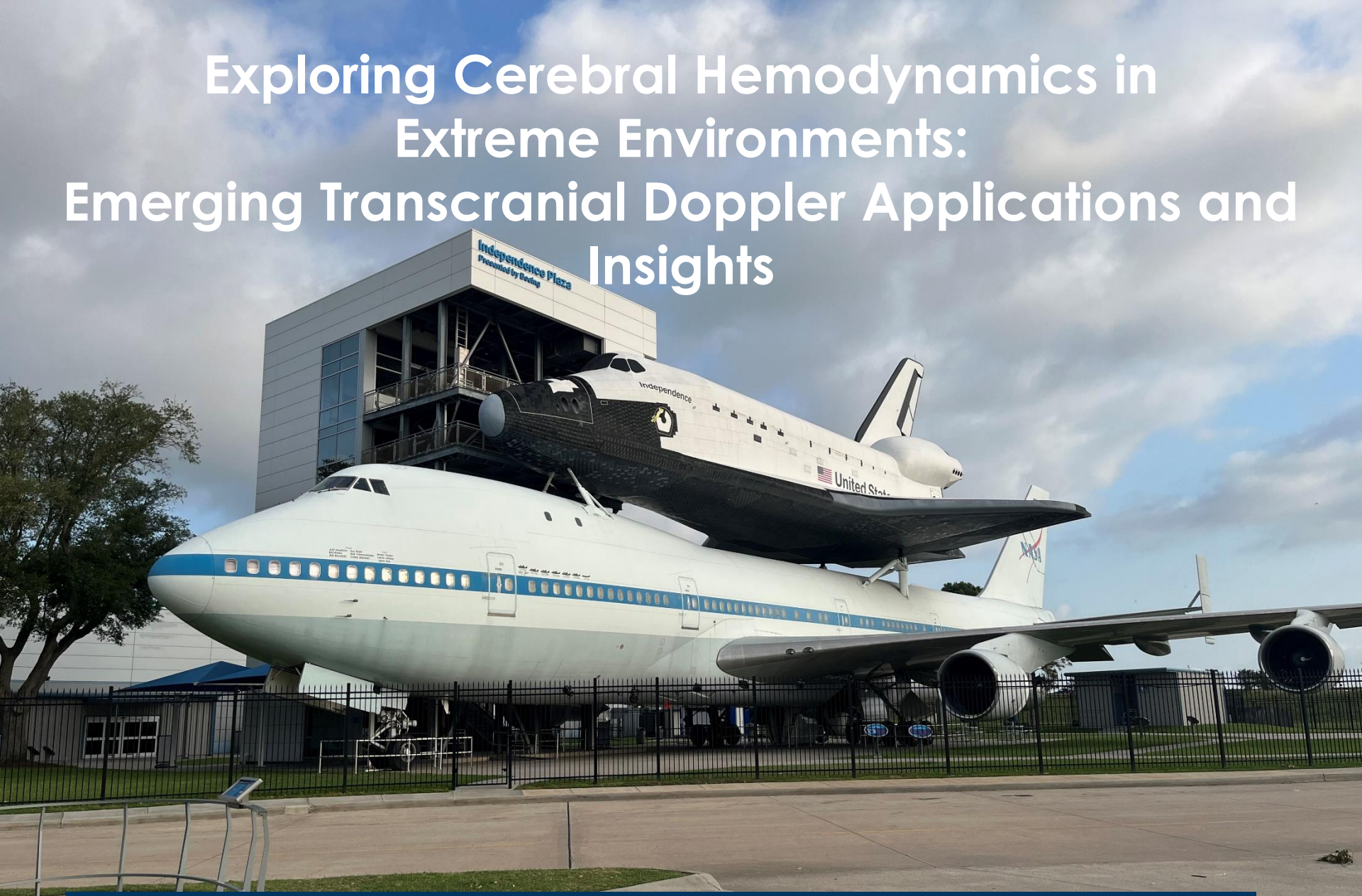
Exploring Cerebral Hemodynamics in Extreme Environments: Emerging Transcranial Doppler Applications and Insights



CASE WESTERN RESERVE UNIVERSITY
School of Medicine

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OBJECTIVES

- Understand the impact of alterations in gravity, pressure, and gas on cerebrovascular hemodynamics
- Discuss potential applications of transcranial doppler and ultrasound within extreme environments
- Measure and apply neurophysiological adaptations and interventions to the aforementioned environmental exposures

EXTREME ENVIRONMENTS

- Spaceflight (microgravity)
- Tactical Aviation (+Gz)
- High Altitude (hypobaria)
- Deep Diving / Subaquatic (hyperbaria)
- Temperature Exposure (heat / cold)
- Gas alteration or administration (hypoxia, hyperoxia, hypercapnia)

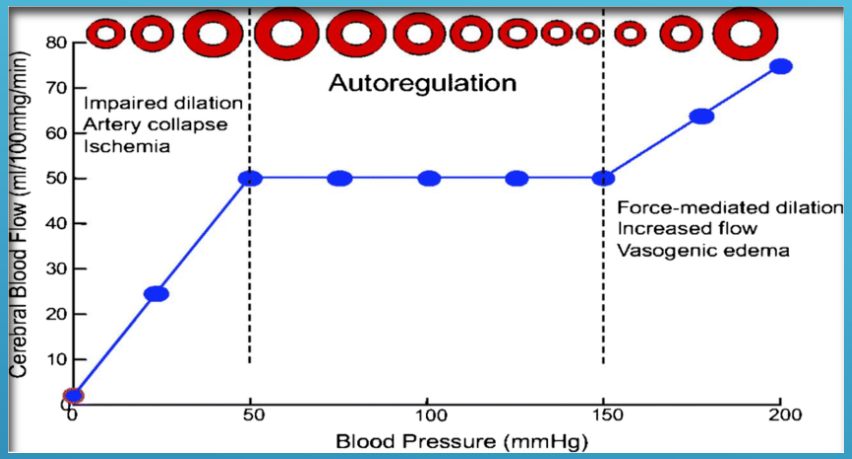
WHY DOES IT MATTER?

- Fitness for duty
- Need for relief
- High risk / high resource / high security missions
- Supplementation / mitigation strategies
  - Iatrogenic consequences
- Frequency, quantity, and duration of interventions
- Individual variability
- Long term implications
- Increasing expansion to public sector

NEED FOR NEUROIMAGING AND CEREBROVASCULAR MONITORING

- Ultrasound / TCDs
  - Portable
  - Dynamic
    - Imaging
    - Hemodynamics
    - Quantitative
  - Low risk / no accumulated exposure concern
  - Noninvasive

THE BASICS: CEREBRAL PERFUSION PRESSURE

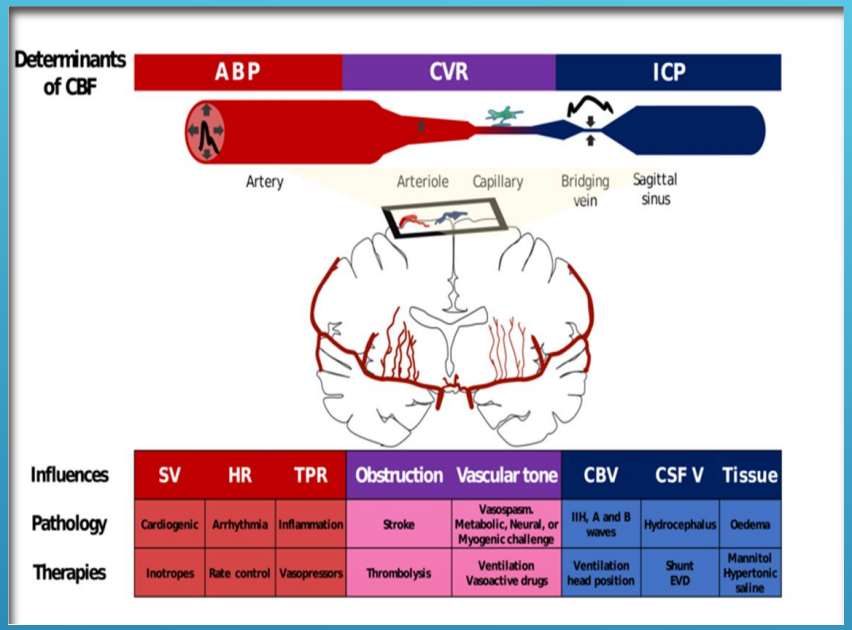


- Cerebral Perfusion Pressure (CPP) =

  Mean Arterial Pressure (MAP) – Intracranial Pressure (ICP)

- Normal 60-80 mmHg
- Increase in ICP → decreases CBF & CPP

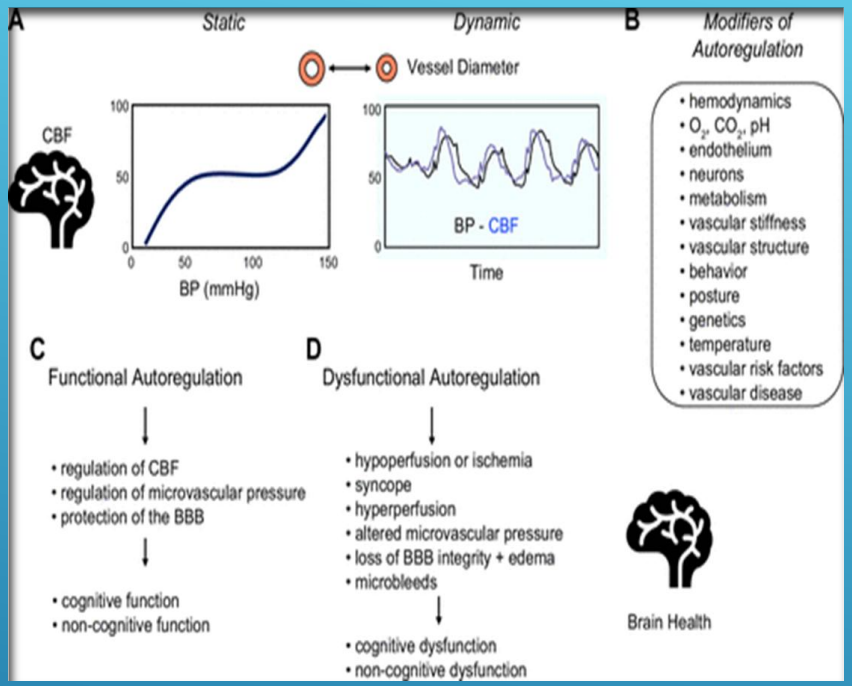
THE BASICS: CEREBRAL BLOOD FLOW



Influences	SV	HR	TPR	Obstruction	Vascular tone	CBV	CSF V	Tissue
Pathology	Cardiogenic	Arrhythmia	Inflammation	Stroke	Vasospasm. Metabolic, Neural, or Myogenic challenge	IIH, A and B waves	Hydrocephalus	Oedema
Therapies	Inotropes	Rate control	Vasopressors	Thrombolysis	Ventilation Vasoactive drugs	Ventilation head position	Shunt EVD	Mannitol Hypertonic saline

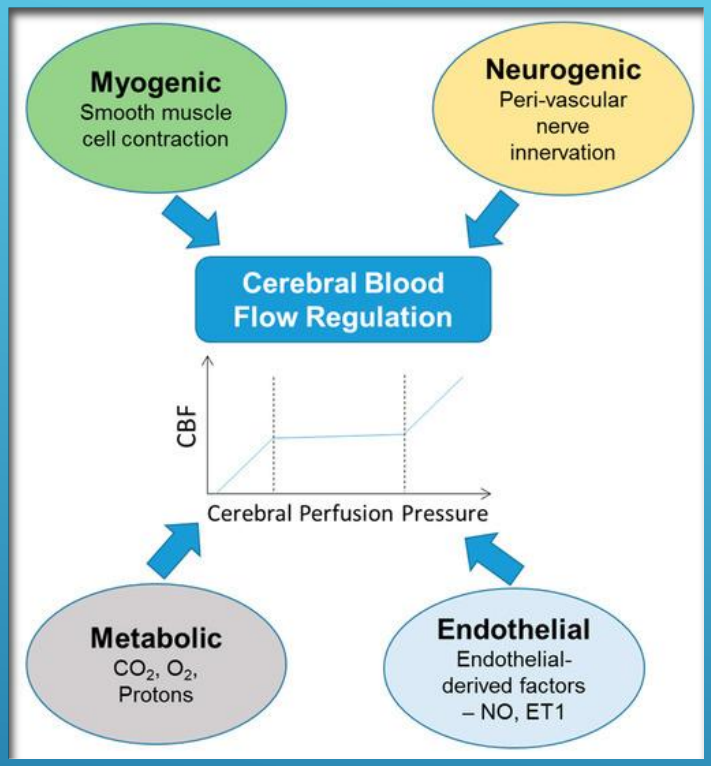
- Cerebral Blood Flow =

  Cerebral Perfusion Pressure / Cerebral Vascular Resistance
- Normal blood flow through the brain of adult: 50 to 65 ml/100 grams of brain tissue per minute
- For entire brain: 750 to 900 ml/min, 15% of the resting cardiac output, 20% of resting oxygen consumption



- If blood flow to the brain drops below 18 to 20 ml/100 g/minute -> Ischemia
- 8 to 10 ml/100 g/minute -> Tissue death
- Too much: Increased ICP, compress and damage delicate brain tissue

THE BASICS: CEREBRAL AUTOREGULATION



- Cerebral blood "auto-regulates" very well between arterial pressure limits of 60 and 140 mmHg
- Acute changes in this range to not cause significant change in cerebral blood flow

THE BASICS: CEREBRAL AUTOREGULATION

MYOGENIC (PRESSURE) AUTOREGULATION

- Arterioles dilate or constrict in response to changes in BP and ICP to maintain a constant CBF
- Myogenic theory: Vascular smooth muscles are highly responsive to changes in pressure, a process called myogenic activity, that contributes to auto-regulation of cerebral blood flow
- Vascular smooth muscle within cerebral arterioles contract to stretch response, regulating pressure changes.
  - BP dependent
- High BP -> need to lower pressure -> arteriolar dilation in the brain
- Low BP -> need to raise BP -> arteriolar constriction
- Meant to minimize effect of changes in the body's overall blood pressure on cerebral perfusion pressure

METABOLIC AUTOREGULATION

- Metabolic factors have potent effects in controlling the cerebral blood flow:
  - CO_2 concentration
  - Hydrogen ion concentration
  - Oxygen concentration
    - Nitric oxide & adenosine are autoregulation mediators (both dilate)
- Oxygen deficiency is a regulator of cerebral blood flow except during periods of intense brain activity
  - CO_2& H more important, faster to respond
- Decrease in cerebral tissue PO_2 below about 30 mm Hg (normal 35 - 40 mm Hg) immediately triggers increased cerebral blood flow
- Brain function becomes unbalanced at PO_2 levels below 20 mm Hg

