Mechanisms and assessment of cerebral autoregulation in health and disease

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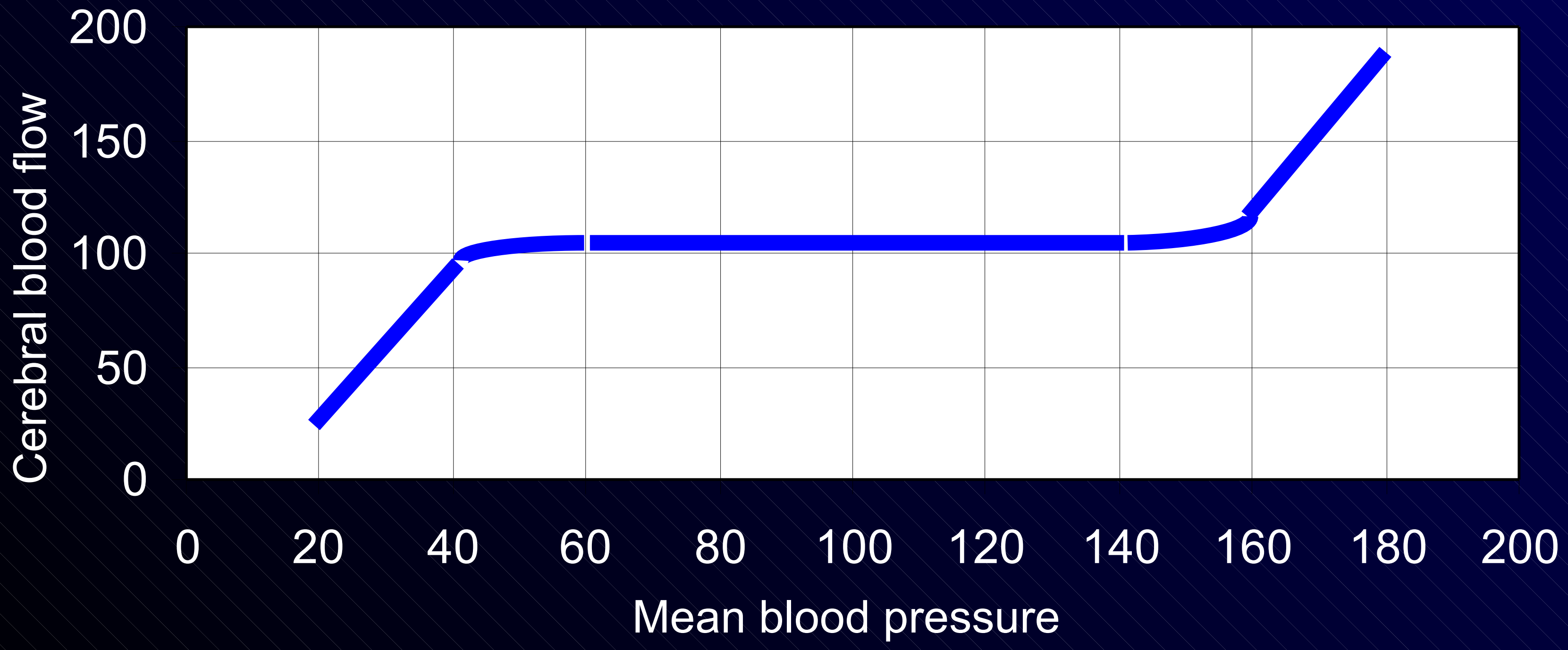
Metabolic demand of the brain

- 2-3% of body weight
- 15% of cardiac output
- 20% of BMR
- 25% of all glucose

Even transient interruption of cerebral blood flow causes loss of consciousness

Cerebral autoregulation

"the intrinsic capacity of cerebral blood vessels to maintain cerebral blood flow constant over a wide range of blood pressures"



Mechanisms of cerebral autoregulation

Not well-established in humans!

LOCAL FACTORS

METABOLIC
Metabolites with vasoactive properties.
- CO_2
- O_2
- K^+
- H^+
- adenosine

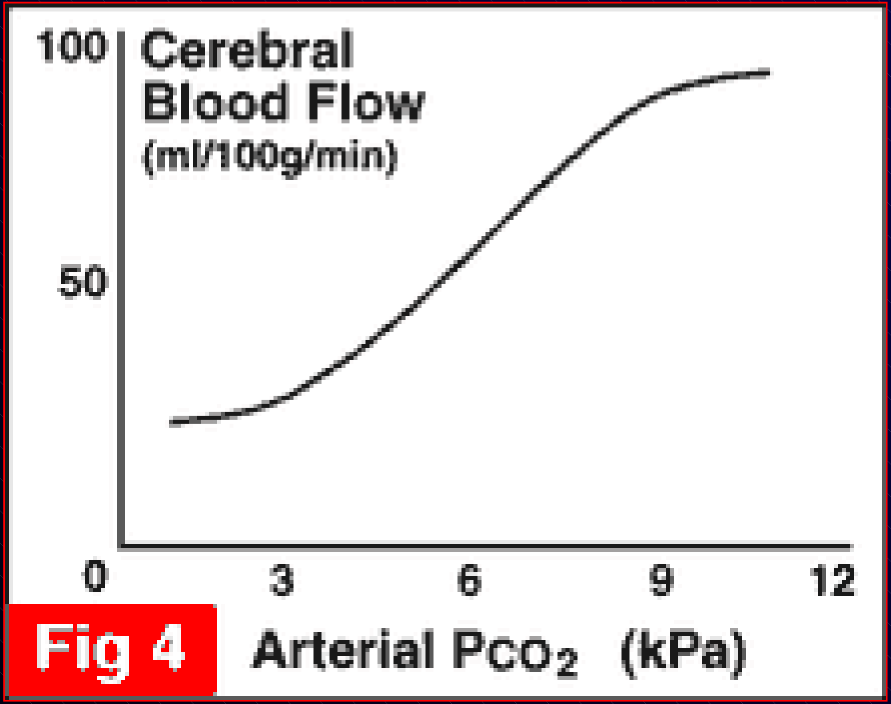
MYOGENIC
- ‘Bayliss effect’

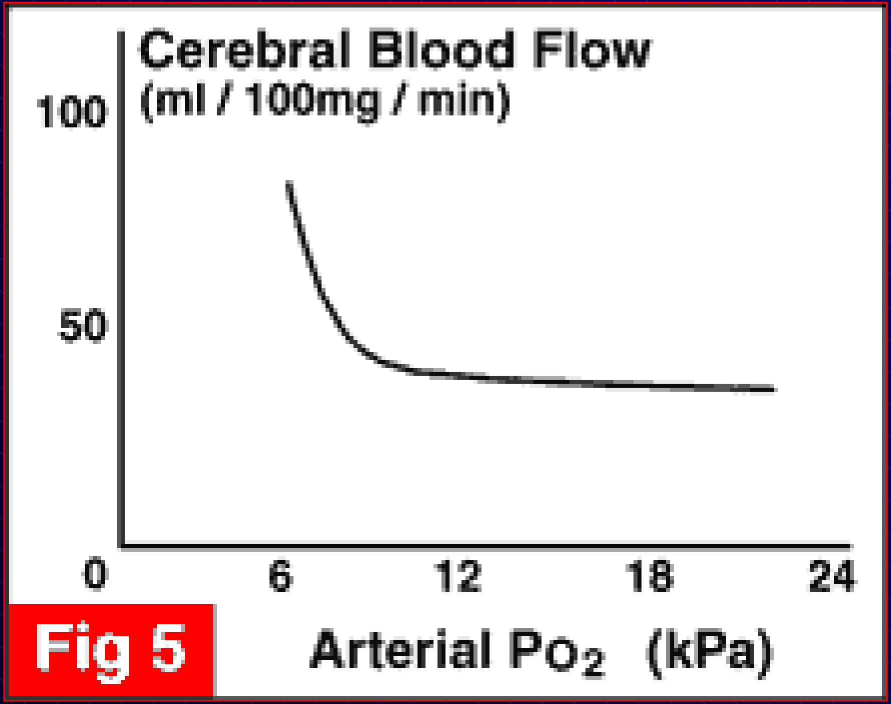
NEURAL CONTROL

Sympathetic Nervous System

Parasympathetic Nervous System

Metabolic influence – hypoxia & hypercapnia





Hypoxia & hypercapnia are potent vasodilators

Myogenic response – the “Bayliss effect”

↑ cerebral perfusion pressure

↓

↑ vessel transmural pressure

↓

↑ smooth muscle length

↓

Activation of smooth muscle tone

↓

↑ resistance

↓

Stabilisation of cerebral blood flow

Role of the sympathetic nervous system in cerebral autoregulation – a controversy

