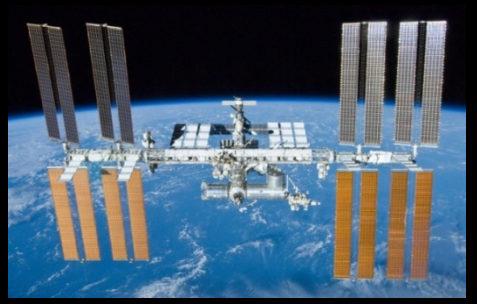


SPACE-COT: Studying the Physiological and Anatomical Cerebral Effects of Carbon Dioxide and Head Down Tilt: An International Collaborative Study

Eric Bershad, MD – Scientific Principal Investigator
Assistant Professor of Neurology and Space Medicine
Associate Director of Biomedical Innovation Lab
Vascular Neurologist and Neurointensivist
Baylor College of Medicine

SPACE-COT Aims

- Assess the operational capabilities of :envihab to simulate features of the space-flight environment.
- Obtain pilot study data on combined effects of head-down tilt (HDT) and elevated CO_2.
- Evaluate innovative non-invasive technologies to evaluate the effects of the environment on the brain, eye, and systemic body systems

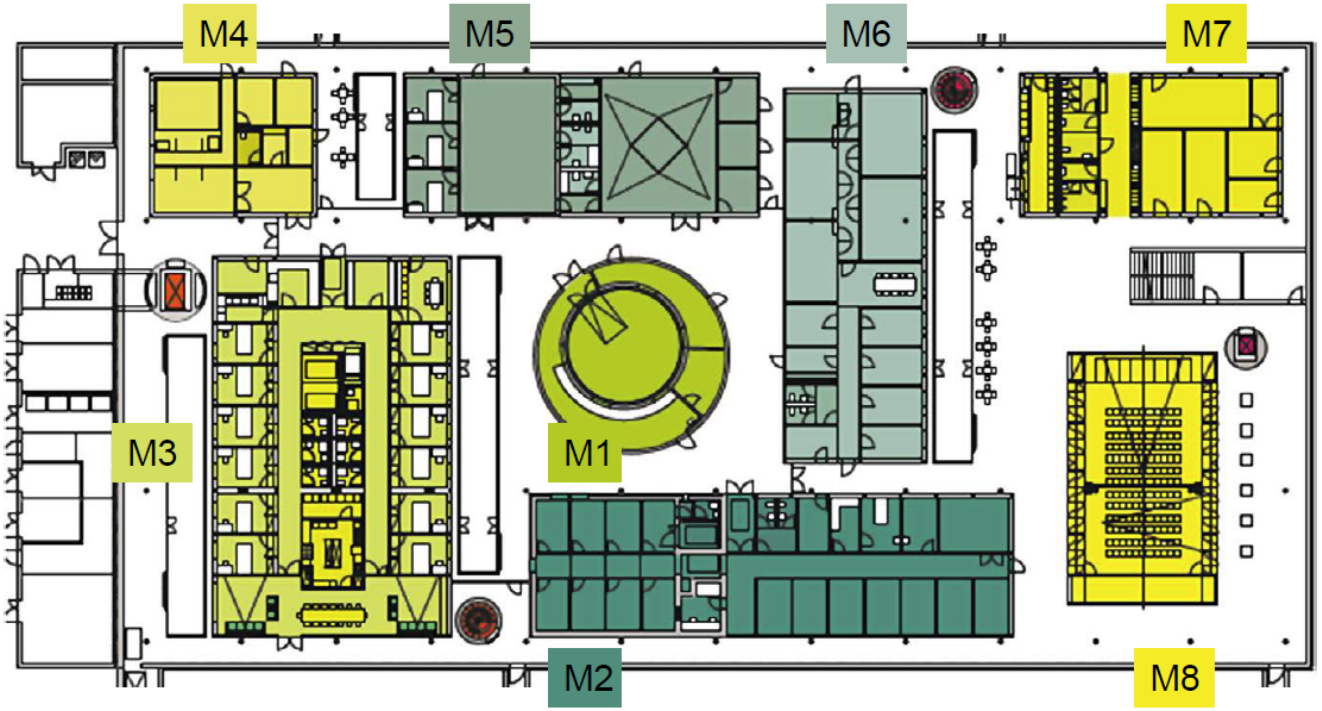
Hypotheses

- Elevated CO_2 would increase cerebral blood flow due to vasodilatory effects
- HDT may increase cerebral blood flow due to hydrostatic increases of cerebral perfusion pressure
- Increased ICP (hydrostatic effects)
- Cognition would worsen with elevated CO_2 exposure.