NEUROGENIC AUTOREGULATION

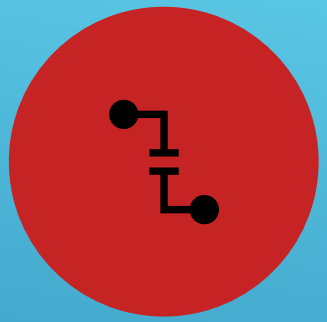
- The cerebral circulatory system has strong sympathetic innervation
  - Passes upward from the superior cervical sympathetic ganglia in the neck and then into the brain along with the cerebral arteries
- Lesser role in autoregulation compared to pressure & metabolic factors
- During acute hypertension, sympathetic input attenuates increase in CBF via vasoconstriction
  - Constricts the large and intermediate-sized cerebral arteries enough to prevent the high pressure from reaching smaller blood vessels
- Important in preventing hemorrhages

ENDOTHELIAL AUTOREGULATION

- Involves vasodilators (nitric oxide, carbon monoxide, prostacyclin) and vasoconstrictors (endothelin-1, thromboxane A2, angiotensin II) secreted by the endothelium in a paracrine fashion

MICROGRAVITY

STILL UNDER INVESTIGATION

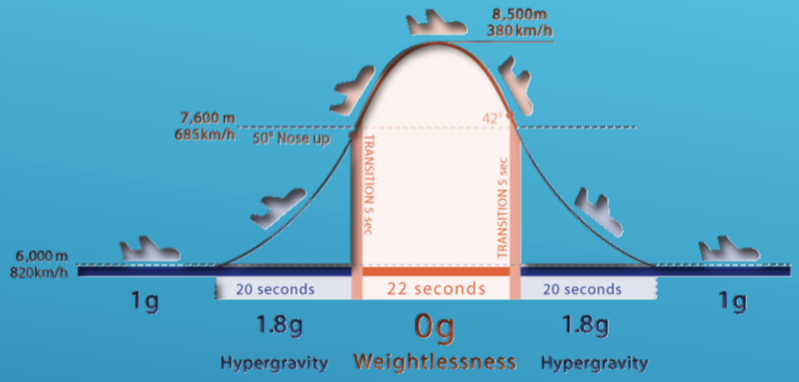


RELIANT ON MANY MIMICS/MODELS

HETEROGENOUS RESULTS

IMPACT OF MICROGRAVITY AND SPACEFLIGHT ON CEREBROVASCULAR HEMODYNAMICS

SIMULATION / MIMICS



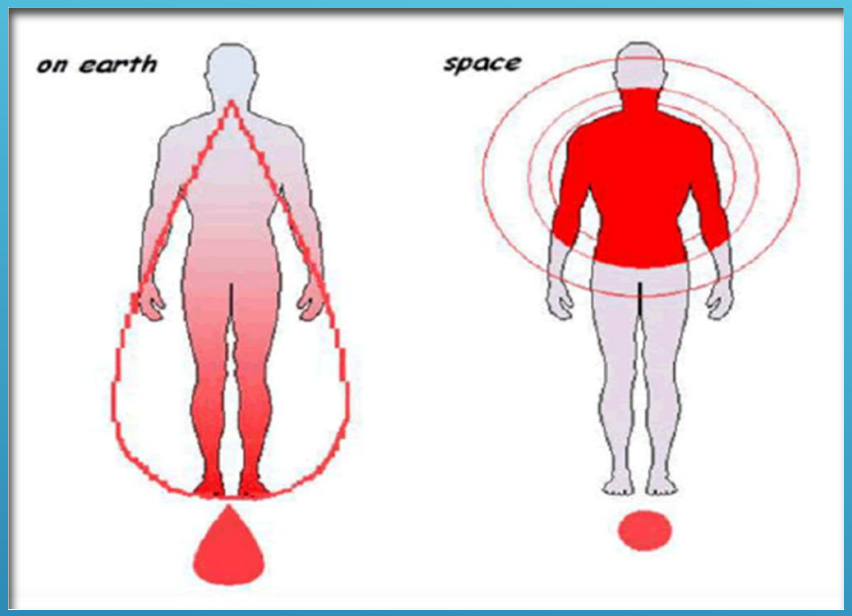
Parabolic flight

Head down bed rest

Water / Dry immersion

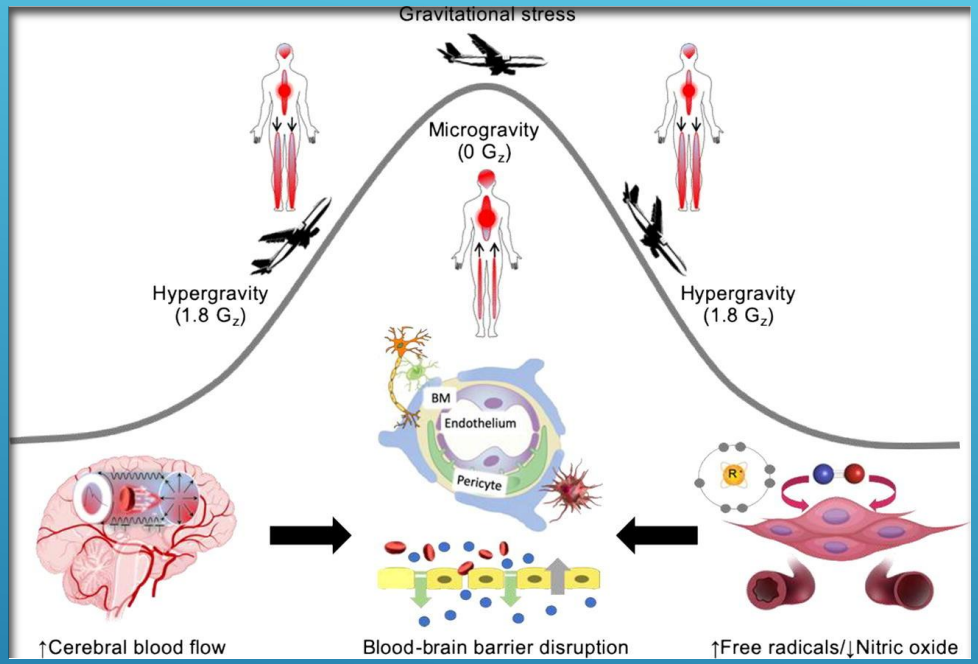
Suspension systems

MICROGRAVITY

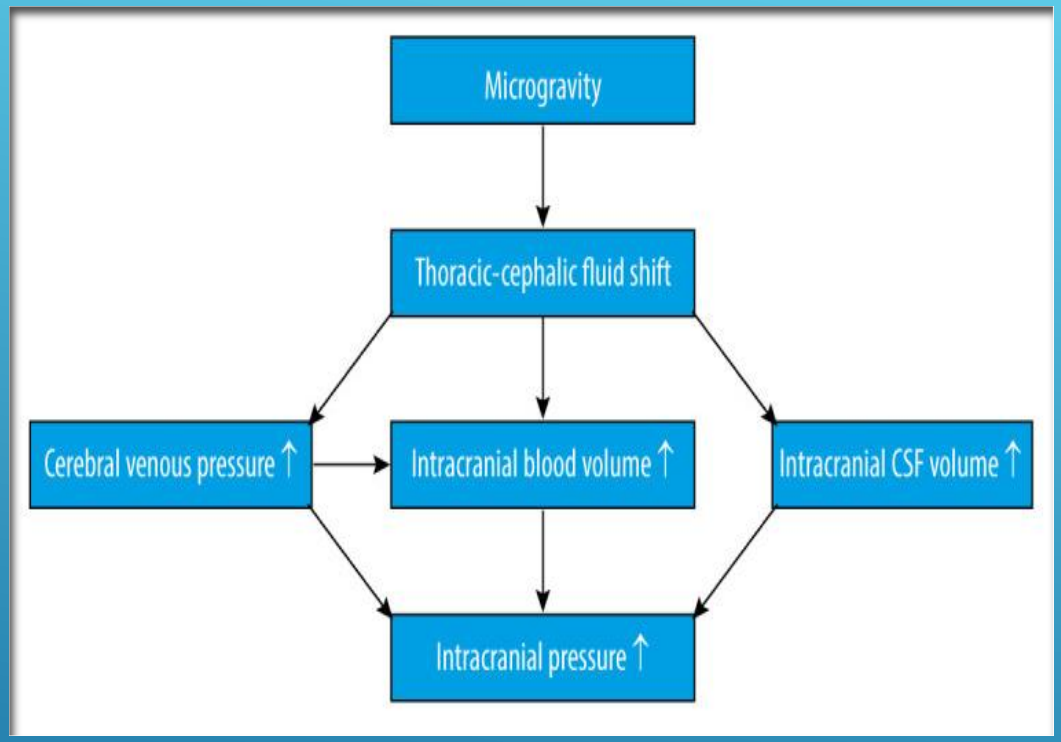


- Prolonged exposure to microgravity removes the head-to-foot gravitational vector
  - Causes cephalic fluid shift
  - Cerebrovascular resistance must increase to compensate for the acute elevation of perfusion pressure

MICROGRAVITY



- Lack of hydrostatic gradients associated with gravity might increase the permeability of the blood-brain barrier
  - Exacerbated by systemic oxidative-nitrosative stress
- Fluid gradient also applies to CSF, resulting in increased intracranial CSF

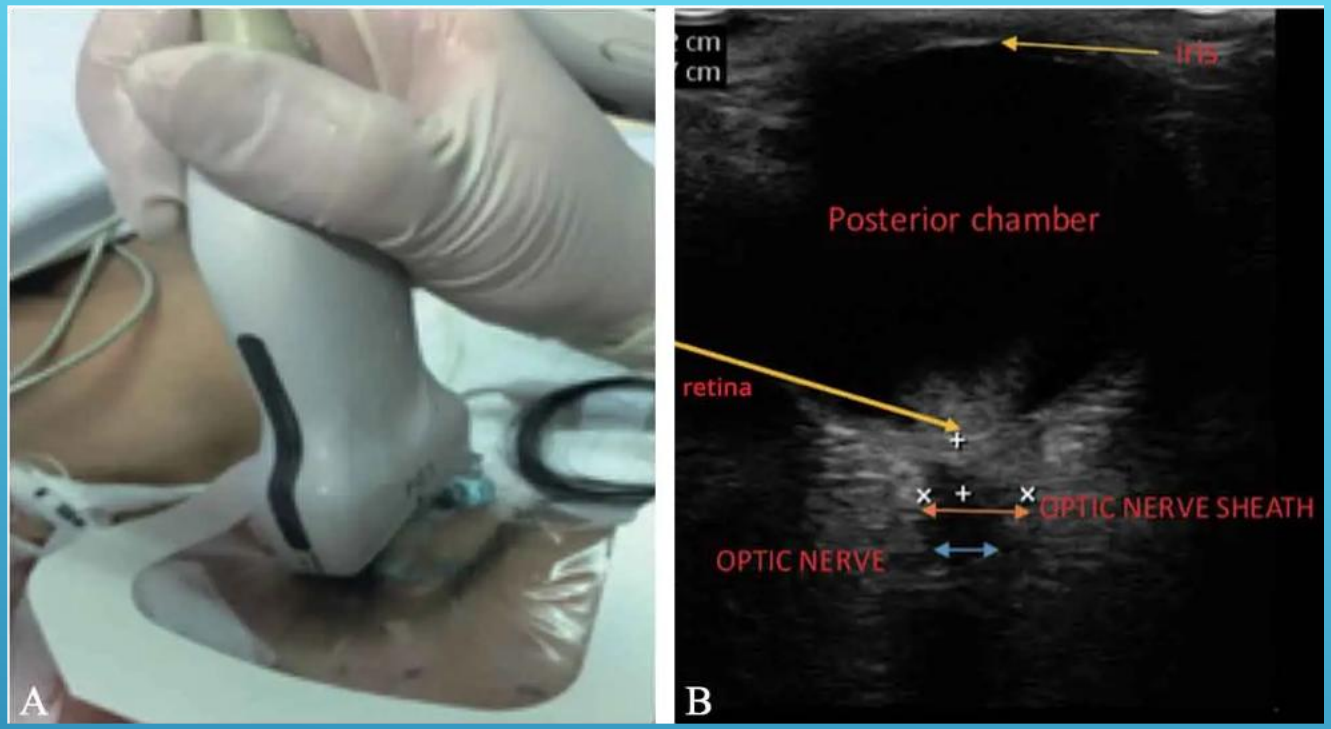


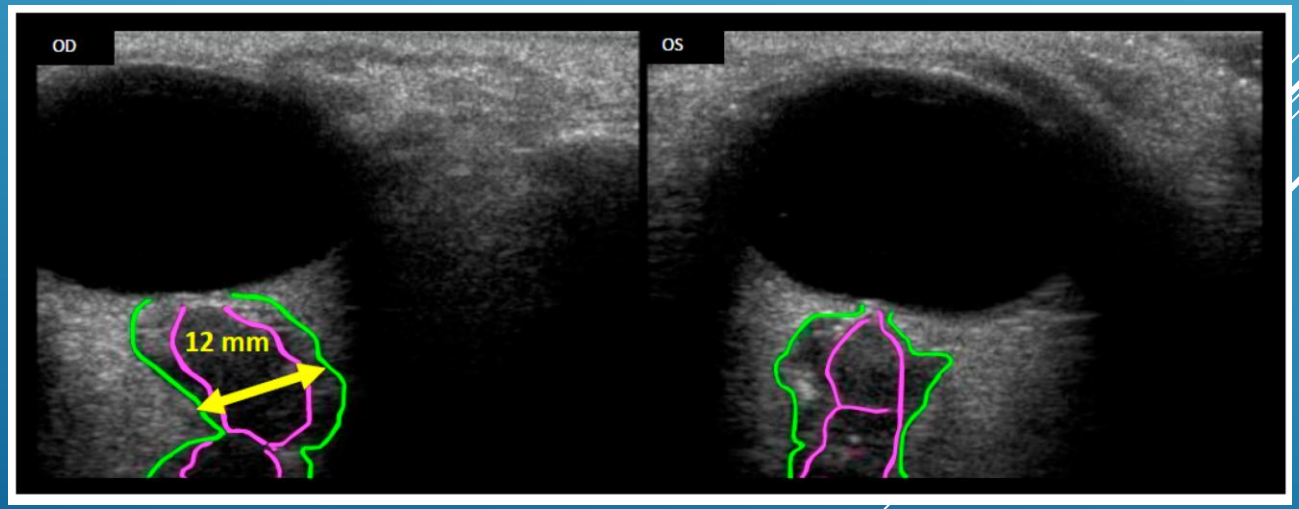
MICROGRAVITY

- Increased blood in cerebral arteries
- CSF disturbance
- Reduced venous drainage
- BBB impairment

- **Increased ICP**

- Increased optic nerve sheath diameter in orbit indicating elevated ICP





MICROGRAVITY

Table 1

Impact of simulated or actual microgravity on intracranial pressure.