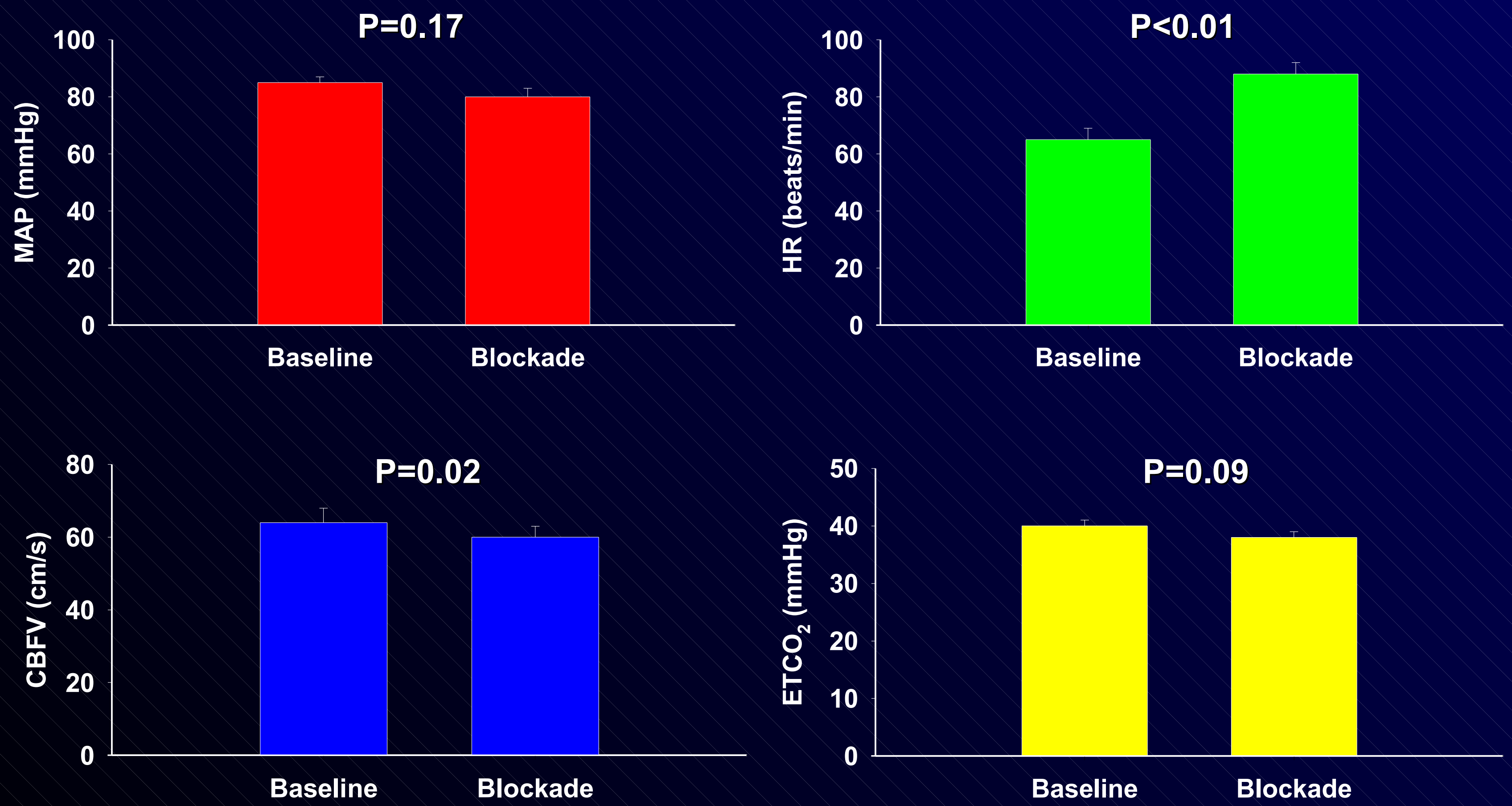
- Cerebral vessels have dense autonomic innervation
- Functional role unclear
- Inconsistent effects of sympathetic stimulation in animal studies
- Parasympathetic stimulation increases CBF in rats

Human studies:

- Situations that increase sympathetic activity (LBNP, head-up tilt, cold pressor test) cause cerebral vasoconstriction
- Some patients with sympathetic failure can tolerate very low BP without losing consciousness (intact autoregulation??)

Effect of ganglionic blockade on cerebral blood flow

Sympathetic and parasympathetic activity blocked with trimethaphan



(*Zhang et al, 2002*)

Cerebral blood flow velocity measurement

Transcranial Doppler

- Cerebral blood flow velocity (CBFV)
- Insonation of middle cerebral artery (MCA)
- MCA diameter constant under several physiological conditions
- MCA perfuses 80% of each hemisphere

Assessment of cerebral autoregulation

Measurement of Δ cerebral blood flow in response to Δ blood pressure

Static autoregulation

"Steady-state" conditions

- Prolonged standing
- Prolonged exercise
- Pharmacological manipulations

Dynamic autoregulation

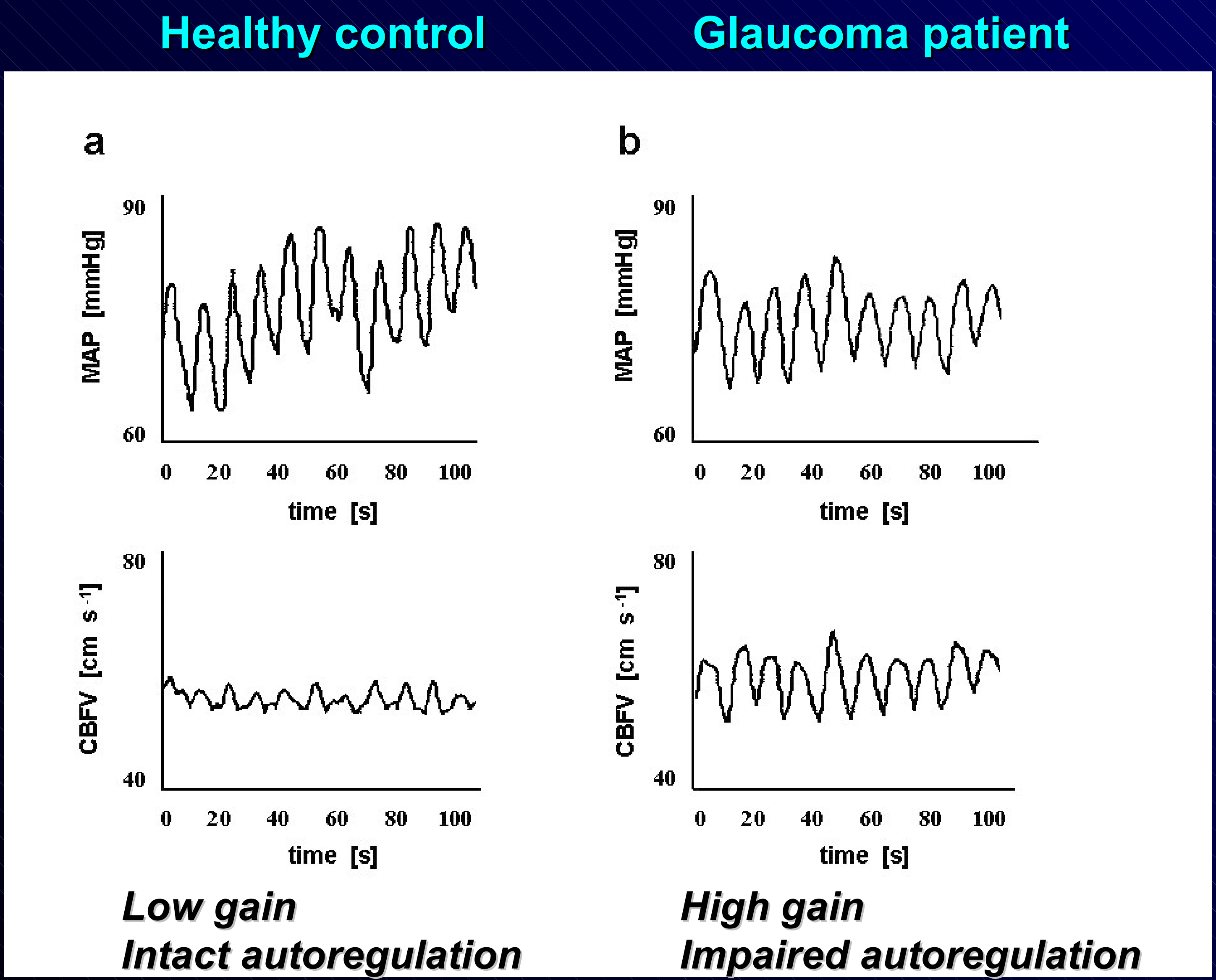
Response to *rapid* pressure changes

- Thigh cuff deflation
- Deep breathing
- Dynamic hand grip
- Active standing
- Spontaneous BP fluctuations

