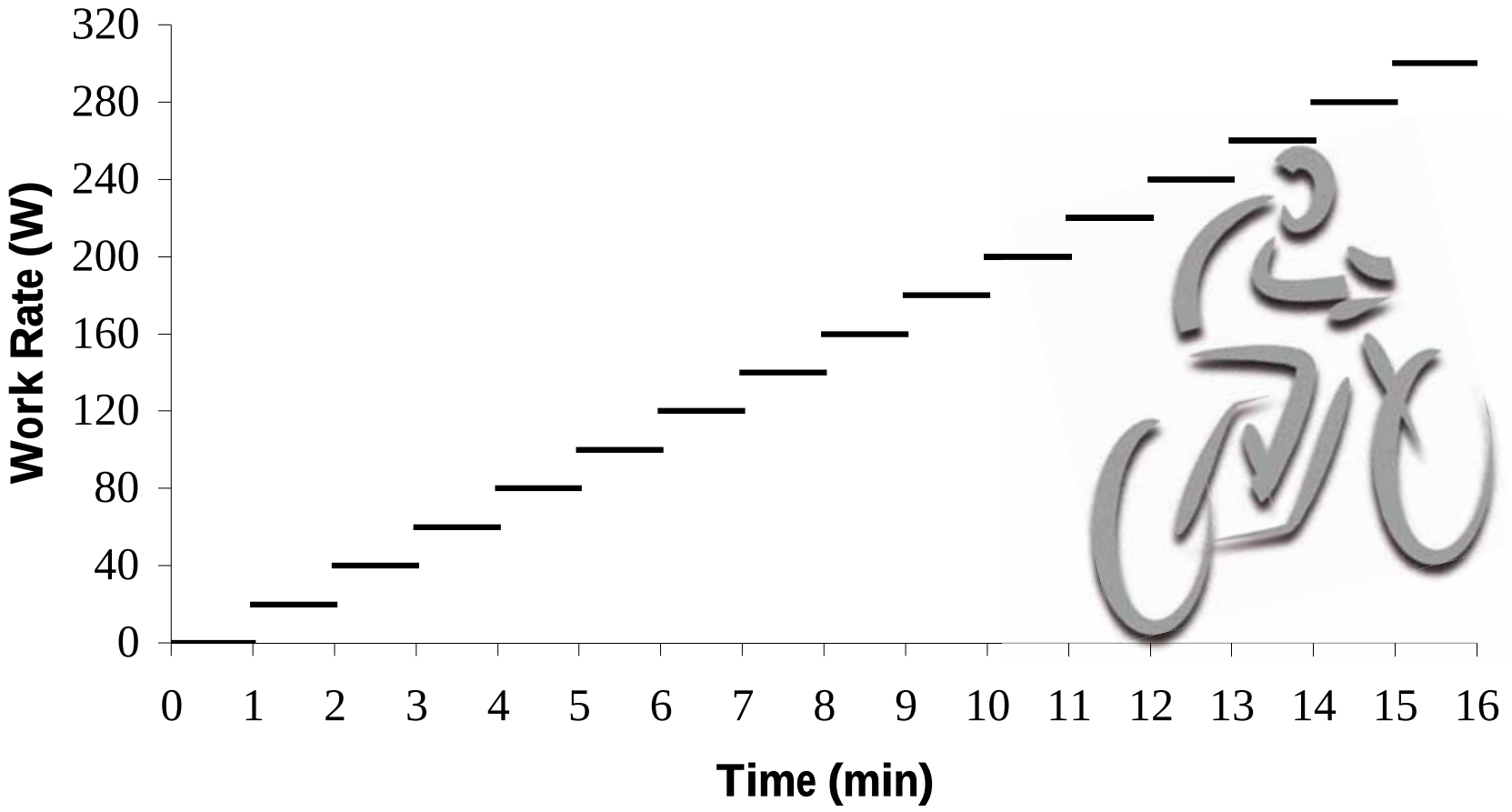
Exercise capacity test

Large muscle mass

Magnetic Resonance Spectroscopy

Small muscle mass

Exercise Capacity Test

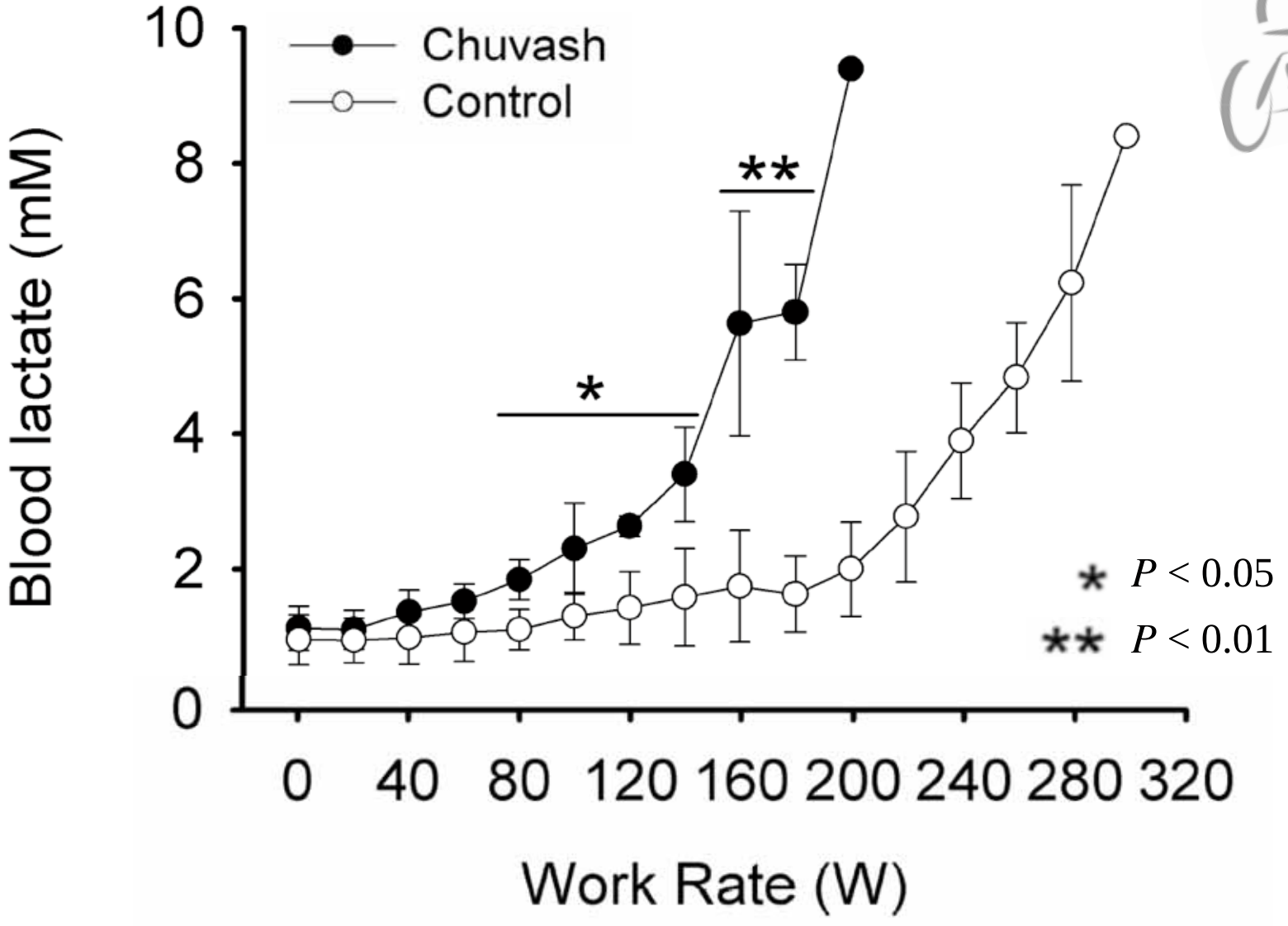


Pedalling frequency: 60 RPM
Measured: Blood Lactate

Limited Exercise Capacity

	Max work rate (W / kg)	Difference	*P* value
Controls	3.4 ± 0.8	-41%	< 0.05
CP patients	2.4 ± 0.9		