Authors	n	Experimental protocol	Conclusion
Kermorgant et al. [16]	12	3 days of DI	3 days of DI, induced an enlarged ONSD, a surrogate value for estimated ICP
Mader et al. [21]	1	6 months of spaceflight	After returned to earth, ICP elevated to 22 mmHg and remained high for a period of time
Avan et al. [22]	40	Parabolic flight	Moderate increased ICP during microgravity
Lawley et al. [19]	8	Parabolic flight and 24 h −6° HDBR	HDBR does not progressively increase ICP, but microgravity does prevent the normal lowering of ICP when upright
Arbeille et al. [23]	10	2 h of DI	Due to large individual variability, no substantial changes in ICP have been observed

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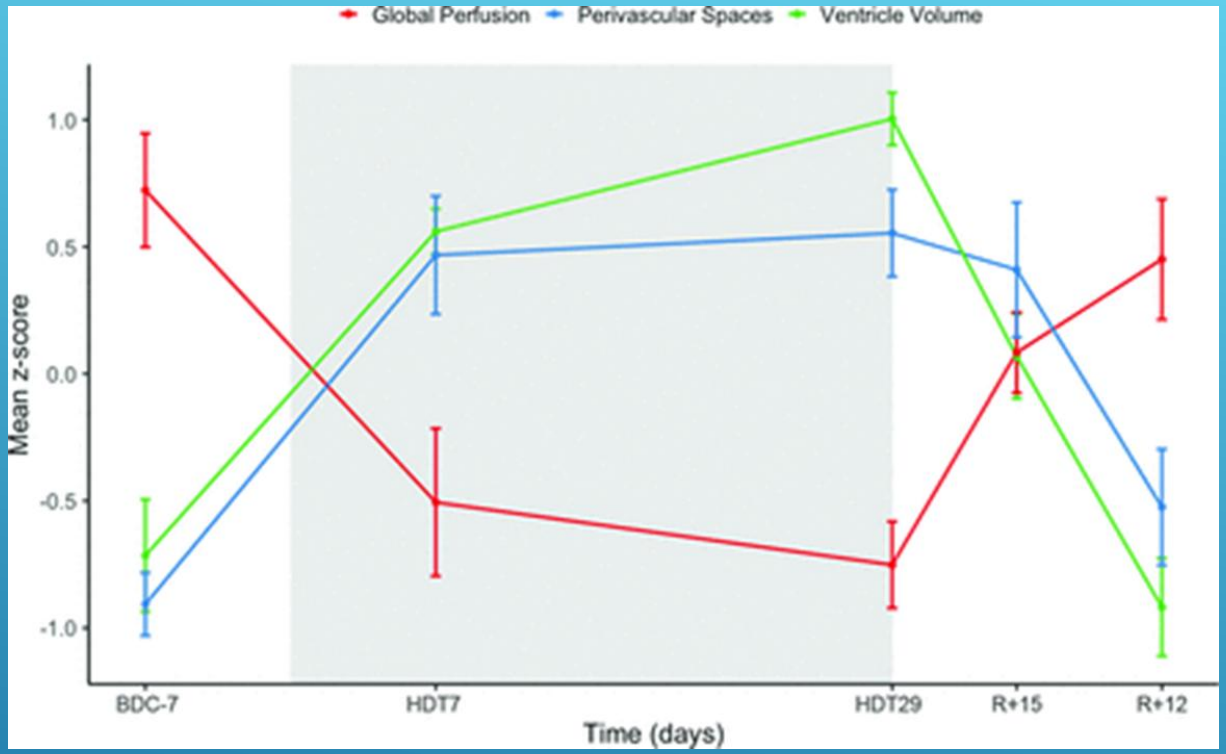
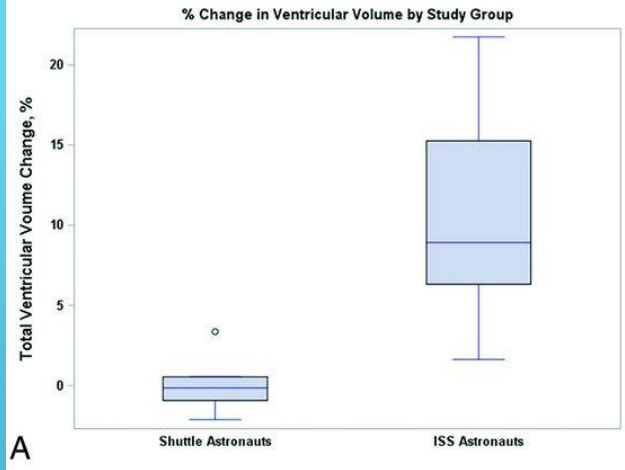
ICP – intracranial pressure; ONSD – optic nerve sheath diameter; DI – dry immersion; ISS – international space station; HDBR – head-down bed rest.



MICROGRAVITY



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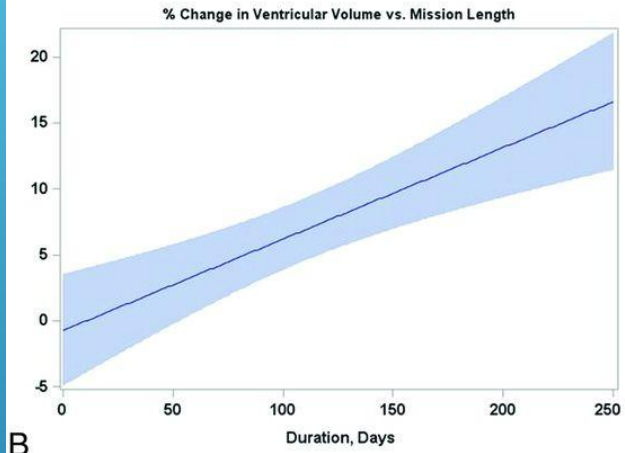

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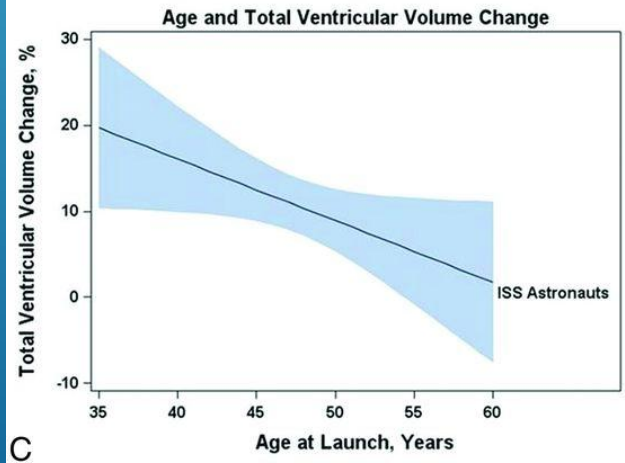

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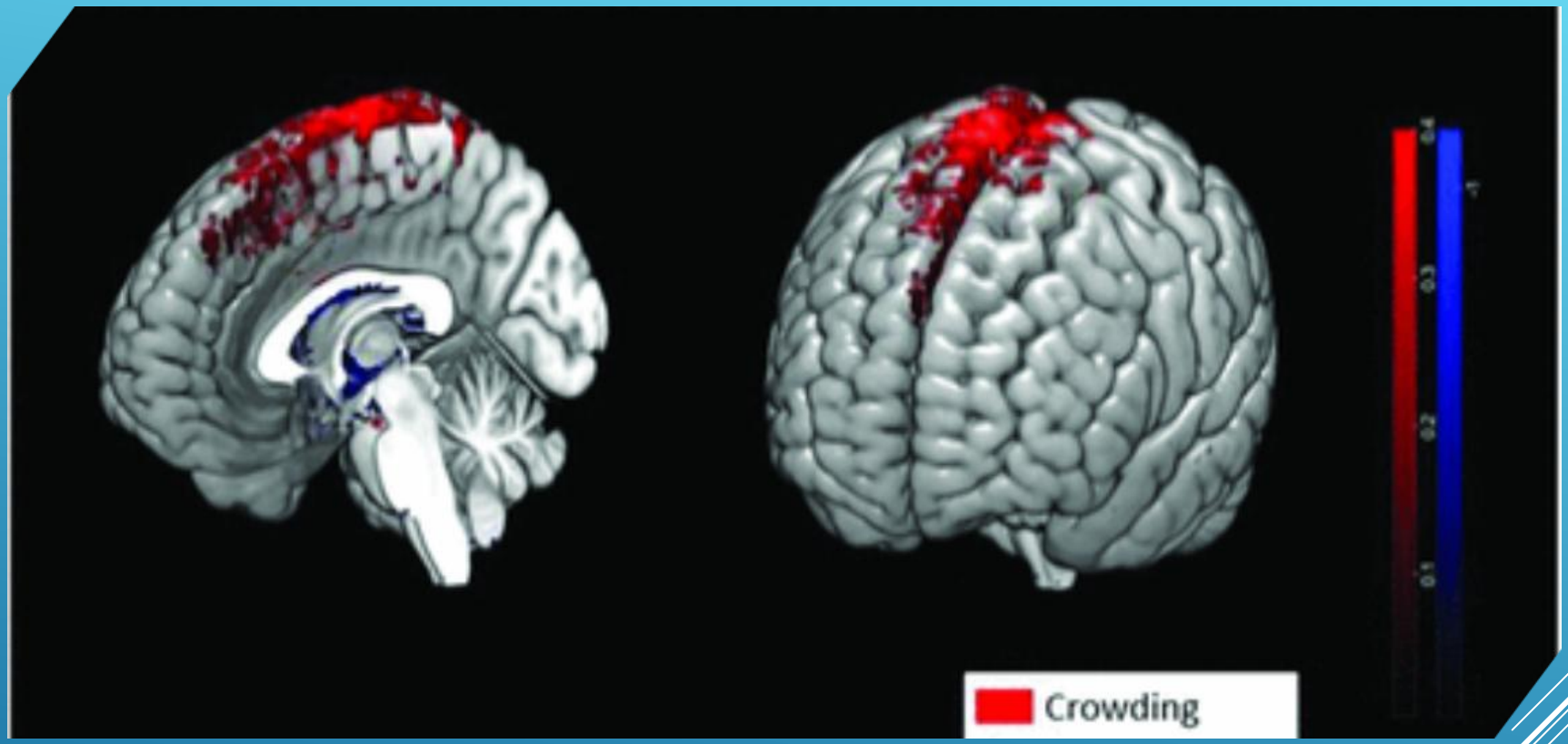


MICROGRAVITY

MICROGRAVITY

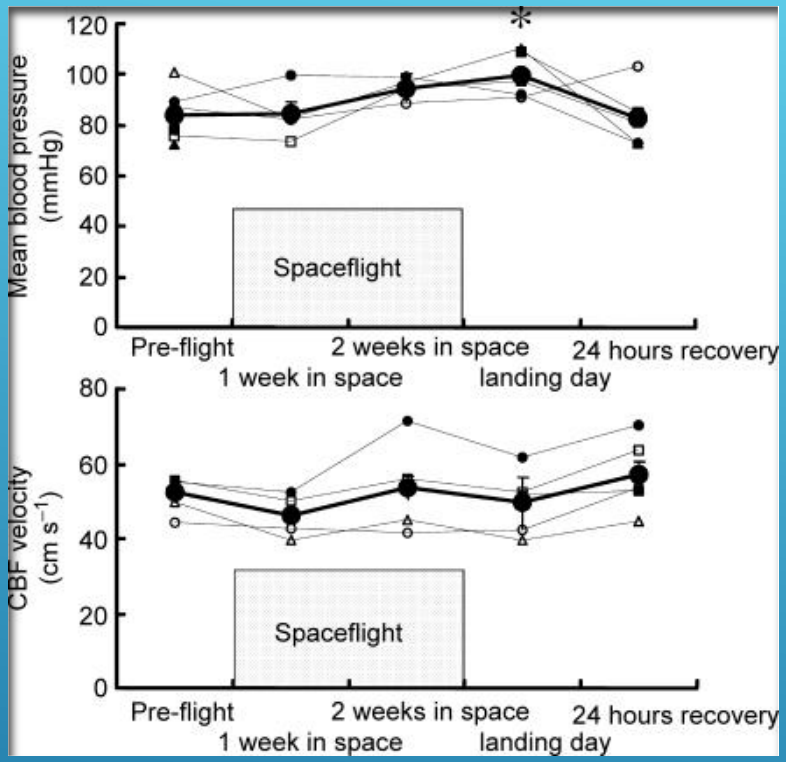
- Impact on tone
  - Reduced gravity affects vascular tone regulation
  - Larger vessel diameter / upward transposition of autoregulation curve
  - Possible difficulty maintaining adequate CBF in varying conditions and across a physiologic range of blood pressure

Table 2

Impact of simulated or actual microgravity on cerebral blood flow and cerebral blood flow velocity.

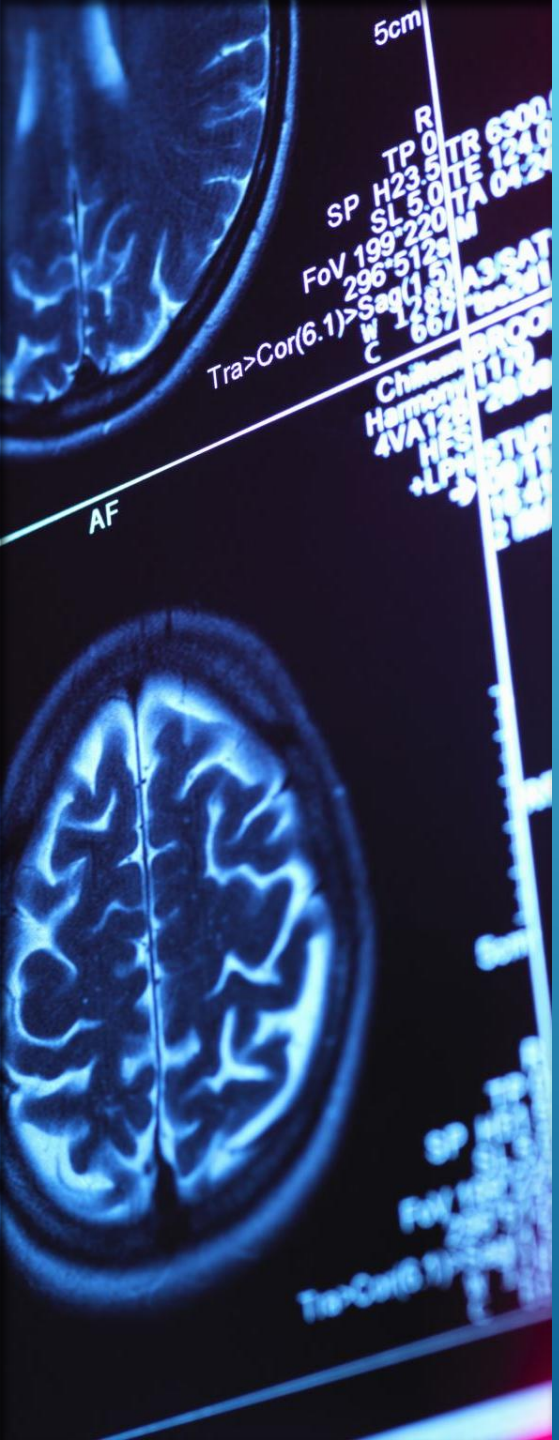
Authors	n	Experimental protocol	Conclusion
Kawai et al. [28]	8	24h, −6° HDBR, TCD, rMCA	CBFv increased at 0.5h of HDBR, during upright seated recovery, CBFv decreased when compared with baseline, and CBFv positively correlated with IAP
Sun et al. [29]	12	21 days, −6° HDBR, TCD, rMCA	CBFv decreased since day 1 and dropped further on day 3 until reaching a minimum value on day 21
Arbeille et al. [30]	24	60 days, −6° HDBR, TCD, rMCA	CBFv significantly decreased on day 55
Iwasaki et al. [31]	6	16 days, space mission, TCD, MCA	Resting CBFv did not change significantly from preflight values during or after spaceflight
Klein et al. [33]	17	15 bouts of 22s intervals Parabolic flight, TCD, rMCA	With decreased MAP and increased CO, CBFv remained unchanged in the microgravity condition
Ogoh et al. [34]	10	3 days, DI, TCD, rICA, rECA, rVA	CBFv in ICA, ECA and VA did not change. A decreased cardiac output associated with CBFv in ICA and VA but not ECA
Marshall-Goebel et al. [35]	9	3 h, −6°, −12°, −18° HDBR, MRI, bilateral ICA and VA	CBFv in ICA decreased at each tilt degree, CBFv in VA did not changed
Ogoh et al. [36]	10	60 days, −6° HDBR, TCD	CBFv in ICA decreased on day 30, returned to baseline on day 57; CBFv in VA remained unaltered throughout HDBR; CBFv in ECA increased on day 30 and 57, indicating long-term microgravity may induce heterogeneous responses in cerebral circulation