Variability in BP and CBFV during deep breathing

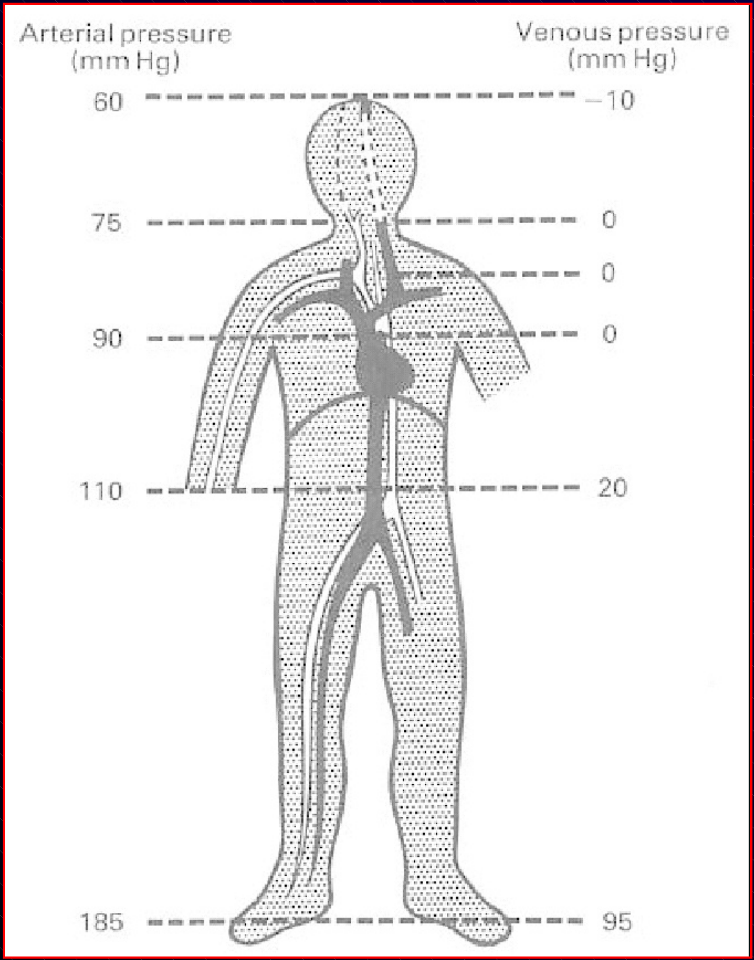
Blood pressure

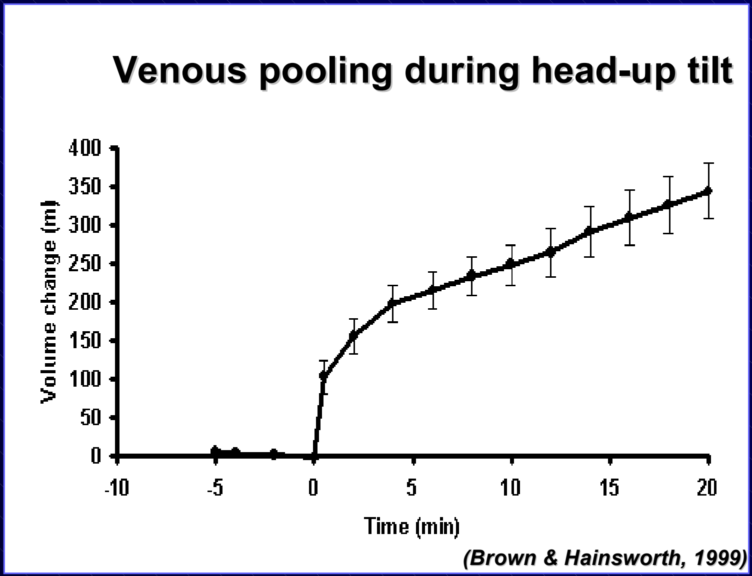
CBFV



(*Tutaj et al. 2004*)

The orthostatic response





Venous return ↓

Cardiac output ↓

Reflex adjustments to maintain blood pressure

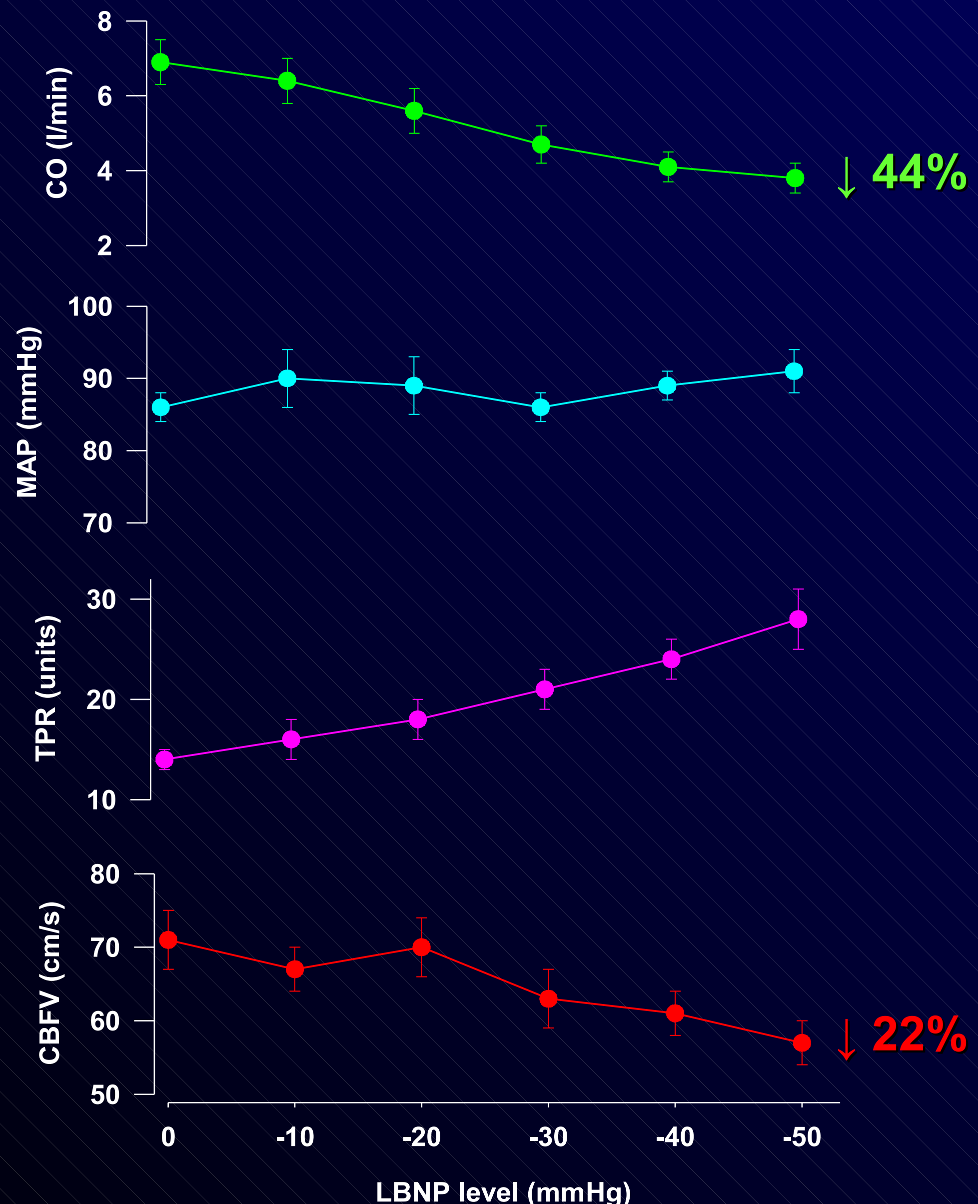
Responses to lower body negative pressure