Early and Marked Lactate Accumulation



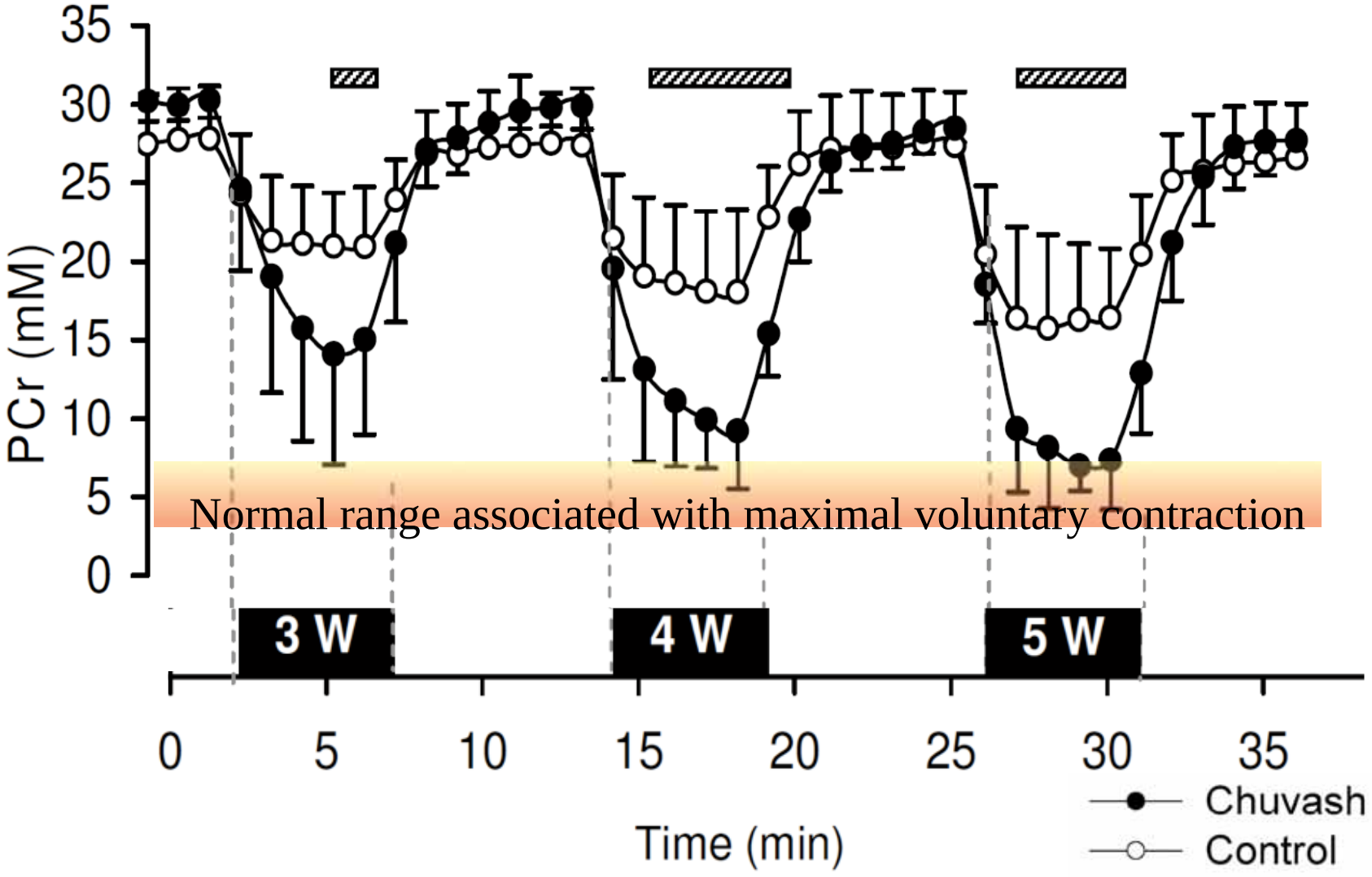
Magnetic Resonance Spectroscopy

Oxford Centre for
Magnetic Resonance

Skeletal muscle energy metabolism investigated using ^{31}P MRS recorded on the calf muscle during three five-minute bouts of plantar-flexion exercise

MRS - Setup

Skeletal Muscle PCr



Summary of Results

Compared with the control group, patients with elevated HIF levels (Chuvash polycythaemia) showed:

In the incremental test

- Limited exercise capacity, with early and marked accumulation of lactate

In calf muscle during light exercise

- abnormal decrease in PCr concentration

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CeBiSM

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