CBF – cerebral blood flow; CBFv – cerebral blood flow velocity; HDBR – head-down bed rest; rMCA – right middle cerebral artery; rICA – right internal carotid artery;



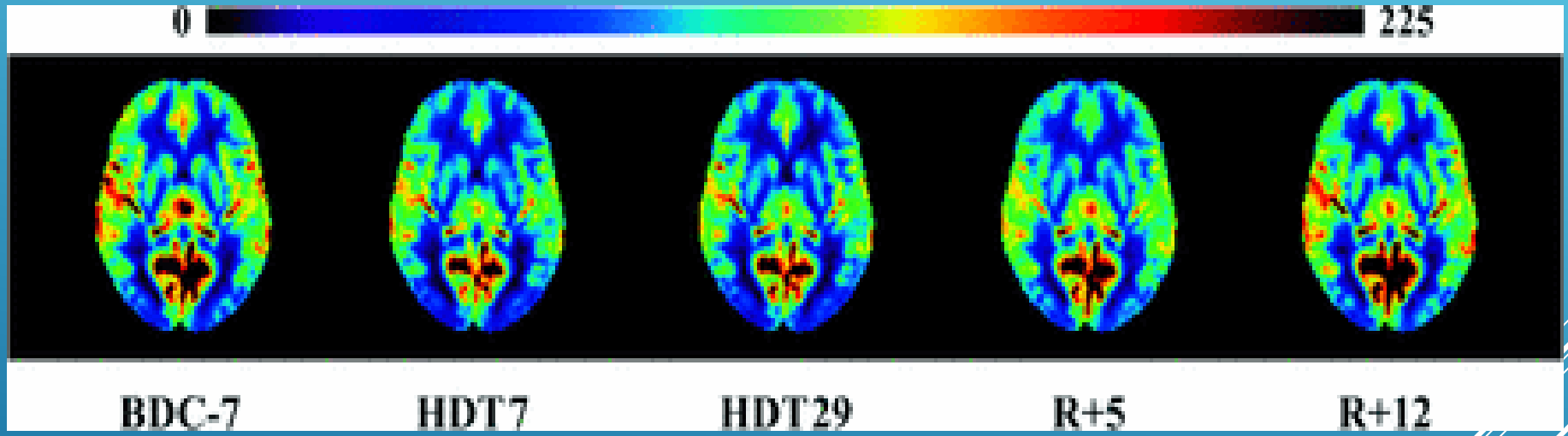
MICROGRAVITY

- Cerebral blood flow velocity spectral powers at very low and high frequencies similar before, during and after spaceflight
- CBFV spectral power at low frequencies significantly less after 1 week in space and on landing day than before spaceflight
- Coherence between arterial pressure and cerebral blood flow velocity fluctuations above 0.5 in all most, unchanged at very low and high frequencies, but significantly lower at low frequencies after 1 week in space.



CBF, CBFV, PERFUSION

- Variable in spaceflight studies
- CBF may initially increase with increased lumen diameter but quickly start to decline as CBFv decreases
  - May change over time
- Elevated cerebral arterial pressure (vector change) results in increased intrinsic vasoconstrictor responsiveness of the cerebral arteries and remodeling of the cerebral arterial vasculature
  - Characterized by the thickening of the medial smooth muscle cell layer
  - May result in a decreased maximal intraluminal diameter
  - Reduced CBFv



CBF, CBFV, PERFUSION

Impact of simulated or actual microgravity on cerebrovascular autoregulation.

Authors	n	Experimental protocol	Conclusion
Blaber et al. [3]	27	8–16 days of spaceflight	A mismatch of cerebral blood flow with blood pressure has been noticed and it may be the cause of presyncope
Pavy-Le et al. [55]	8	7-day of −6° HDBR	No major changes found in cerebral autoregulation responses. Nevertheless, the association between cerebral autoregulatory responses and orthostatic intolerance has been noticed
Jeong et al. [51]	21	18-day of −6° HDBR	CA was preserved or improved after HDBR. Furthermore, changes in plasma volume may play an important role in CBF regulation
Iwasaki et al. [31]	6	1–2 week of spaceflight	CA was preserved, even improved by short-duration spaceflight. This could be attributed to raising responsiveness of cerebral vascular smooth muslce to changes of transmural pressure
Kermorgant et al. [57]	12	21-day of HDBR	Dynamic CA was improved after 21-day of HDBR
Kermorgant et al. [16]	12	3-day of DI	CA was improved, however, a persistent elevation ICP favours poor CA recovery after 3 days of DI
Kurazumi et al. [53]	15	4 bouts 10-min of −10° HDBR/supine combined with placebo/CO_2	The combination of mild hypercapnia and HDBR attenuated dynamic cerebral autoregulation

CA – cerebrovascular autoregulation; DI – dry immersion; ICP – intracranial pressure; HDBR – head-down bed rest.

ON THE ISS

Current TCD machine on ISS
(Limited by astronaut training)

In spaceflight:

Decreased MAP

Increased central blood volume

Increased PI

Increased flow velocities in long-term spaceflight

- MCAv 44-115% above preflight supine values
- Largely due to reduction in hgb, not ICP driven

Venous velocities (less reliable)

LONG TERM AUTOREGULATION

- No conclusive evidence showing that the duration of exposure to microgravity impacts long term cerebrovascular autoregulation
- However, orthostatic intolerance is common during long-term microgravity
  - Association between orthostatic intolerance and impaired cerebrovascular autoregulation
- Persistently elevated ICP (after return to 1G) attributed to poor cerebral autoregulation recovery

CLINICAL IMPLICATIONS

Risk of cerebral edema

- Altered perfusion, autoregulation
- More risk on longer exposure

Clinical manifestations

- Increased susceptibility to migraine, cognitive impairment, and neurodegenerative disease

Neuroplasticity

- Brain may undergo adaptive changes in response to microgravity and altered perfusion
- Long term effects still under investigation

COUNTERMEASURES

Exercise regimens

Lower body negative pressure

Regular exercise

Fluid loading

Pharmacological interventions

B vitamins, folate, antioxidants

Impact on homocysteine metabolism

CAROTID ULTRASOUND IN SPACE

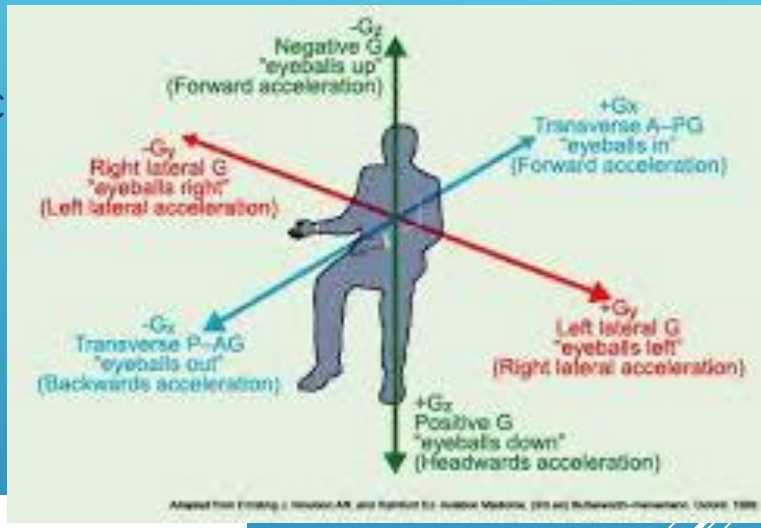
- Also on ISS currently
  - Ease of operator training
- Used for arteries and veins
  - Sluggish venous flow / return
  - Some concern for incidence of IJ thrombus
    - Vector and fluid dynamic shifts impairing venous returning
- More monitoring is needed

- Individual monitoring
- ICP changes
- MCA MFV and/or PI changes
  - Increases above expectation initiate:
    - Hgb / blood test
    - Fluid loading
    - Exercises / LBNP
    - Ground consultation
    - Pharmacologic intervention
- IJ flow
  - Thrombus prevention
  - LBNP

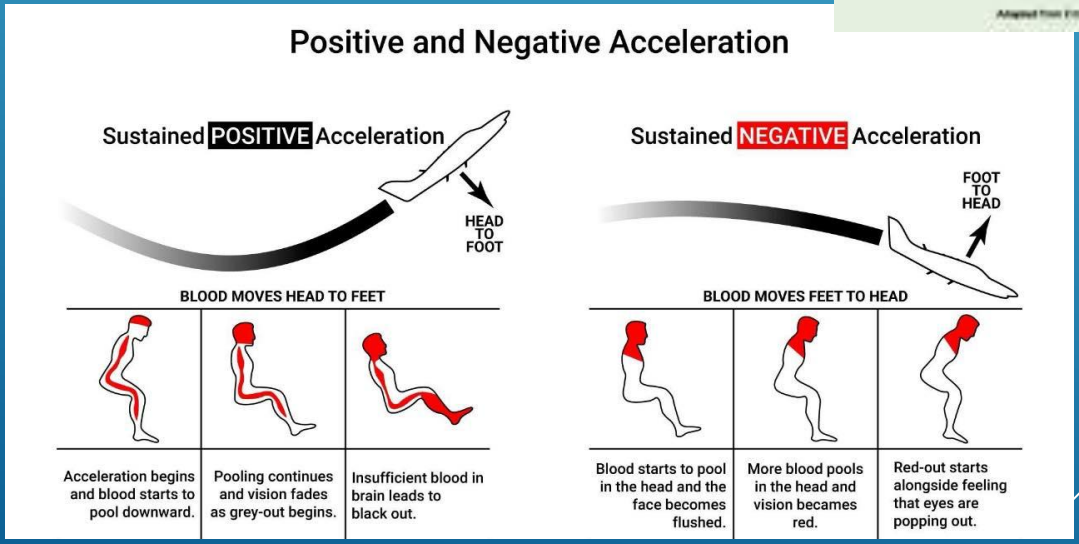
POTENTIAL TO USE TCD/US TO DETERMINE COUNTERMEASURES, INTERVENTIONS

+GZ

- Essentially hyper-gravity (pressure with defined vector, different from generalized pressure / hyperbaria)
  - Vector typically angulated / dynamic
  - Brief, bursts
- Pilots, training, simulated gravity
- Lateralizing differences



+GZ



- Human centrifuge
- Parabolic flight
- Tactical aviation

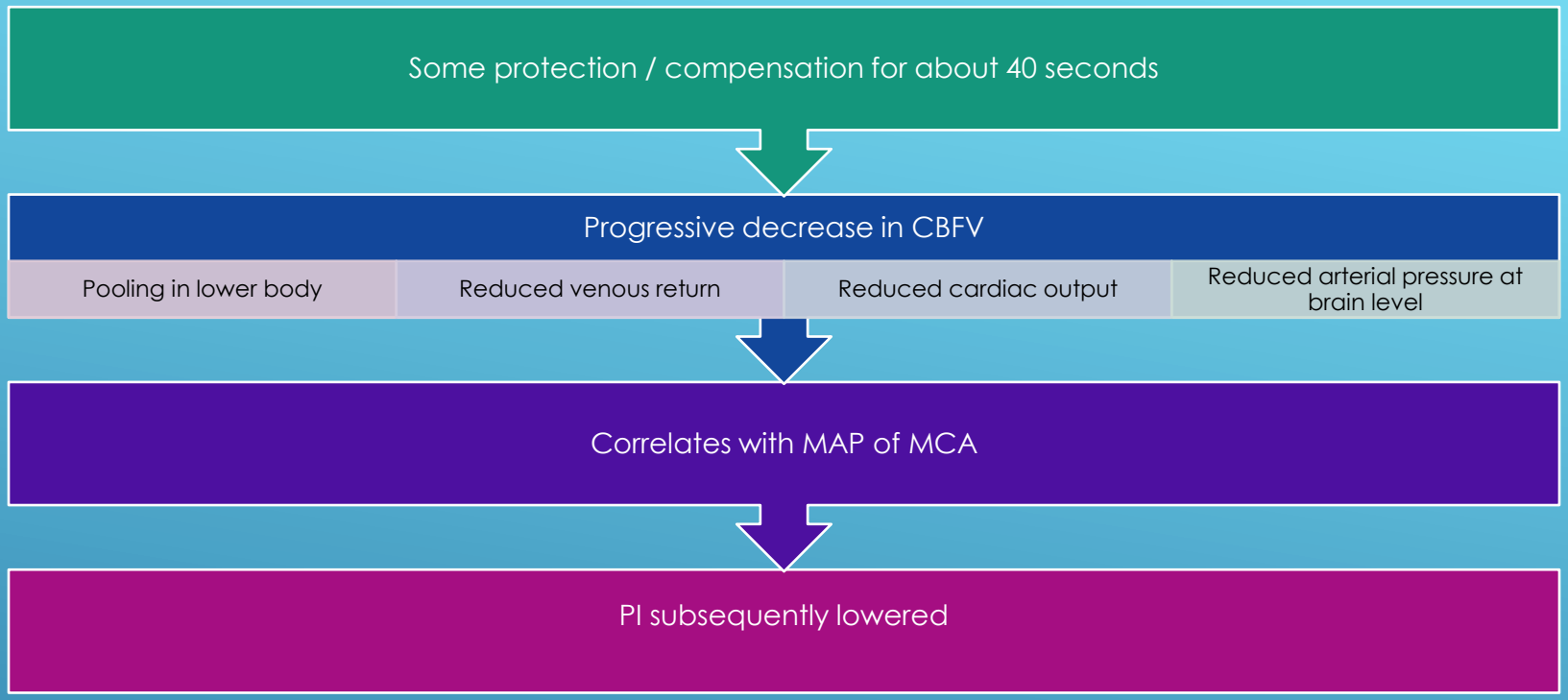
+GZ

+GZ

- Significant reduction in CBF
  - Can progress to ischemia, LOC
  - Hydrostatic pressure redistribution
  - Even mild (+1.5 Gz) reduces mean cerebral blood flow velocity by 5-7% (and MCAv) within 5-20min
    - Cerebral oxygen saturation measured by NIR spectroscopy does not decrease despite lower CBFv
      - Suggests compensatory increase in o2 extraction, altered arteriovenous volume ratios
  - G-LOC at about 76% reduction from baseline (ischemic, not stress)
- Major mechanism: Arterial pressure at brain level (MAPMCA) decreases significantly (17-25%) even when heart-level pressure stable