Cardiac output

Blood pressure

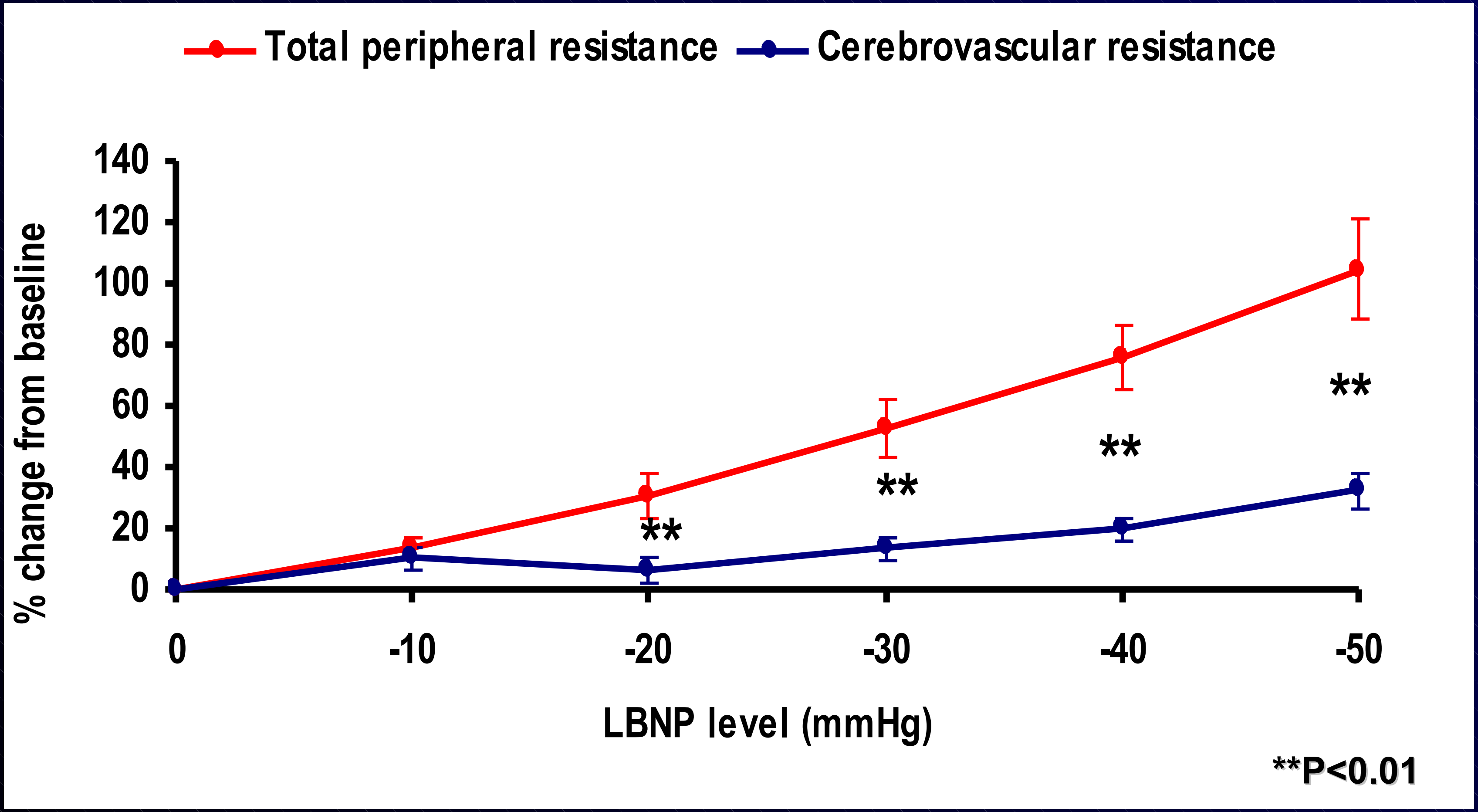
Total peripheral resistance

Cerebral blood Flow velocity



(*Brown et al. 2003*)

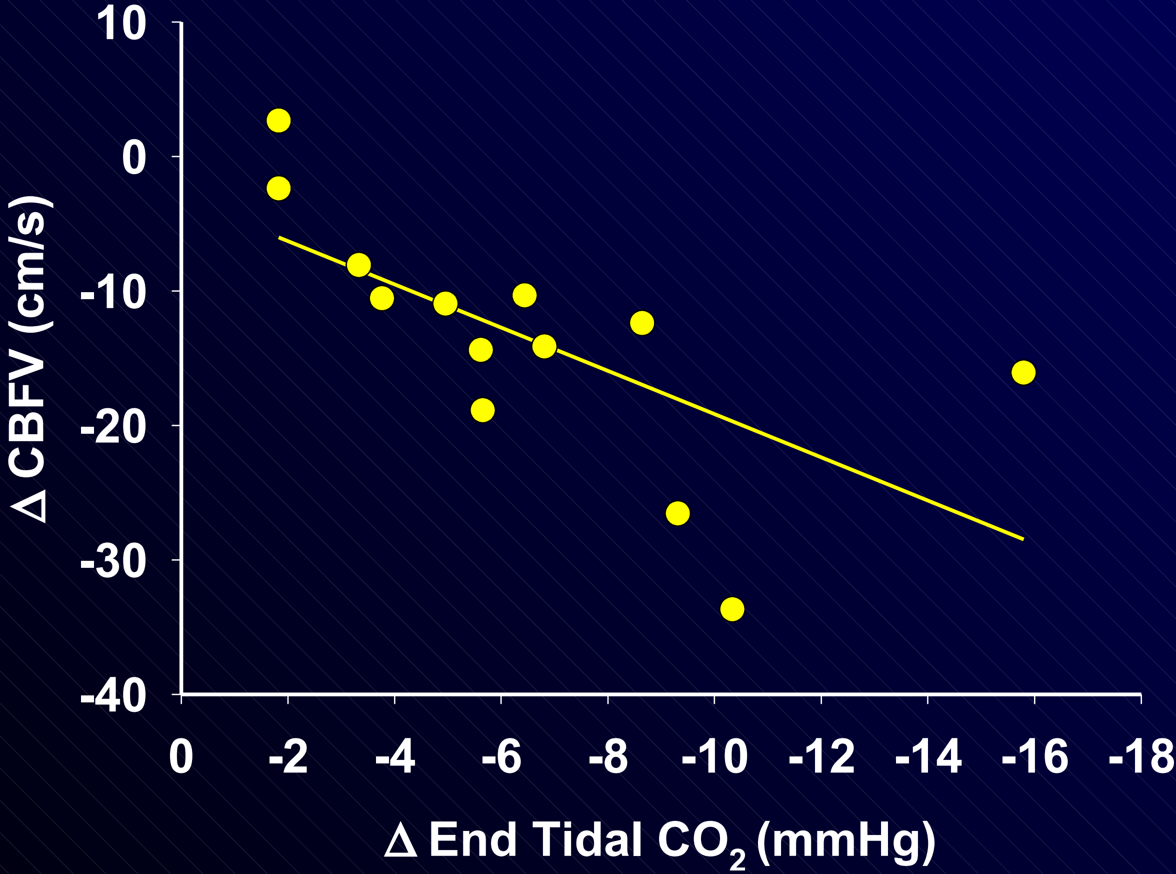
Cerebrovascular & peripheral vascular responses to LBNP



Blood pressure remained near-constant at all LBNP levels

(*Brown et al. 2003*)

Cerebral blood flow velocity and CO_2 during LBNP



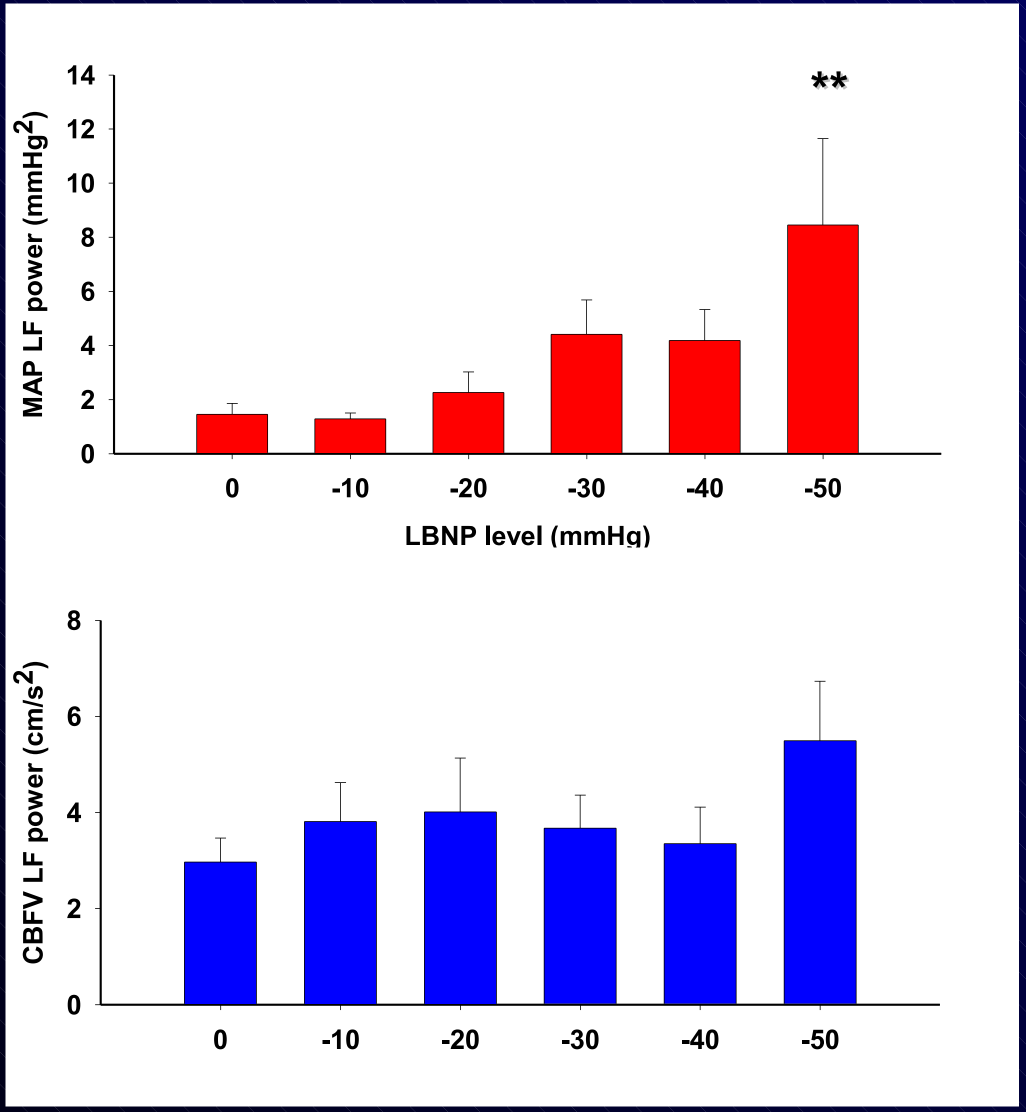
(*Brown et al. 2003*)