Setting - :Envihab (Environment + Habitat) (German Aerospace Center (DLR) Cologne, Germany)

http://www.dlr.de/envihab/en/

Study modules:
M3 (living/testing module)

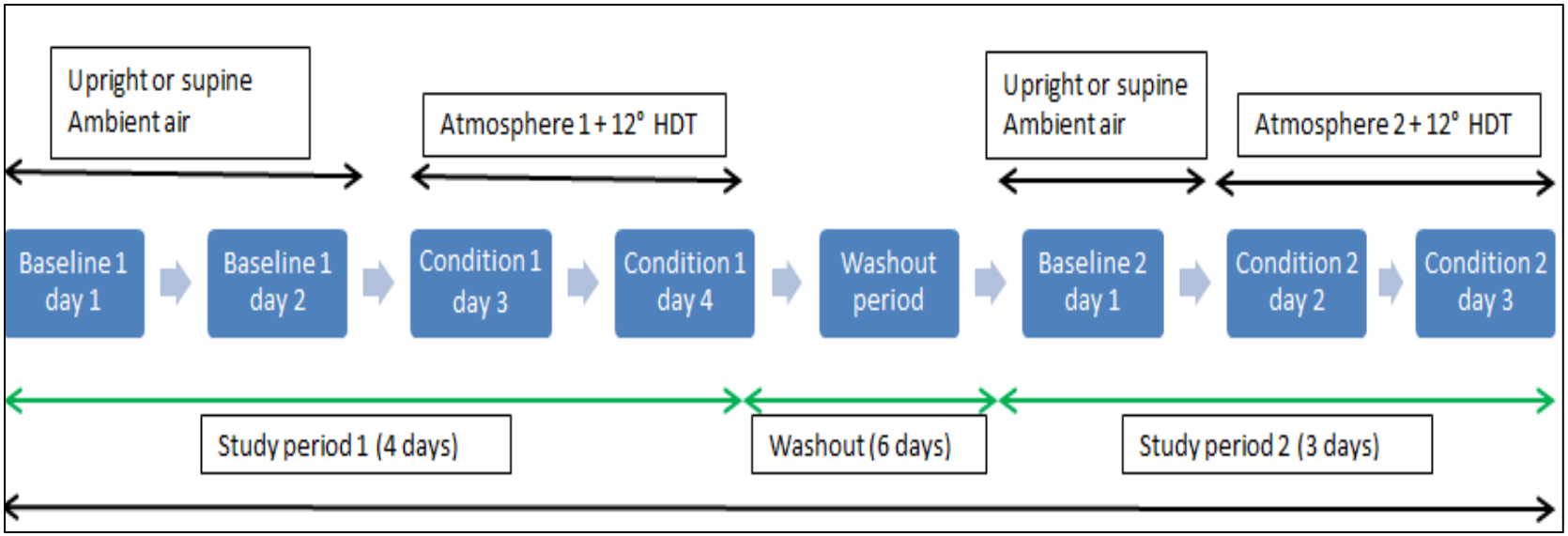


:envihab Module/:envihab moduls

M1 Kurzarmzentrifuge I/Short Arm Centrifuge I
M2 Physiologielabor I/Physiology Lab I | Barolabor I/Baro Lab I
M3 Wohn- und Simulationsbereich I/Living and Simulation Area I
M4 PET-MRT/MRI-PET
M5 Psychologielabor/Psychology Lab
M6 Biologielabor/Biology Lab
M7 Infrastruktur/Infrastructure
M8 Forum/Forum

DLR Deutsches Zentrum für Luft- und Raumfahrt
Institut für Luft- und Raumfahrtmedizin

Study overview: Randomized crossover design



Study schedule: Day 1 and 2

Monday, June 15 2015

study day	BDC-2	BDC-2	BDC-2	study day
Condition	Standard atmosphere	Standard atmosphere	Standard atmosphere	Condition
wake-up order	NA	NA	NA	wake-up order
subject	A	B	C	subject
6:30	formalities	formalities	formalities	6:30
6:45	Urine 0	Urine 0	Urine 0	6:45
7:00	Base headache quest	Base headache quest	Base headache quest	7:00
7:15	Temp, BP, HR, BW	Temp, BP, HR, BW	Temp, BP, HR, BW	7:15
7:30	Breakfast/Drink	Breakfast/Drink	Breakfast/Drink	7:30
7:45				7:45
8:00	Anthropometrics	seated spiro/CO/ETCO2	Cognition fam	8:00
8:15		Phono fam	upright	8:15
8:30		Plasma volume fam		8:30
8:45				8:45
9:00	Cognition fam	Anthropometrics	seated spiro/CO/ETCO2	9:00
9:15	upright		Phono fam	9:15
9:30			Plasma volume fam	9:30
9:45				9:45
10:00				10:00
10:15	seated spiro/CO/ETCO2	Cognition fam	Anthropometrics	10:15
10:30	Phono fam	upright		10:30
10:45	Plasma volume fam			10:45
11:00				11:00
11:15	MRI fam	IOP and OCT fam	FMD fam	11:15
11:30				11:30
11:45	FMD fam	MRI fam	IOP and OCT fam	11:45
12:00				12:00
12:15	IOP and OCT fam	FMD fam	MRI fam	12:15
12:30				12:30
12:45	Lunch/Drink	Lunch/Drink	Lunch/Drink	12:45
13:00				13:00
13:15				13:15
13:30	TCD / Finometer	Vittamed fam	Tilt Table +	13:30
13:45			Echocardiography fam	13:45
14:00	Cflow / Fino			14:00
14:15	Cerebrotech / Fino	Sniffin' Sticks		14:15
14:30	Vittamed fam	Tilt Table +	TCD / Finometer	14:30
14:45		Echocardiography fam		14:45
15:00			Cflow / Fino	15:00
15:15	Sniffin' Sticks		Cerebrotech / Fino	15:15
15:30	Tilt Table +	TCD / Finometer	Vittamed fam	15:30
15:45	Echocardiography fam			15:45
16:00		Cflow / Fino		16:00
16:15		Cerebrotech / Fino	Sniffin' Sticks	16:15
16:30	CO2-response curve	Cognition fam		16:30
16:45		upright		16:45
17:00			Cognition fam	17:00
17:15			upright	17:15
17:30	Cognition fam	CO2-response curve		17:30
17:45	upright			17:45
18:00				18:00
18:15				18:15
18:30			CO2-response curve	18:30
18:45				18:45
19:00	Dinner	Dinner		19:00
19:15				19:15
19:30			Dinner	19:30
19:45				19:45
20:00	Headache questionnaire	Headache questionnaire	Headache questionnaire	20:00
20:15				20:15
20:30				20:30
20:45				20:45
21:00				21:00
21:15				21:15
21:30	Drink	Drink	Drink	21:30
21:45	LOG	LOG	LOG	21:45
22:00				22:00
22:15	Bedtime	Bedtime	Bedtime	22:15
22:30				22:30
22:45				22:45