G FORCES AND AUTOREGULATION

- Compensatory autoregulation:
  - Mild +Gz: Cerebral autoregulation improves in low and high frequency ranges, stabilizes CBF despite increased arterial pressure oscillations
  - More severe, > +3 Gz (gravitational or centrifuge): Cause leftward shift of autoregulation curve, indicative of adaptation to reduced CPP


Some protection / compensation for about 40 seconds
Progressive decrease in CBFV
Pooling in lower body
Reduced venous return
Reduced cardiac output
Reduced arterial pressure at brain level
Correlates with MAP of MCA
PI subsequently lowered

+GZ

Regional variability/heterogeneity

Anterior circulation (MCA) shows impaired dynamic cerebrovascular reactivity during head-up tilt while posterior is preserved

During gravitational transitions in parabolic flight, posterior circulation shows selective increase in flow during micro- to hyper-gravity changes

Secondary effects (beyond hypoperfusion):

Repeated transitions increase systemic oxidative-nitrosative stress and may promote BBB disruption (seen with elevated gliovascular biomarkers)

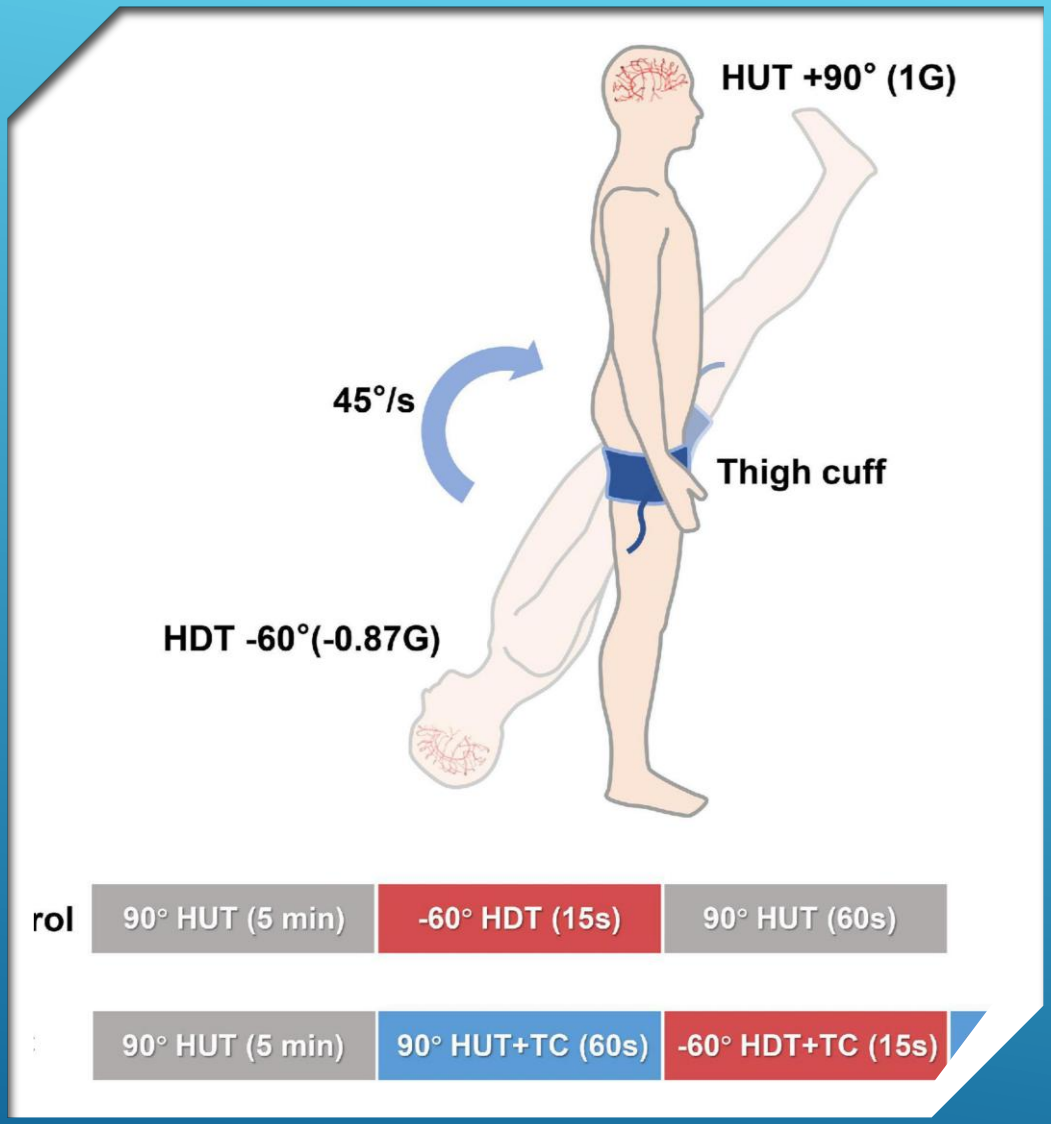
High +Gz exacerbate pulmonary ventilation-perfusion gradients, potentially impairing circulatory oxygenation

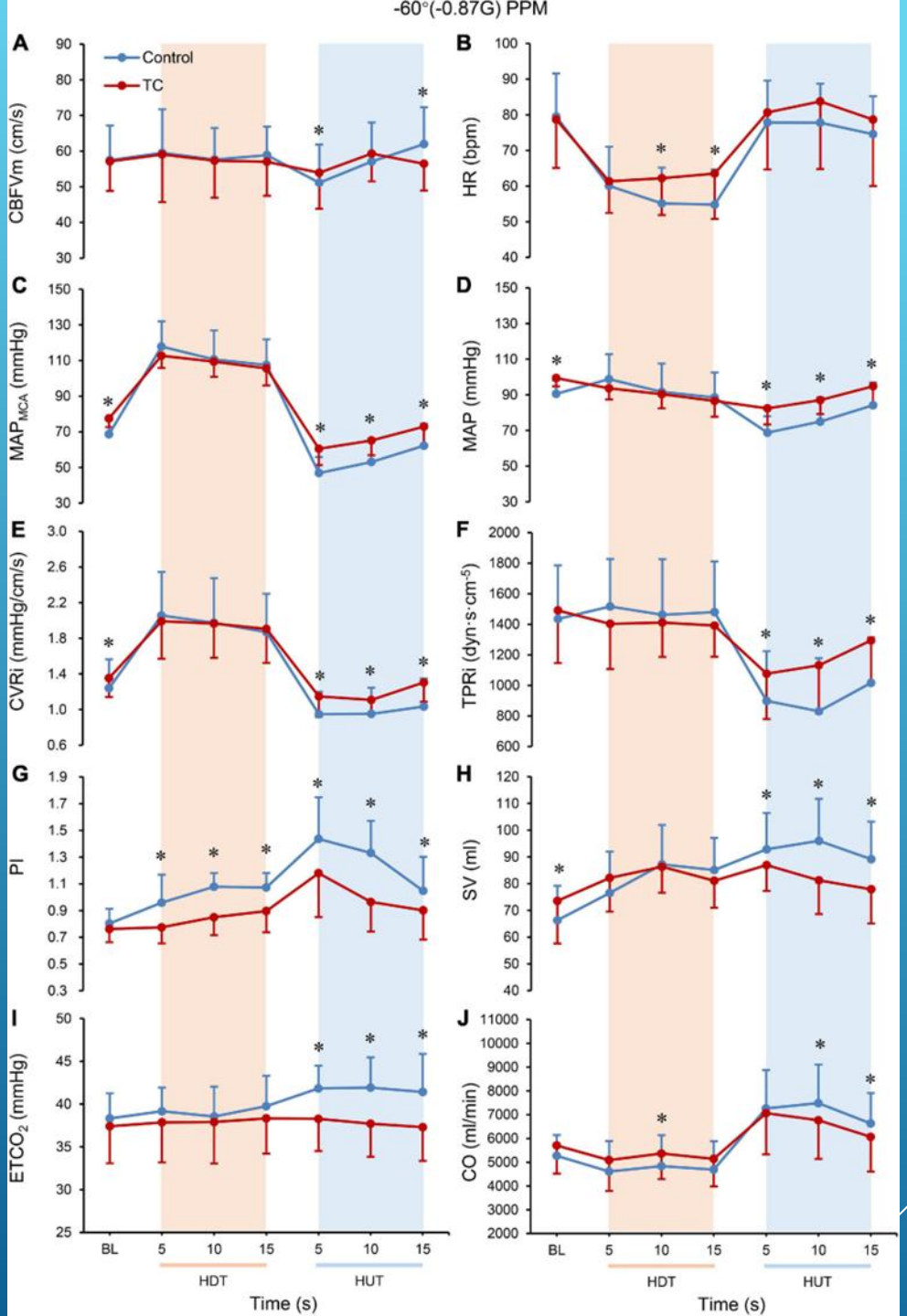
+GZ

SIMULATION AND MITIGATION

- Acute transition from negative (−Gz) to positive (+ Gz) gravity (push-pull maneuver for high-performance pilots) significantly impairs cerebral perfusion
- Loss of consciousness in pilots generally happens just after the rapid transition from −Gz to + Gz (risk phase)
- The dramatic reduction of MAP_{MCA} and cerebral perfusion during transition from "pull" (−Gz) to "push" (+ Gz) constitutes the direct reasons for loss of vision or conscious during PPM

SIMULATION AND MITIGATION




-60°(-0.87G) PPM
A
Control
TC
CBFVm (cm/s)
B
HR (bpm)
C
MAP$_{MCA}$ (mmHg)
D
MAP (mmHg)
E
CVRi (mmHg/cm/s)
F
TPRi (dyn·s·cm^{-5})
G
PI
H
SV (ml)
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CO (ml/min)
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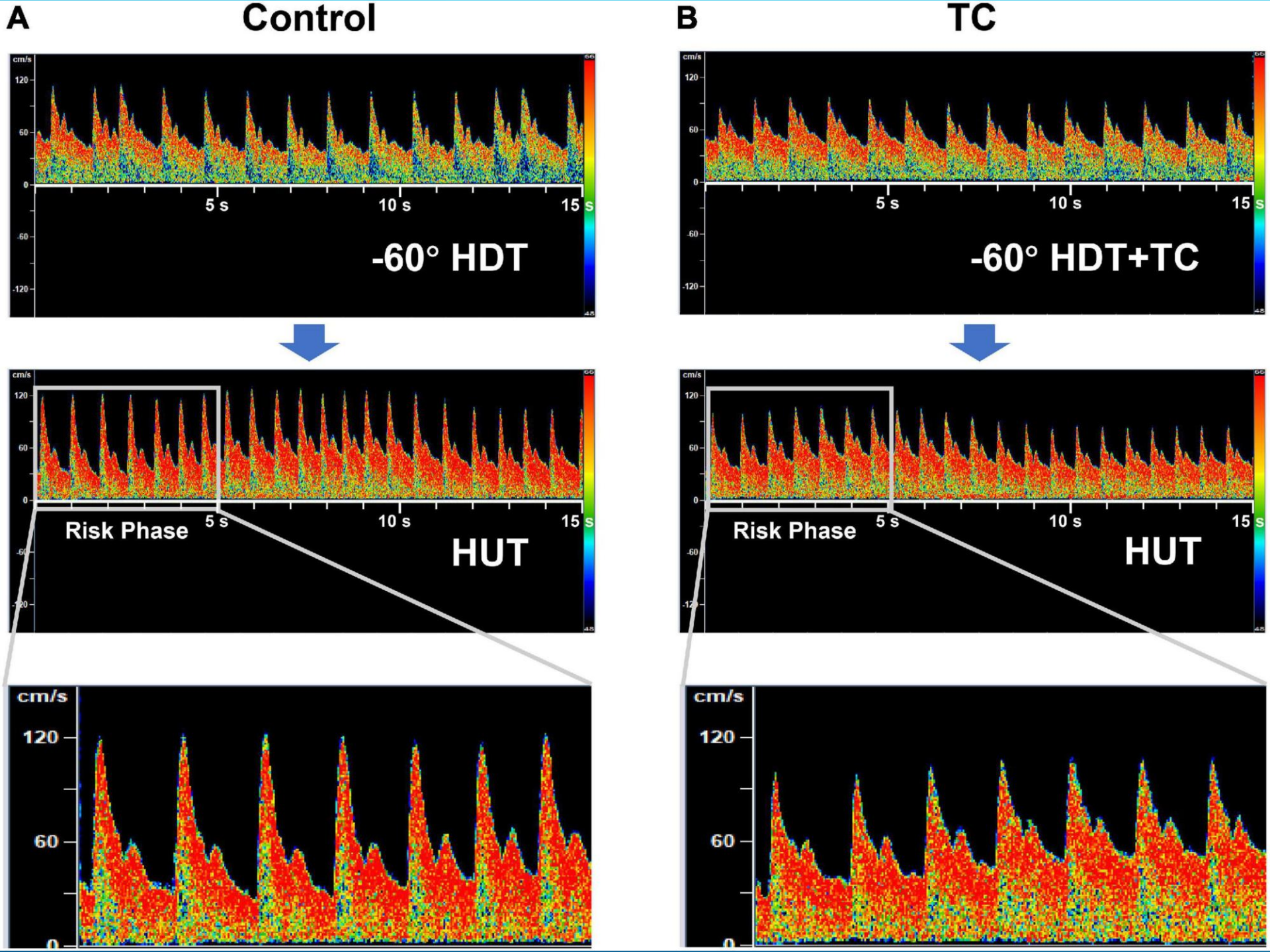

A
Control
B
TC
cm/s
120
60
0
-60
-120
5 s
10 s
15 s
-60° HDT
-60° HDT+TC
Risk Phase
HUT

SIMULATION AND MITIGATION

- High pulsatility in the control bout due to reduction of diastolic cerebral blood flow
- Reduced CBF during simulated PPM caused by dramatic and acute drop of MCA blood pressure
- Both the magnitude and timescale of blood pressure changes are too large and too fast to be fully corrected by autoregulation
- Cerebral autoregulation itself not affected in healthy young subjects during the rapid gravitational transition

- Passive hydrostatic increases in ICP help prevent hyperperfusion
- ECA may be shunting pathway in certain individuals
- Anti-G straining maneuver: sustained isometric muscle contraction (legs and abdomen) and synchronized breathing to maintain cerebral perfusion
  - Increased intrathoracic pressure and peripheral vascular resistance