Dynamic cerebral autoregulation is intact during LBNP

Spectral analysis of spontaneous BP and CBFV fluctuations

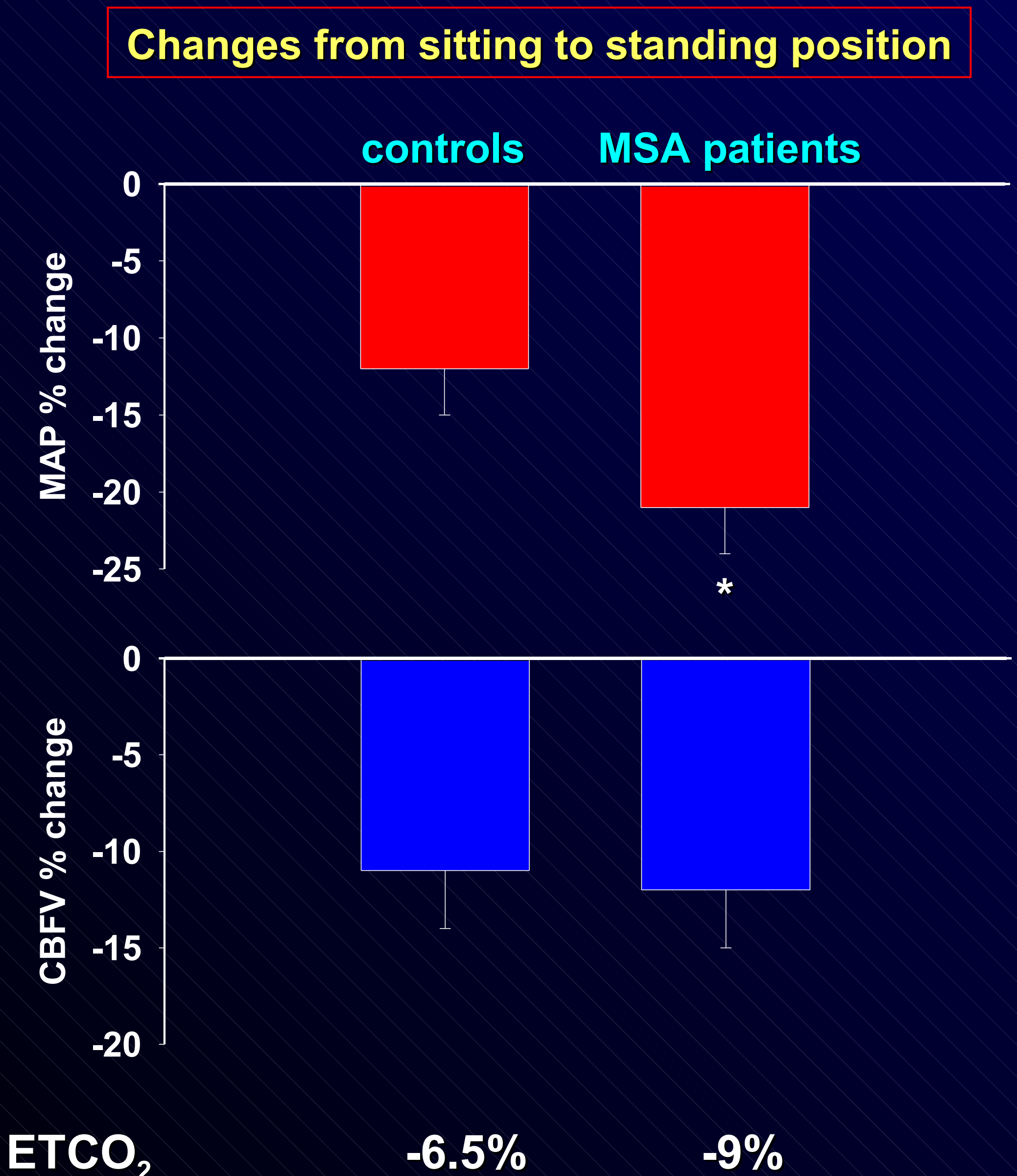
BP variability ↑

CBFV variability - No change



(*Brown et al. 2003*)

Intact cerebral autoregulation in multiple system atrophy



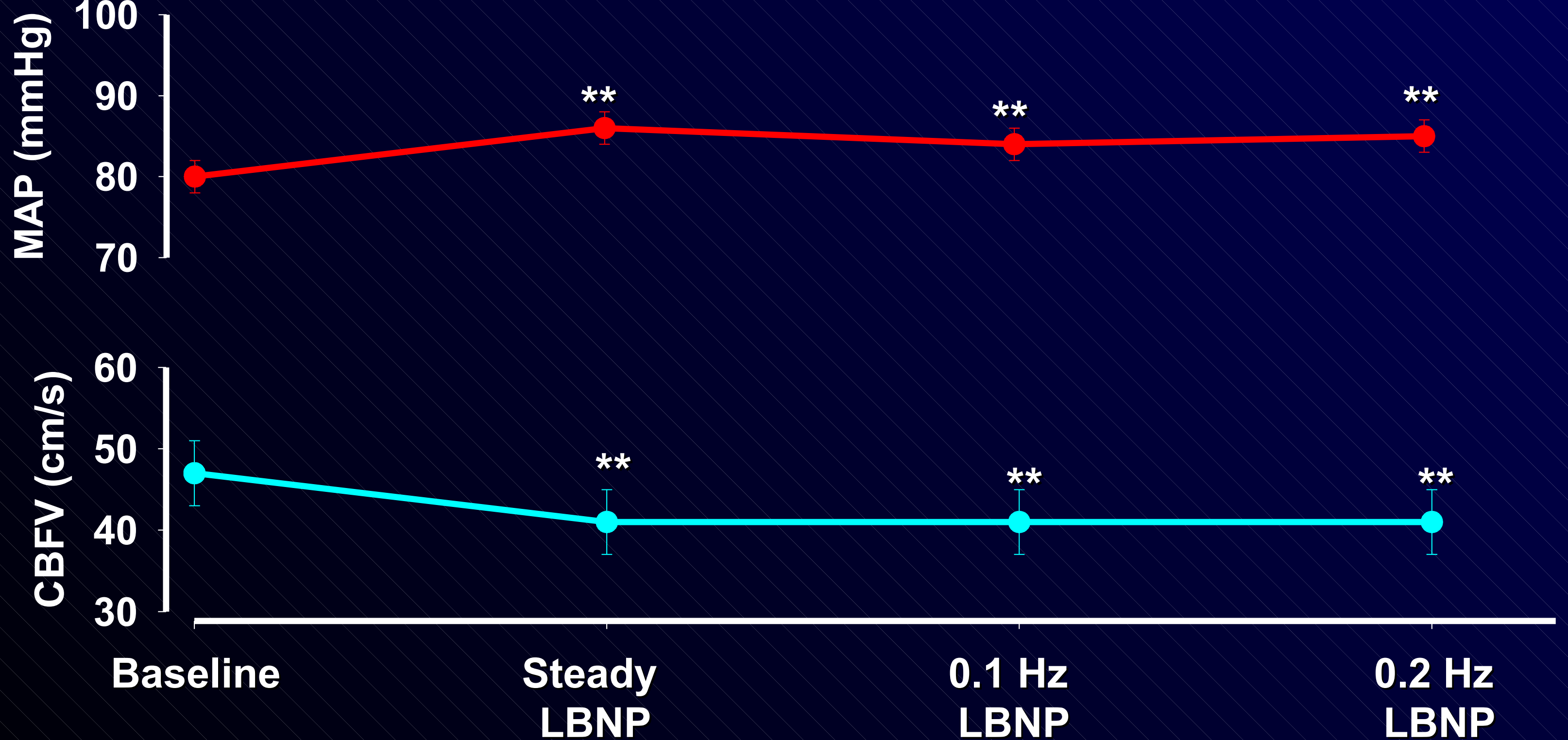
(*Le Traon et al. 2006*)