SIMULATION AND MITIGATION

TCD OPPORTUNITIES

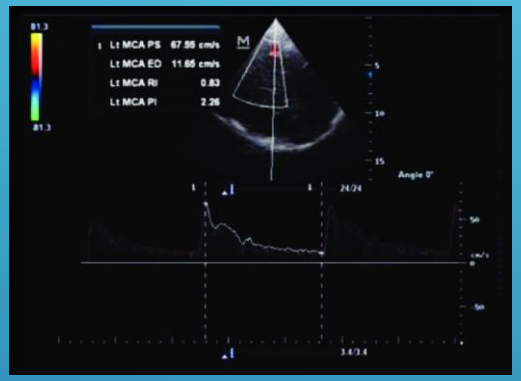
- Feedback in training / maneuver execution
- Evaluate pilot candidacy / eligibility
- Determine effectiveness of mitigation strategies and devices
  - Thigh cuffs
  - G suits

HYPOBARIA (ALTITUDE)

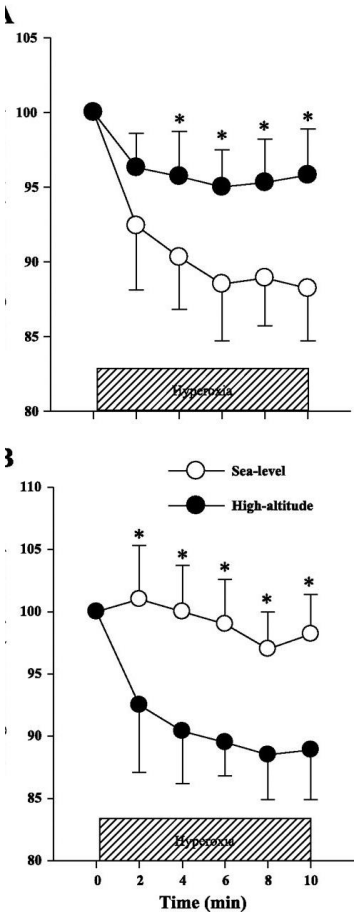
HYPOBARIA

- Cerebral vasodilation (due to hypoxia)
  - Competing with compensatory hyperventilation-induced hypocapnia (constriction)
  - Further complicated by supplemental O2
- Increased CBF
  - 24-53% increase in CBF within hours to days (hypoxic vasodilation)
    - Attempt to maintain O2 delivery despite lower O2 content
- Some potential for cerebral edema
- Normalizes over days to weeks (increased Hgb, ventilatory acclimation)

HYPOBARIA

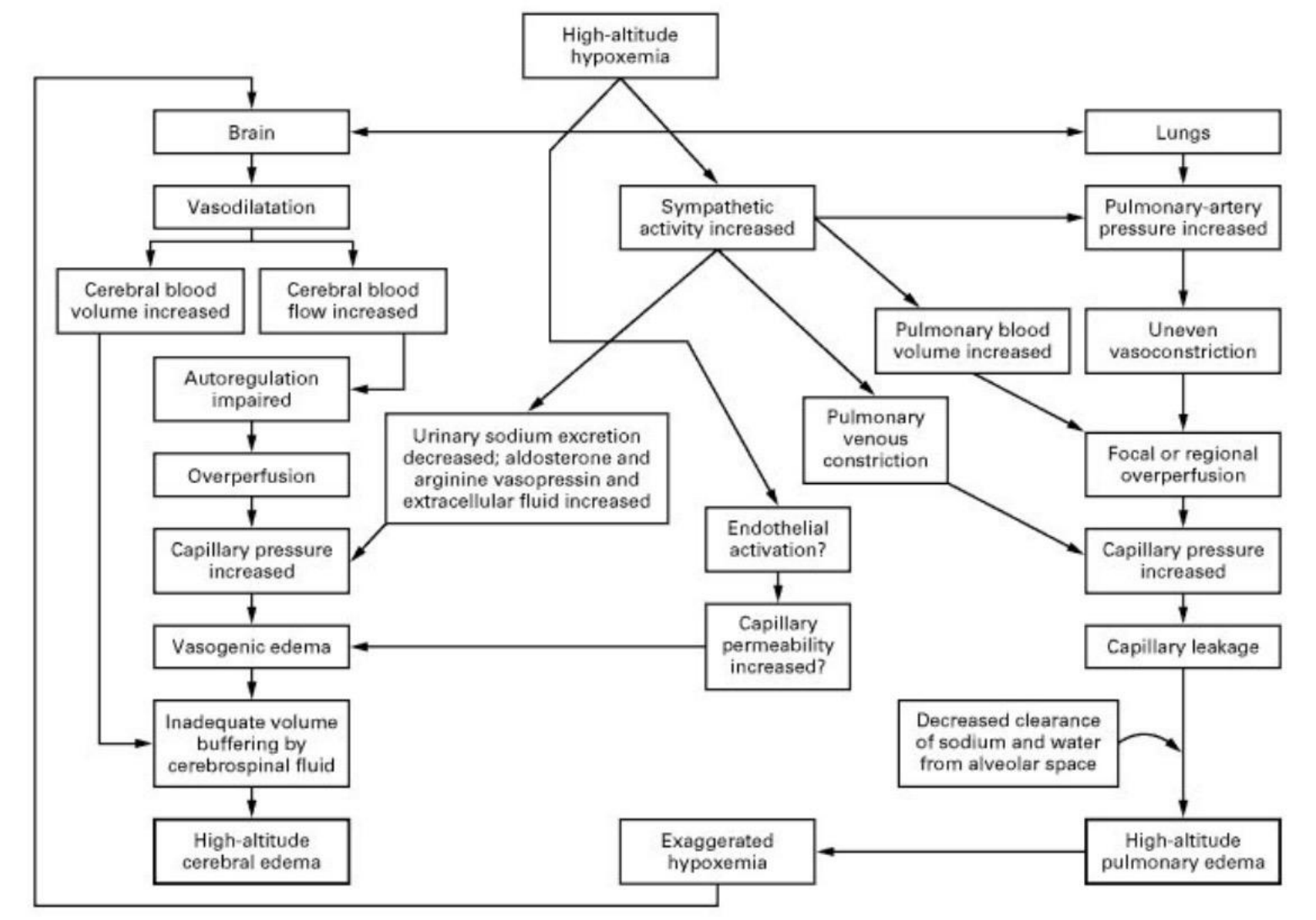


- Vasogenic edema
  - Elevated cerebral capillary pressure
  - Impaired autoregulation
  - Hypoxia-induced changes in BBB permeability
- Mediated by VEGF, NO, bradykinin
- Intracranial pressure fluctuations combined with vascular stretch from vasodilation activate trigeminovascular system, contributing to headaches

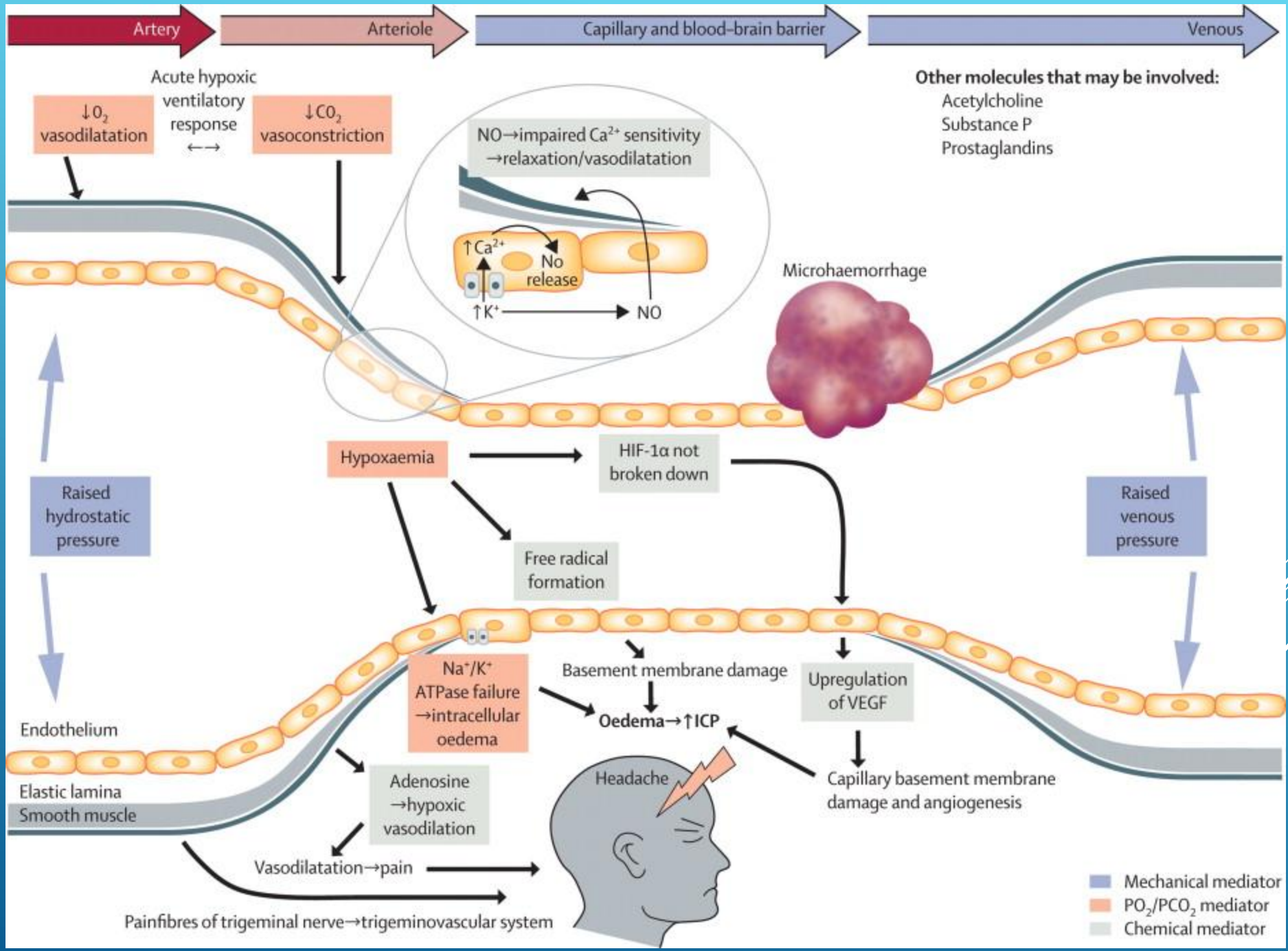


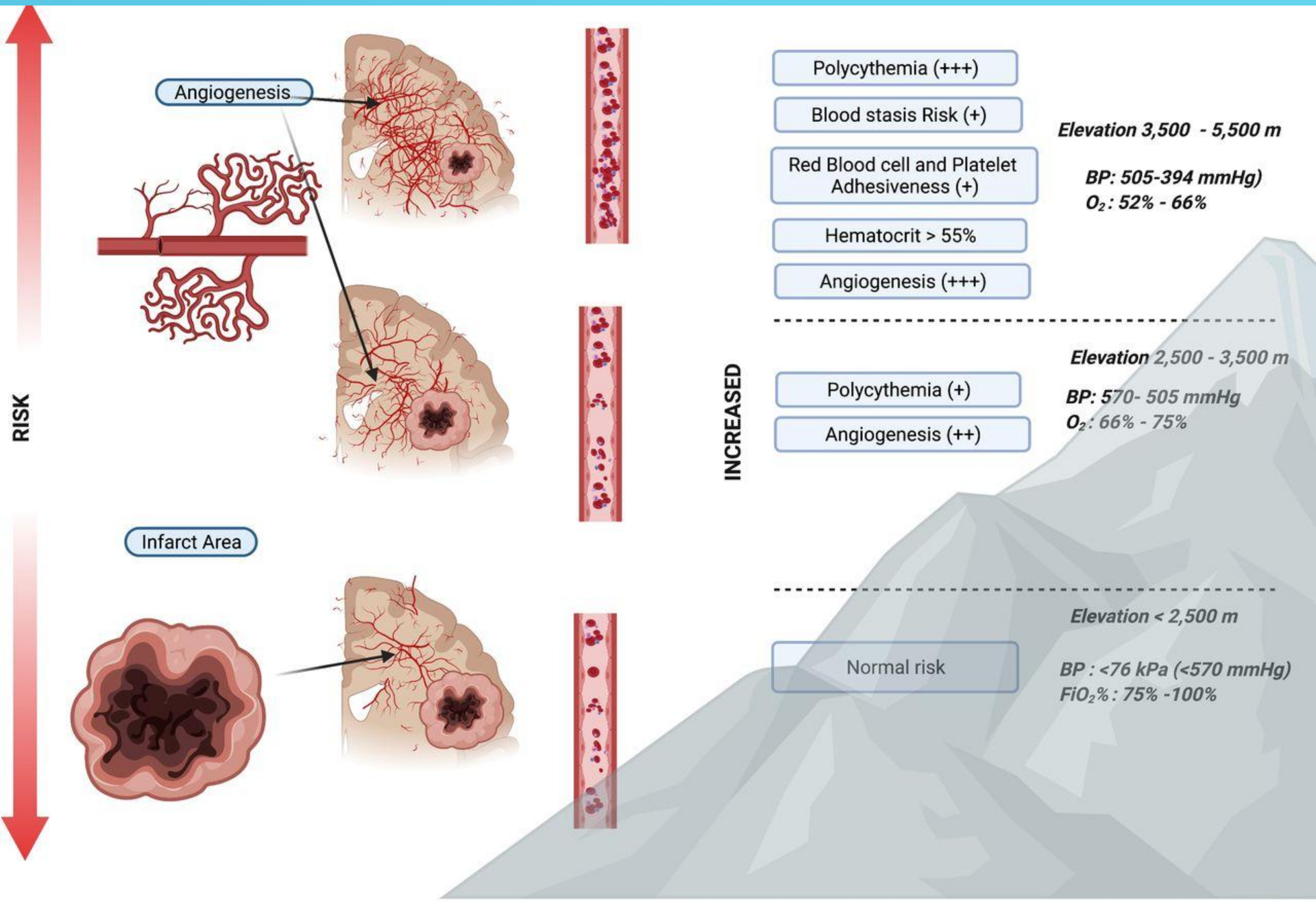
- Percent changes in MCAv and MAP during 10 min of hyperoxia at sea level (○) and at high altitude (•)
- Hyperoxia caused a greater decrease in MAP and lesser of a change in MCAv at high altitude compared with sea level. (*$P < 0.05$)

HYPOBARIA


High-altitude hypoxemia
Brain
Lungs
Vasodilatation
Sympathetic activity increased
Pulmonary-artery pressure increased
Cerebral blood volume increased
Cerebral blood flow increased
Pulmonary blood volume increased
Uneven vasoconstriction
Autoregulation impaired
Urinary sodium excretion decreased; aldosterone and arginine vasopressin and extracellular fluid increased
Pulmonary venous constriction
Focal or regional overperfusion
Overperfusion
Endothelial activation?
Capillary pressure increased
Capillary pressure increased
Capillary permeability increased?
Vasogenic edema
Capillary leakage
Inadequate volume buffering by cerebrospinal fluid
Decreased clearance of sodium and water from alveolar space
High-altitude cerebral edema
Exaggerated hypoxemia
High-altitude pulmonary edema

HYPOBARIA


Artery
Arteriole
Capillary and blood–brain barrier
Venous
Other molecules that may be involved:
Acetylcholine
Substance P
Prostaglandins
Acute hypoxic ventilatory response
↓O_2 vasodilatation
↓CO_2 vasoconstriction
NO→impaired Ca^{2+} sensitivity →relaxation/vasodilatation
↑Ca^{2+}
No release
↑K^+
NO
Microhaemorrhage
Hypoxaemia
HIF-1α not broken down
Raised hydrostatic pressure
Raised venous pressure
Free radical formation
Na^+/K^+ ATPase failure →intracellular oedema
Basement membrane damage
Upregulation of VEGF
Oedema→↑ICP
Endothelium
Elastic lamina
Smooth muscle
Adenosine →hypoxic vasodilation
Headache
Capillary basement membrane damage and angiogenesis
Vasodilatation→pain
Painfibres of trigeminal nerve→trigeminovascular system
Mechanical mediator
PO_2/PCO_2 mediator
Chemical mediator


RISK
INCREASED
Angiogenesis
Infarct Area
Polycythemia (+++)
Blood stasis Risk (+)
Red Blood cell and Platelet Adhesiveness (+)
Hematocrit > 55%
Angiogenesis (+++)
Elevation 3,500 - 5,500 m
BP: 505-394 mmHg)
O2: 52% - 66%
Polycythemia (+)
Angiogenesis (++)
Elevation 2,500 - 3,500 m
BP: 570- 505 mmHg
O2: 66% - 75%
Normal risk
Elevation < 2,500 m
BP : <76 kPa (<570 mmHg)
FiO2% : 75% -100%

HYPOBARIA

- Higher rate of:
  - TIA in younger individuals
    - More robust vasospasm / hypocapneic vasoconstriction
  - CVST
    - Dehydration, polycythemia

TCDS

No changes for most people in hyperacute period

Initial increase in MCAv 20-27% within 12-24 hours

- Important for long-duration flights

Normalization over days / weeks

High individual variability

TCDS

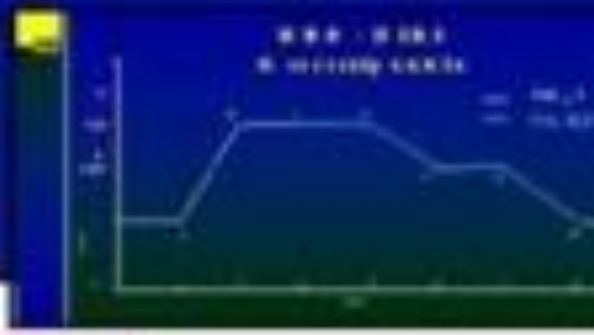
- Potential role for TCD utilization in determining safety of non-pressurized aircraft
  - Mission duration
  - Mid-air refueling
- Individual susceptibility
- Determination of contribution to fatigue, rest periods
- Severity of altitude sickness / development of edema
  - Extraction need

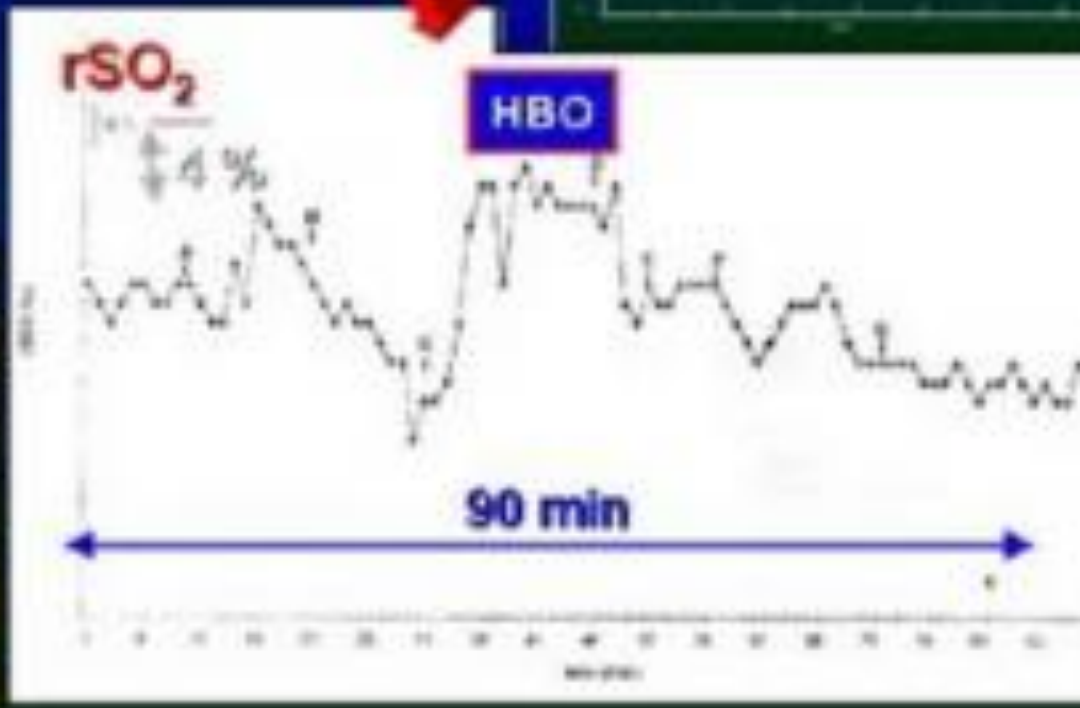
HYPERBARIA (SUBAQUATIC)

- Even after single scuba session, subtle alterations in cerebral blood flow regulation at rest can be measured
  - Extracranial vasodilation (ICAs)
  - Reduced shear patterns in ICA and verts
  - Elevated intracranial velocities
  - Does not translate to reductions in cerebrovascular reactivity, neurovascular coupling (regional CBF response to local increases in cerebral metabolism), or global CBF after single dive
    - May not be the case with repeated, prolonged, or deeper dives / exposure

HYPERBARIA

CEREBRAL OXYMETRY during HYPERBARIC OXYGENATION



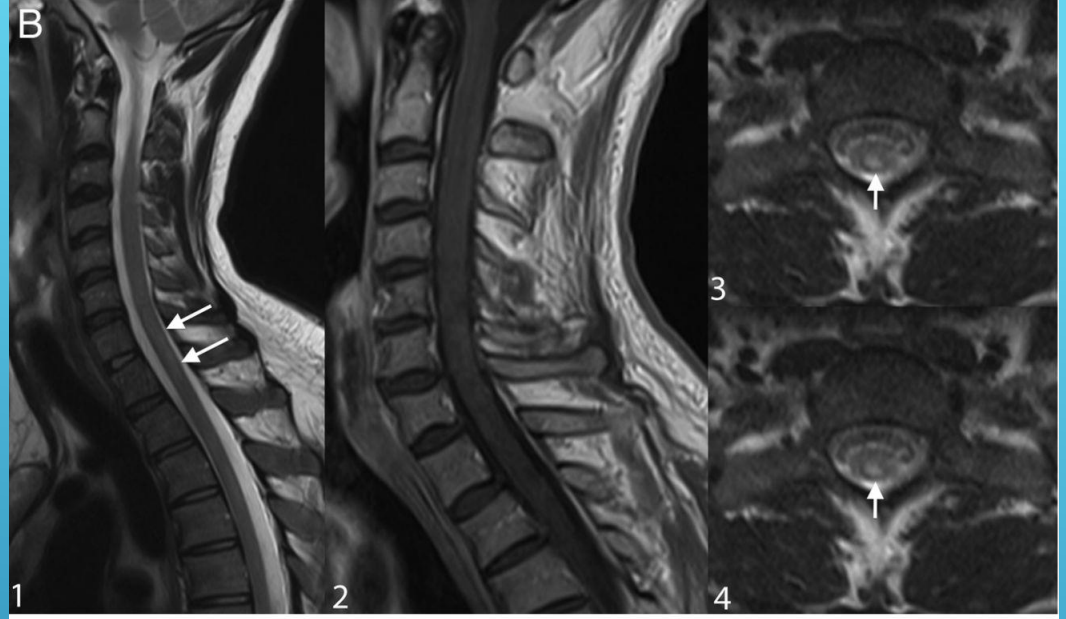


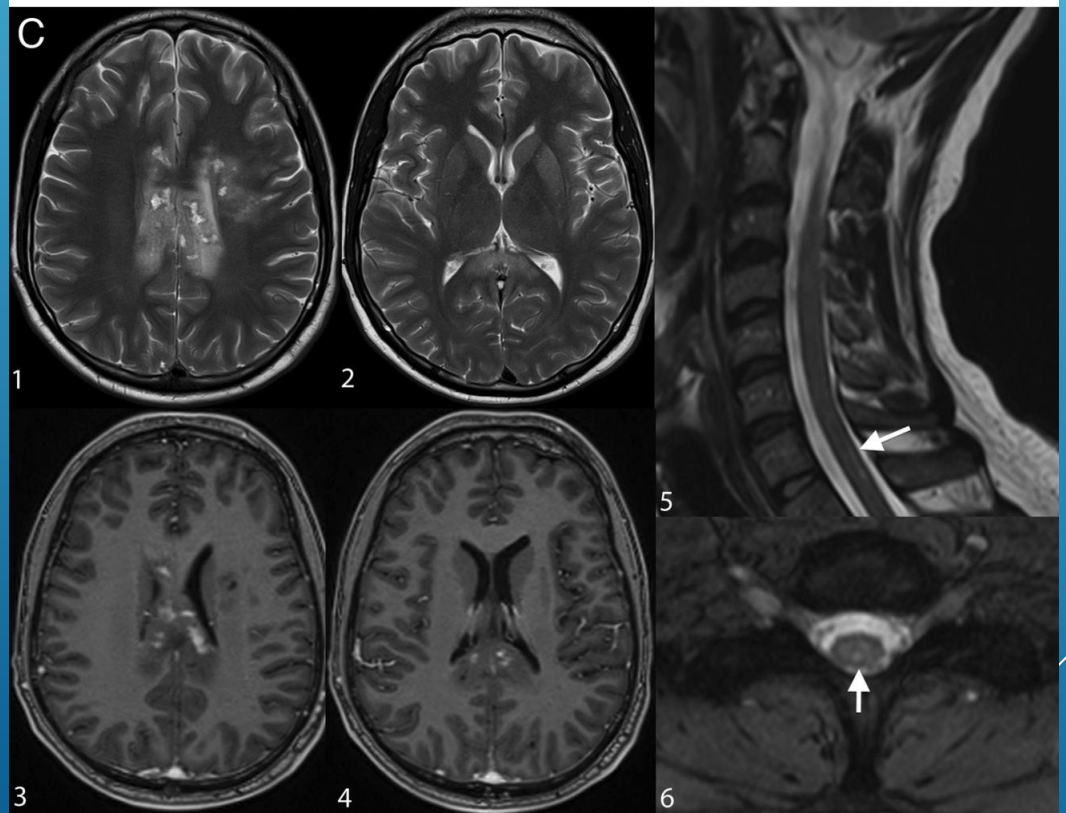
HYPERBARIA

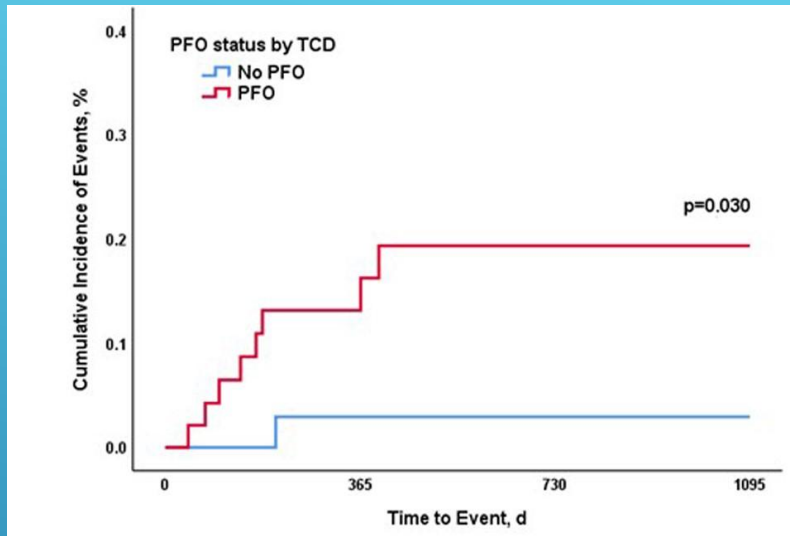
- Breath holding
  - If repetitive, can cause cerebral decompression illness
    - Nitrogen accumulation with short surfaces between dives, causing ischemic lesions
    - “taravana” – pearl divers

- Expanding gas ruptures alveolar-capillary membrane
  - Can occur even in shallow dives (1m)
  - Endothelial stripping causes impaired tone regulation and plasma leak
  - Inflammatory/thrombogenic response
  - Small doses of arterial gas can cause progressive decline in CBF via neutrophil-mediated mechanism
- Decompression sickness
  - Venous gas emboli
  - PFO, shunt make this more likely / dangerous (higher risk of DCI)
  - If gas emboli become arterial, can grow through inward gas diffusion in supersaturated tissues
  - Diverse patterns of corpus callosum hyperintensities (hallmark finding, vulnerable to ischemia and vasogenic edema)
  - Can affect spinal cord

ASCENT

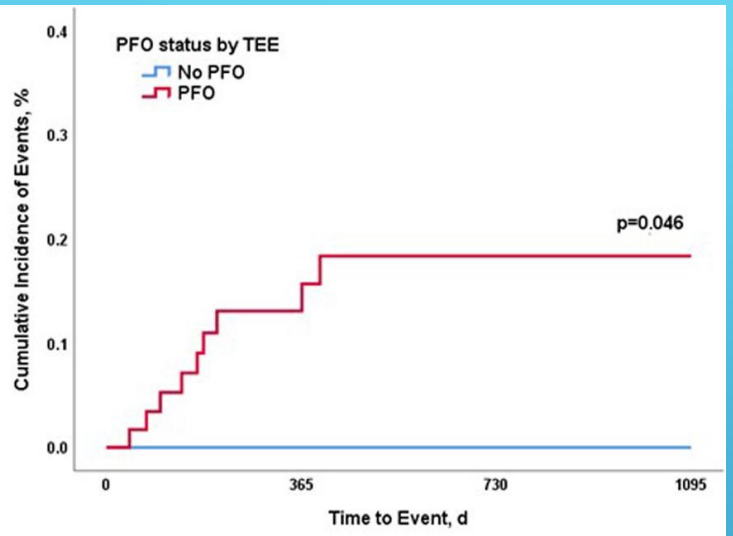

B
1
2
3
4


C
1
2
3
4
5
6



At risk, n

PFO	47	34	24	16
No PFO	35	32	29	18



At risk, n

PFO	59	46	34	19
No PFO	23	20	20	15

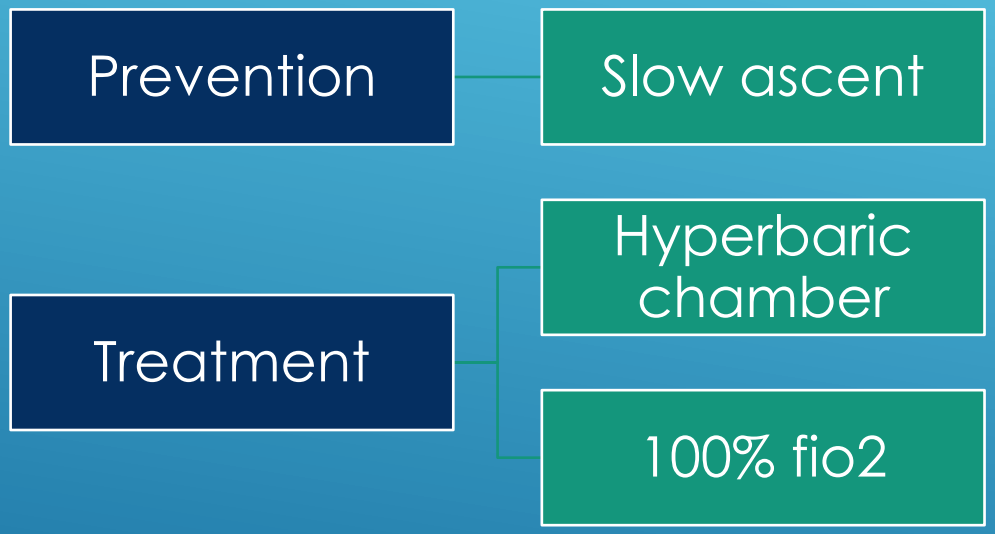
- TCD just as effective as TEE for predicting DCI