Cerebral autoregulation during fluctuations in gravitational stress

- Pilots subjected to rapid changes in gravitational stress "push-pull" effect
- Occurrence of syncope during certain manoeuvres "G-induced loss of consciousness (G-LOC)"
- Fluctuations in gravitational stress simulated using oscillatory LBNP

Static autoregulation during oscillatory LBNP

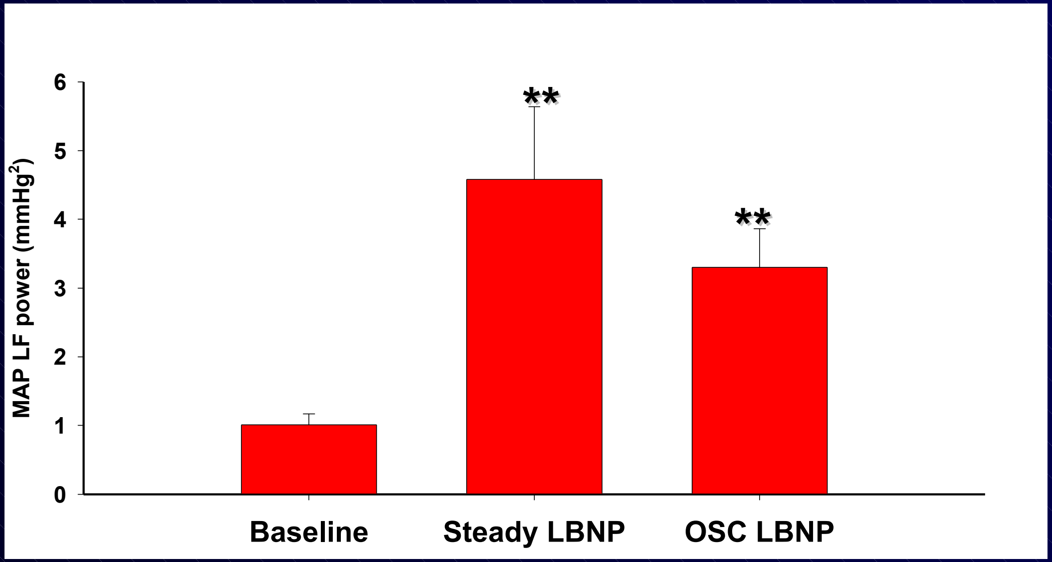
1. Baseline: No LBNP
2. Steady LBNP at 40 mmHg
3. Oscillating LBNP 0 to -40 mmHg at 0.1 Hz
4. Oscillating LBNP 0 to -40 mmHg at 0.2 Hz



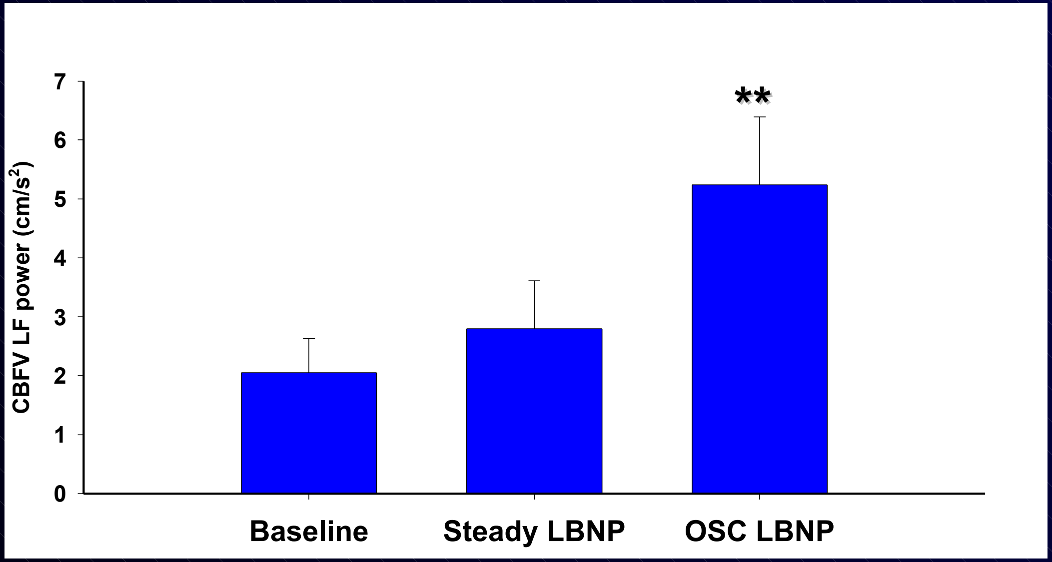
(*Brown et al. 2004*)

Dynamic autoregulation during 0.1 Hz oscillatory LBNP

Blood pressure variability

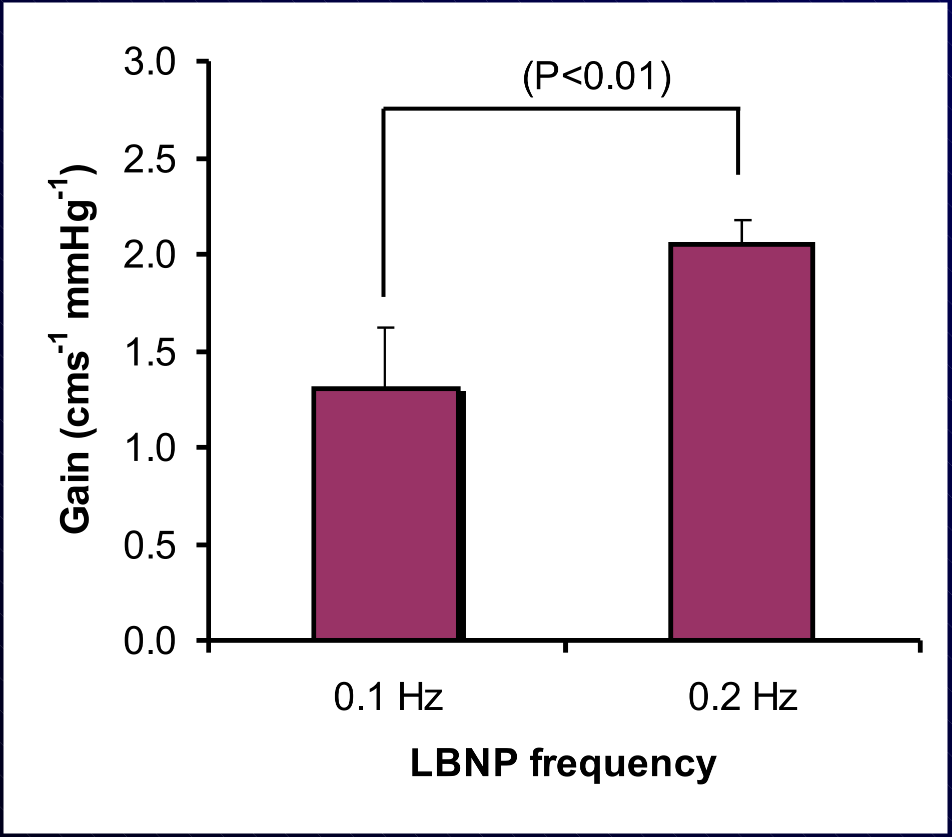


CBFV variability



(*Brown et al. 2004*)

MAP – CBFV gain during 0.1 Hz and 0.2 Hz oscillatory LBNP



- **Enhanced gain during 0.2 Hz LBNP: Greater transfer of MAP oscillations onto cerebral circulation**
- **Consistent with "high-pass filter" model of cerebral autoregulation**

(***Brown et al. 2004***)

Summary of responses to oscillatory LBNP

During simulated fluctuations in gravitational stress:

• ‘Static’ autoregulation is well-maintained

• ‘Dynamic’ autoregulation is compromised – increased CBFV oscillations

• ‘Dynamic’ autoregulation deteriorates further when the frequency of gravitational fluctuations is increased