ASCENT

POST-DIVE

- Hyperbaria reduces MCAv through hyperoxia induced vasoconstriction, with post-dive transient elevation in intracranial velocities for about 30 min
  - Driven by hyperoxia, not pressure itself

TREATMENT


Prevention
Slow ascent
Treatment
Hyperbaric chamber
100% fio2

FUTURE CUS / TCD OPPORTUNITIES

- Safety of repeated dives/ depths/ durations
  - Vessel diameter
  - Flow patterns
  - Intracranial velocities
  - Reactivity
- Duration of recovery period / return to high-performance activity
  - Normalization of velocities post-dive
- DCI prediction
  - Screening for PFO/shunt
  - Portable for ships/submarines
  - Noninvasive

TEMPERATURE

TEMPERATURE

- Cold more dangerous than heat
- Every 1C decrease + 7.77% increase in plt aggregation
  - Mediated by elevated CIRBP levels and activation of p-AKT/p-ERK pathways
- Cold activates sympatheic nervous and renin-angiotensin systems, promoting inflammation, platelet activation, and immune dysfunction
- More vulnerable to hemorrhage (and increased mortality if it occurs)
- 1.2 % increase in cerebrovascular events per 1C decrease in environmental temperature
  - Multifactorial

TEMPERATURE

MCAv reduced in proportion to reduction of core temperature

- Despite increased MAP, indicating cerebral vasoconstriction
- MCAv down 20-30% when core down 1C
- Independent of environmental O2
- MCAv reduction also seen in therapeutic cooling
  - Activation of cold-sensitive TRPM8 channel, attenuates endotherlium-dependent cerebral vasodilation

Regional variation

- In arctic (high latitude) expeditions, reduced temperatures caused mV and PSV reduction in L MCA and increased PI in R MCA
  - Possible shunting, hemisphere dominance

TEMPERATURE

Heat

High temperatures cause inflammation, oxidative stress, and alters the coagulation system

Exacerbation of Afib and HTN

1.2% increase in ischemic stroke per 1C, but protective for hemorrhage (-1.9% per 1C)

- Theorized that elevated temperatures cause relaxation of peripheral vessels, reducing afterload and BP in people without HTN

TEMPERATURE

- Passive heating in hot, humid environment decreases CBF by 30% while cerebral metabolic demand increases 10%
  - Mismatch, O2 delivery reduced 12-19%
- Non-invasive ICP estimates (TCD) increase by 18% at thermal tolerance across all heating modes
- Extreme heating may increase BBB permeability resulting in vasogenic edema

TEMPERATURE

- Elevated body temperature decreases MCAv during passive hyperthermia (up to 20-30% from baseline when core up 1-2C)
  - Driven by hyperthermia-induced hyperventilation and hypocapnia
  - Regional variability- greater flow reduction in vertebral arteries
- PI increases during and immediately after hyperthermic exposure
    - Alteration in cerebrovascular resistance, ICP

GAS ALTERATIONS

GAS DISRUPTION

- O2
  - Environmental, but more often administered
    - Pilots in high G exposure
      - Oscillatory vs steady state
    - High altitude
    - Diving
- CO2
  - Space

GAS DISRUPTION- CO2

- CO_2 = potent vasodilator, also combines with water to form carbonic acid -> dissociates to form hydrogen ions (vasodilator)
- Excess carbon dioxide can dilate blood vessels up to 3.5 times their normal size.
- Impaired dynamic cerebral autoregulation and neurovascular coupling
- As the arterial tension of CO_2 rises, CBV and CBF increase.
- A 70 % increase in arterial PCO_2 approximately doubles the cerebral blood flow.

GAS DISRUPTION- CO_2

- High CO_2 causes increased CBF and CBV, however increased CBF is disproportionate to increase in CBV
  - Disproportionate response of vasodilation affecting resistance vessels
  - Reduces cerebrovascular resistance and decreases effective cerebral perfusion pressure (zero flow pressure)
    - Temporally uncoupled from neuronal activity

GAS DISRUPTION- CO2

- Artificial atmosphere (ISS / space) may have elevated CO2 content
- Despite vasodilation, interplay between pressure/fluid shifts and vessel caliber may exacerbate vascular / venous congestion
- Headaches, thrombus

GAS DISRUPTION- HYPOXIA

Hypoxia dilates blood vessels and increases blood flow

MCAv increased on TCDs

Elevated activity in a given region results in increase in CO_2 and H^+, causing cerebral vasodilatation and more blood delivery to the area to meet the increased demand

Oxygen metabolism for local regulation of CBF is an important protective response against diminished cerebral neuronal activity

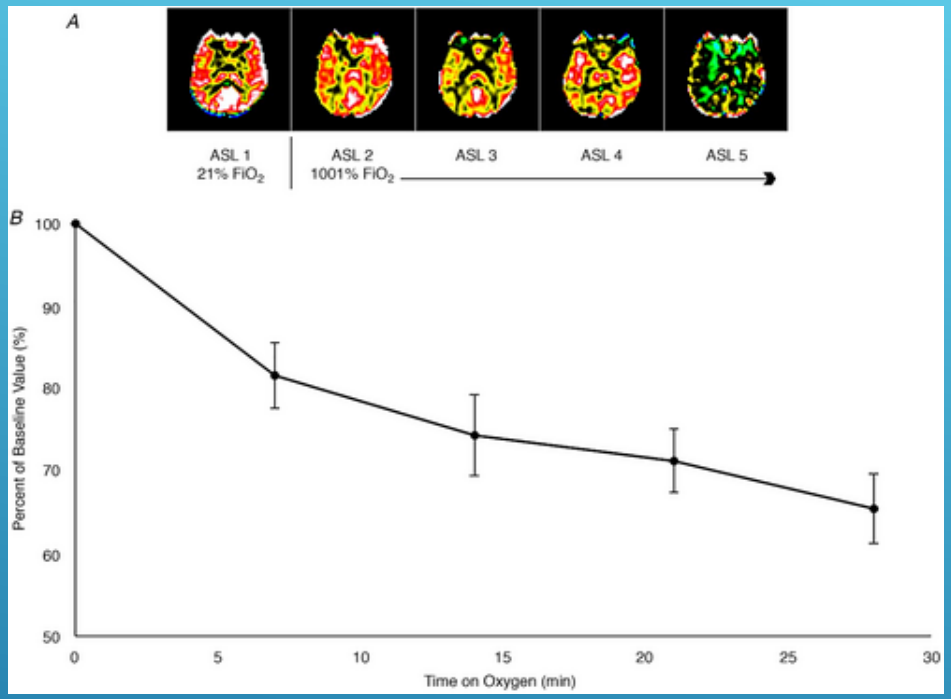
Prevents derangement of mental capability

GAS DISRUPTION- HYPEROXIA

- O2 administered to tactical aviators for neuro-protection
- Paradoxical reduction in gGBF
- Anecdotal improvement
- Cognitive testing: faster, less accurate

GAS DISRUPTION- HYPEROXIA

- High O2 delivery:
  - Constriction of cerebral blood vessels
  - No/minimal change in gCBF up to FiO2 50%
  - Vasoconstriction at FiO2 >50%, plateau at 80%
  - 35% reduction in gCBF during 30 min 100% FiO2 exposure on MRI with arterial spin labeling



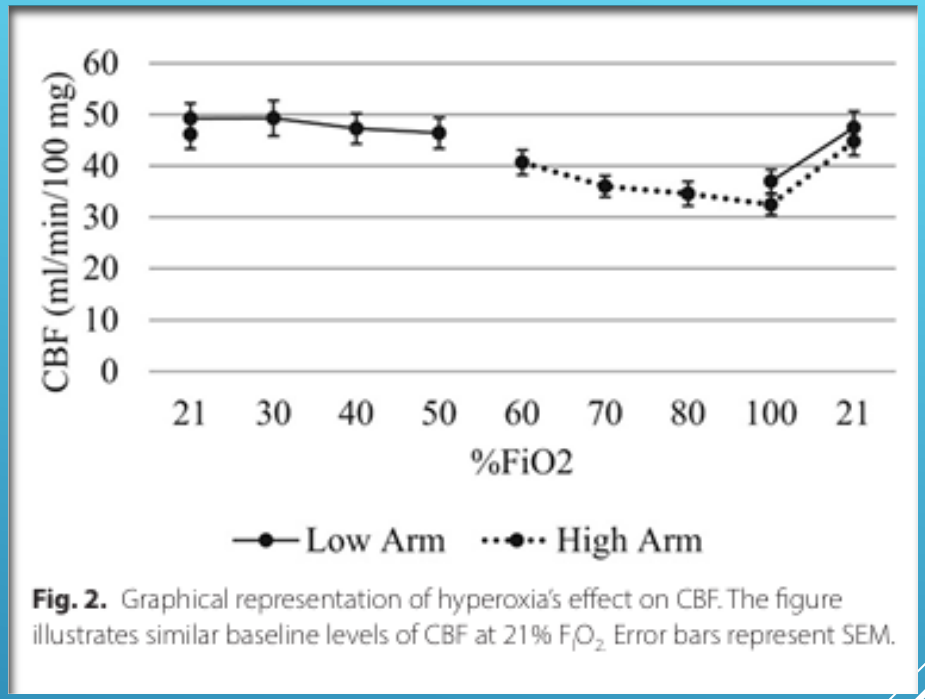
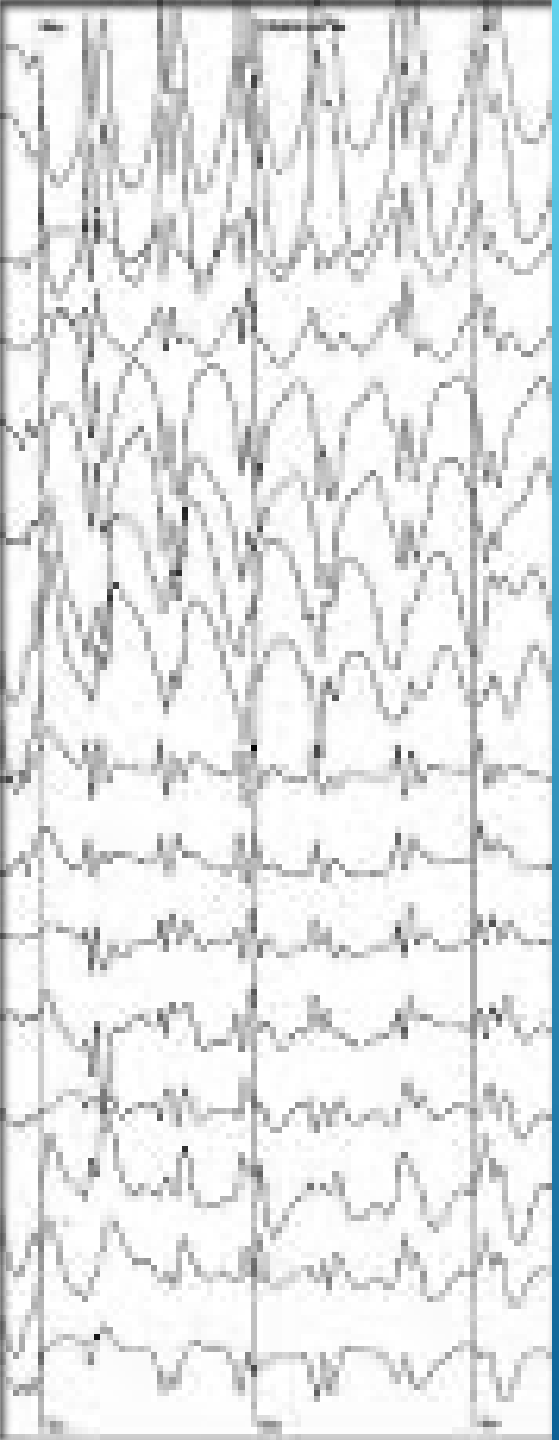


Fig. 2. Graphical representation of hyperoxia's effect on CBF. The figure illustrates similar baseline levels of CBF at 21% F_iO_2. Error bars represent SEM.

GAS DISRUPTION- HYPEROXIA



- Vasoconstriction a result of: Reduced NO, increased reactive O2 species, possible hypocapnia
- Regional variability of constriction, reduction of perfusion in key territories (ACA, MCA)
  - Lower MCA territory activation at 100% compared to 21%
- Correlates with EEG power/activation
- Heterogenous reactivity seen in other clinical pathologies

GAS DISRUPTION- HYPEROXIA

GAS DISRUPTION- HYPEROXIA

- Oscillation vs steady state
  - Greater physiological response with oscillatory administration
  - Reduction in cortical (prefrontal) activity
    - Cognitive fog described by aviators
    - Possibly mediated by inflammation, pro-imflammatory cytokines (increased over week-long flying schedule and correlate with frequency, duration, and exposure to +Gz maneuvers)
    - Individual vulnerability (sleep)

GAS DISRUPTION- HYPEROXIA

- Higher FiO2 -> higher EEG power/lower activation (beta), correlated with reduced perfusion / regional CBF due to hyperoxia induced vasoconstriction
- Most prominent in anterior, central, frontal, temporal regions (anterior circulation, cortical)
  - Bad for cognitive/executive
  - Good for reaction times, vision, reflexes
- More prominent in oscillatory O2 delivery
  - May be due to difficulty adapting to rapidly changing O2 levels, leading to transient disruption in neurovascular coupling and cortical function
- Theory: evolutionary favoring of occipital lobe and basal ganglia (vision and motor) for survival

GAS DISRUPTION- TCDS

- TCDs may demonstrate increased MFV and increased PI correlating with regions of vasoconstriction and impaired neuronal functioning in key areas of cortex
- Essential for determining optimal O2 delivery
- Early detection of fatigue / impairment

- Need for more data
  - Identification of normalized values
  - Protocols for monitoring
  - Thresholds for intervention
  - More rigorous testing of mitigation strategies
  - Continuous technological improvements
  - Application to non-optimal subjects/ pathology

IN CONCLUSION

THANK YOU