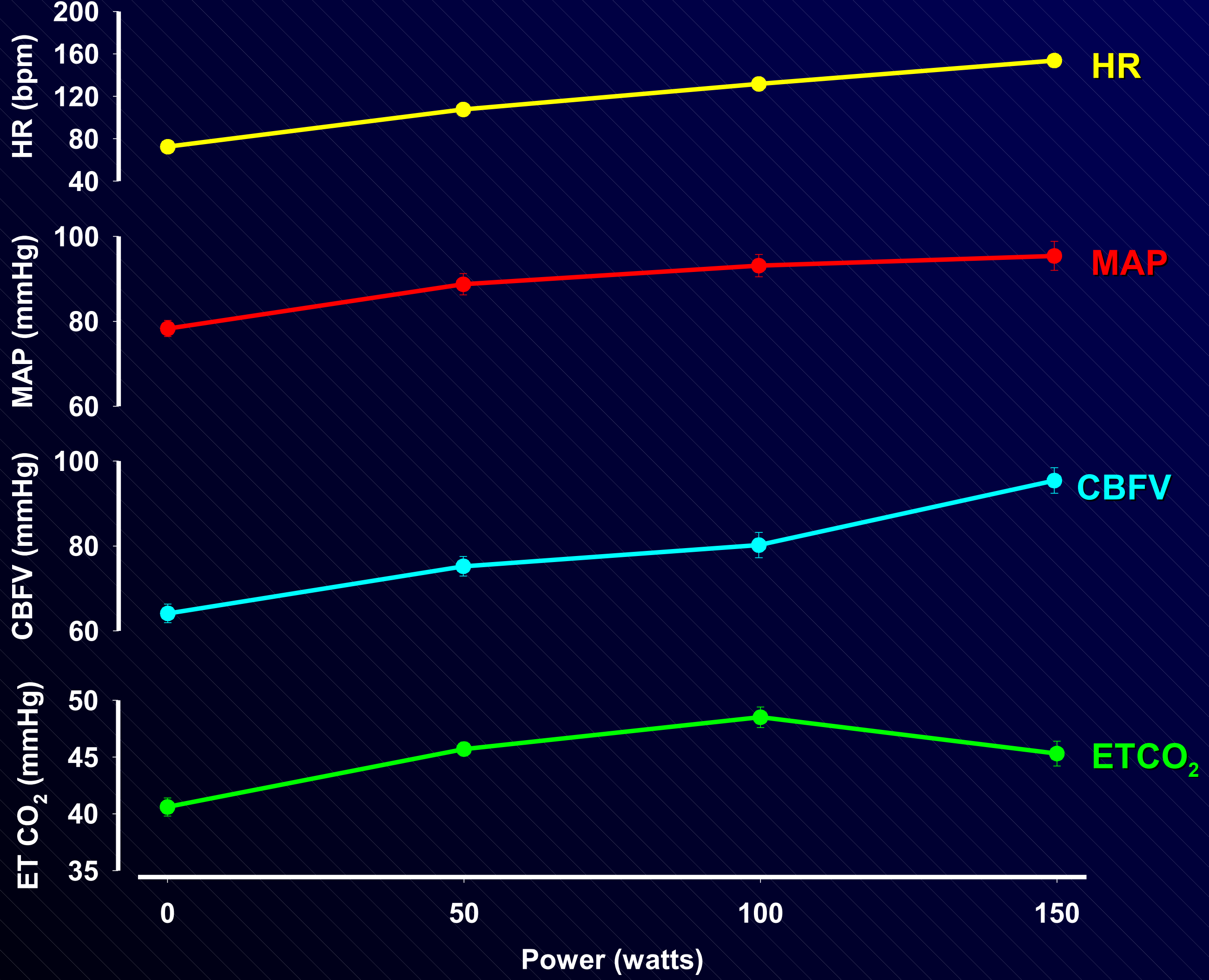
Cerebral autoregulation during exercise

- 40 healthy subjects studied
- Submaximal cycling exercise
- 3-min @ 50, 100, 150 W

- Static & Dynamic cerebral autoregulation determined

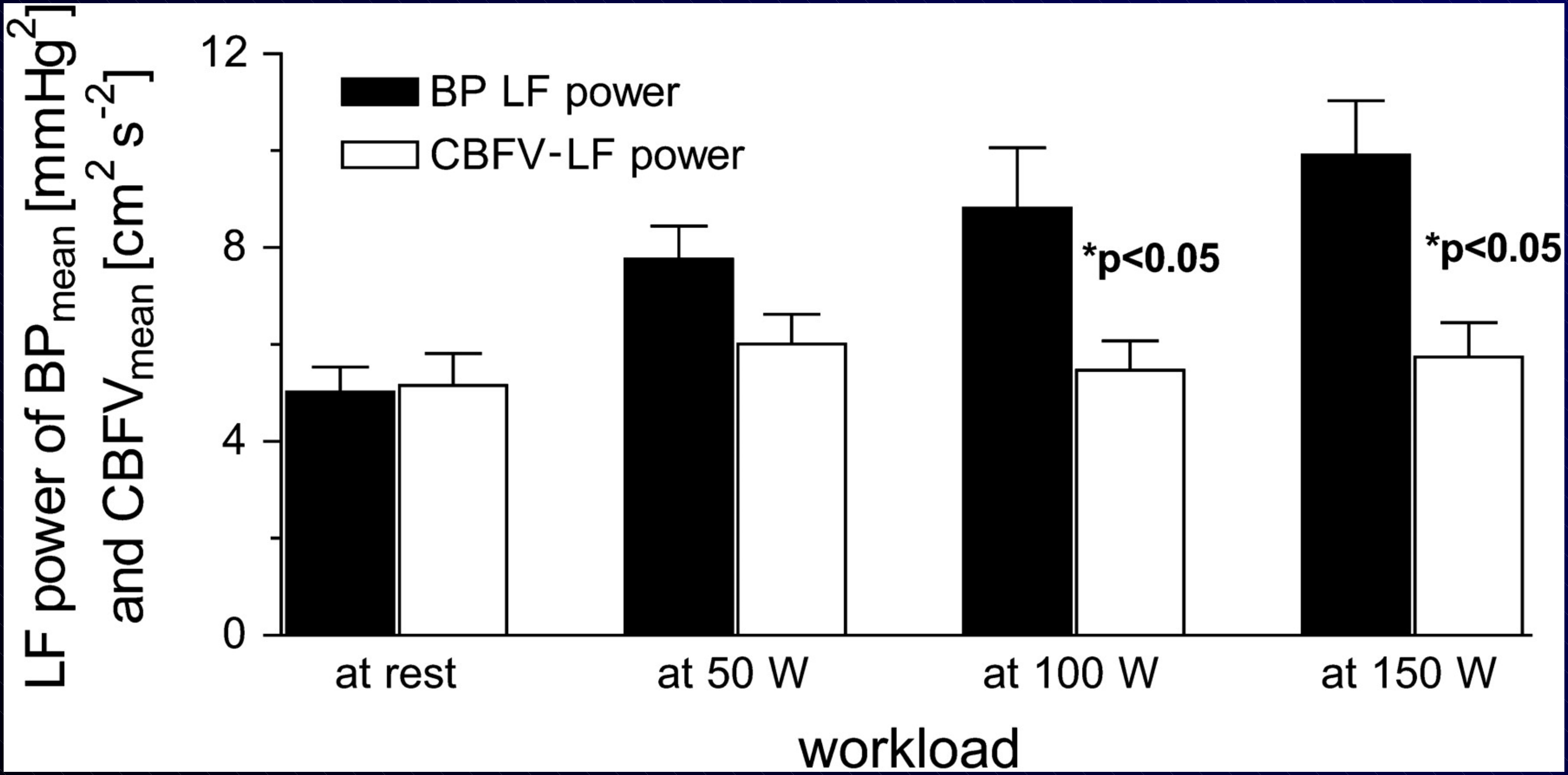
(Brys et al, 2003)

Responses to graded cycling exercise



(Brys et al, 2003)

BP and CBFV variability during cycling exercise



BP variability ↑

CBFV variability – no change

(Brys et al, 2003)

Cerebral autoregulation during exercise - summary

- Physical exercise raises cardiac output and blood pressure
- Cerebral blood flow increases during exercise
- During submaximal exercise, cerebral autoregulation is preserved
- During exhaustive exercise, dynamic cerebral autoregulation is impaired (Ogoh et al, 2004) – possibly related to hyperventilation-induced hypocapnia

The diving reflex and cerebral autoregulation

Diving reflex:

Profound bradycardia & vasoconstriction during water immersion in diving animals

Less dramatic response in humans

- bradycardia
- ↑ sympathetic activity to muscles
- peripheral vasoconstriction
- involves trigeminal nerve pathways
- can be activated by facial immersion or cold stimulus to the forehead

- Assumed to divert blood towards the brain

Effect of cold face stimulation on cerebral blood flow

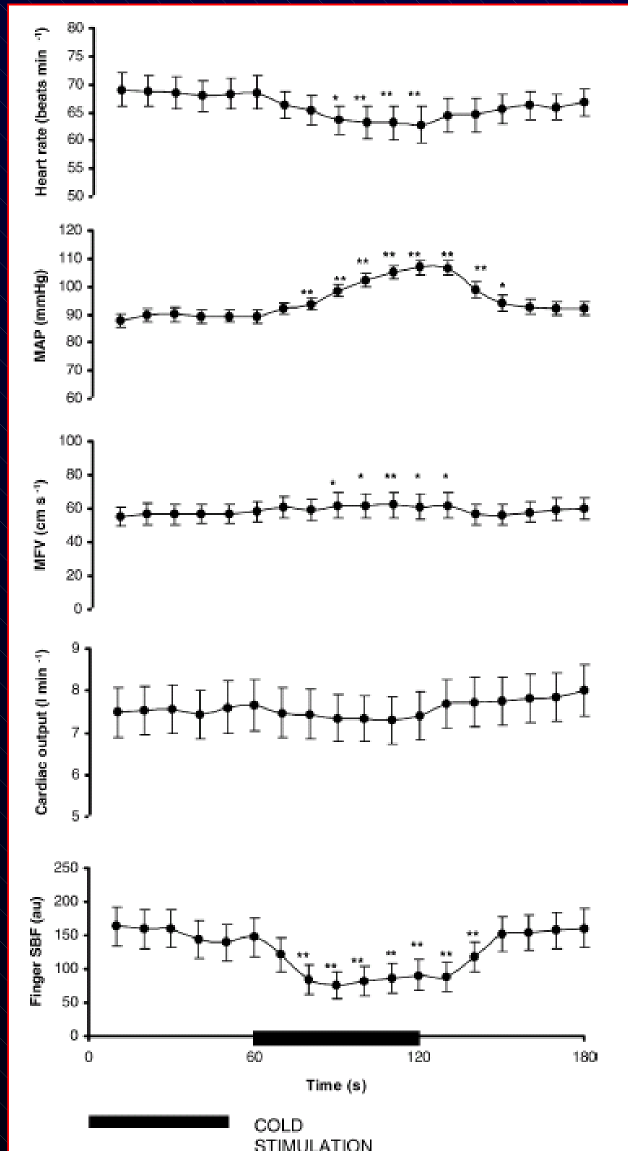
Heart rate

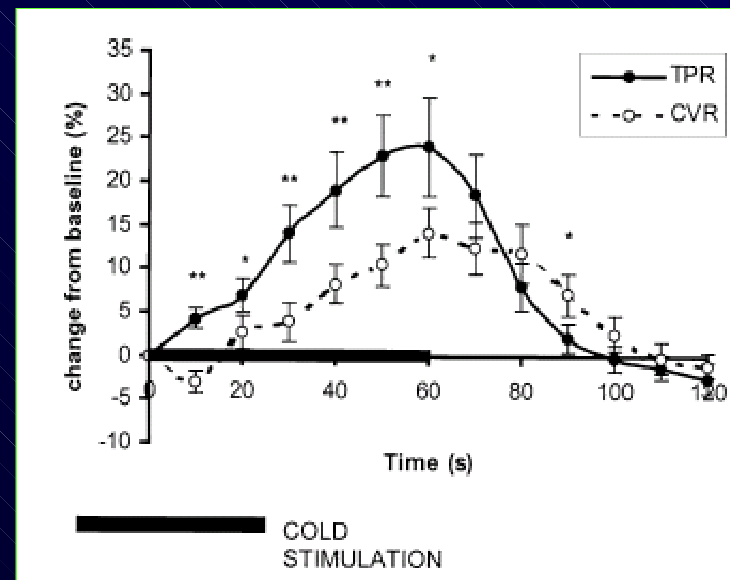
Mean arterial pressure

CBFV

Cardiac output

Skin blood flow





(Brown et al, 2003)

Effect of ageing on cerebral autoregulation

Age related cardiovascular changes:

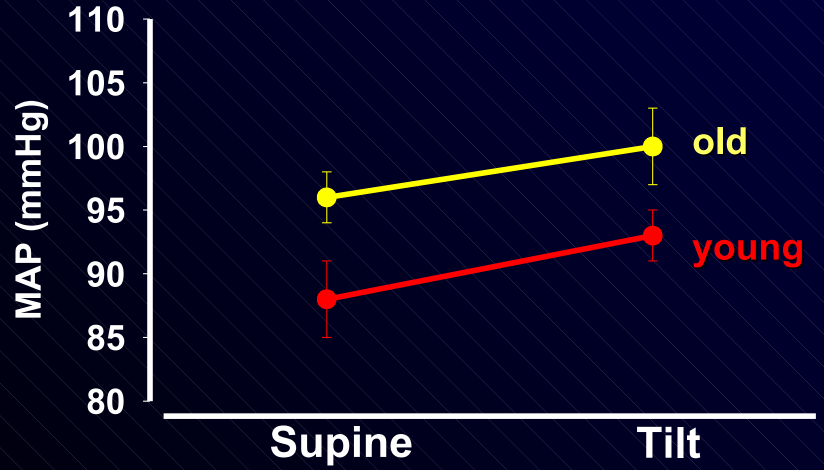
- Increase in blood pressure
- Increase in sympathetic tone
- Decreased systemic artery compliance
- Reduced parasympathetic autonomic responses
- Decreased cardiovagal baroreflex sensitivity
- Mostly preserved sympathetic control of the blood vessels

- Reduction in cerebral blood flow (and velocity)

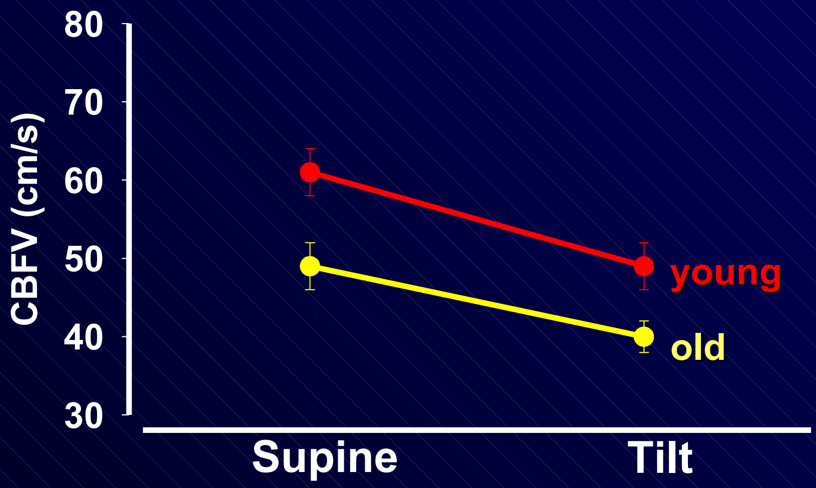
Ageing and the orthostatic cerebrovascular response

Preserved static autoregulation with ageing

Mean arterial pressure



Cerebral blood flow velocity



No difference in $ETCO_2$ values

(*Carey et al, 2003*)

Cerebral autoregulation and hypertension

- Dynamic & static indicies of CA maintained (or even enhanced) in treated & untreated hypertensives (Eames et al, 2003; Serrador et al, 2004; Lipsitz et al, 2000; Traon, 2002)

- Lower limit of cerebral autoregulation increased in chronic hypertensives (Hoffman, 1981)

- Upper limit not determined in humans (shifted right in baboons (Strandgaard, 1975))

Conditions in which cerebral autoregulation is impaired

- **Acute stroke** *(Eames et al, 2001; Novak et al, 2003)*
- **Glaucoma** *(Tutaj et al, 2004)*
- **Diabetes** *(Novak et al, 2006)*
- **Liver cirrhosis** *(Lagi et al, 2002)*
- **Fabry disease** *(Hilz et al, 2004)*
- **Migraine** *(Muller & Marziniak, 2005)*
- **Chronic heart failure** *(Gruhn et al, 2001)*
- **Chronic mountain sickness** *(Claydon et al, 2005)*

Summary

- Cerebral autoregulation modulates the transfer of blood pressure fluctuations onto the cerebral circulation
- Can be assessed by comparing changes in CBFV in response to changes in blood pressure
- The role for autonomic innervation of the cerebral circulation is still unclear
- Changes in CO_2 often account for cerebral vasoconstriction in various situations