Tuesday, June 16 2015

study day	BDC-1	BDC-1	BDC-1	
Condition	Standard atmosphere	Standard atmosphere	Standard atmosphere	
wake-up order	1	2	3	
subject	A	B	C	
6:30	Temp, BP, HR	Temp, BP, HR	Temp, BP, HR	6:30
6:45	Urine 1, BW	Urine 1, BW	Urine 1, BW	6:45
7:00	BD; CO-Hb	BD; CO-Hb	BD; CO-Hb	7:00
7:15				7:15
7:30	Breakfast/Drink	Breakfast/Drink	Breakfast/Drink	7:30
7:45				7:45
8:00	Cognition fam			8:00
8:15	supine			8:15
8:30	Plasma volume			8:30
8:45				8:45
9:00	CO-Hb	Cognition fam		9:00
9:15	Flow-mediated dilation	supine		9:15
9:30		Plasma volume	Cognition fam	9:30
9:45	Puffy face		supine	9:45
10:00		CO-Hb		10:00
10:15	internal jugular vein + tilt	Flow-mediated dilation		10:15
10:30			Plasma volume	10:30
10:45		Puffy face		10:45
11:00	Cognition / NIRS		CO-Hb	11:00
11:15		internal jugular vein + tilt	Flow-mediated dilation	11:15
11:30	TCD / Finometer			11:30
11:45	Cflow / Fino / BGA		Puffy face	11:45
12:00		Cognition / NIRS		12:00
12:15			internal jugular vein + tilt	12:15
12:30	IOP and OCT	TCD / Finometer		12:30
12:45				12:45
13:00	Lunch/Drink	Cflow / Fino / BGA		13:00
13:15			Lunch/Drink	13:15
13:30	Vittamed	IOP and OCT		13:30
13:45			Cognition / NIRS	13:45
14:00		Lunch/Drink		14:00
14:15	Sniffin' Sticks		TCD / Finometer	14:15
14:30	supine spiro/CO/ETCO2	Vittamed		14:30
14:45	Phono / BGA		Cflow / Fino / BGA	14:45
15:00	Cerebrotech / Fino			15:00
15:15		Sniffin' Sticks	IOP and OCT	15:15
15:30	MRI	supine spiro/CO/ETCO2		15:30
15:45		Phono / BGA	Vittamed	15:45
16:00		Cerebrotech / Fino		16:00
16:15			Sniffin' Sticks	16:15
16:30	Tilt Table +	MRI	supine spiro/CO/ETCO2	16:30
16:45	Echocardiography		Phono / BGA	16:45
17:00			Cerebrotech / Fino	17:00
17:15				17:15
17:30		Tilt Table +	MRI	17:30
17:45		Echocardiography		17:45
18:00				18:00
18:15				18:15
18:30				18:30
18:45			Tilt Table +	18:45
19:00	Dinner	Dinner	Echocardiography	19:00
19:15				19:15
19:30			Dinner	19:30
19:45				19:45
20:00	PANAS + GHQ-28	PANAS + GHQ-28	PANAS + GHQ-28	20:00
20:15	Headache questionnaire	Headache questionnaire	Headache questionnaire	20:15
20:30				20:30
20:45				20:45
21:00				21:00
21:15				21:15
21:30	Drink	Drink	Drink	21:30
21:45	LOG	LOG	LOG	21:45
22:00				22:00
22:15	Bedtime	Bedtime	Bedtime	22:15
22:30				22:30
22:45				22:45

Study schedule: Days 3 and 4

Wednesday, June 17 2015

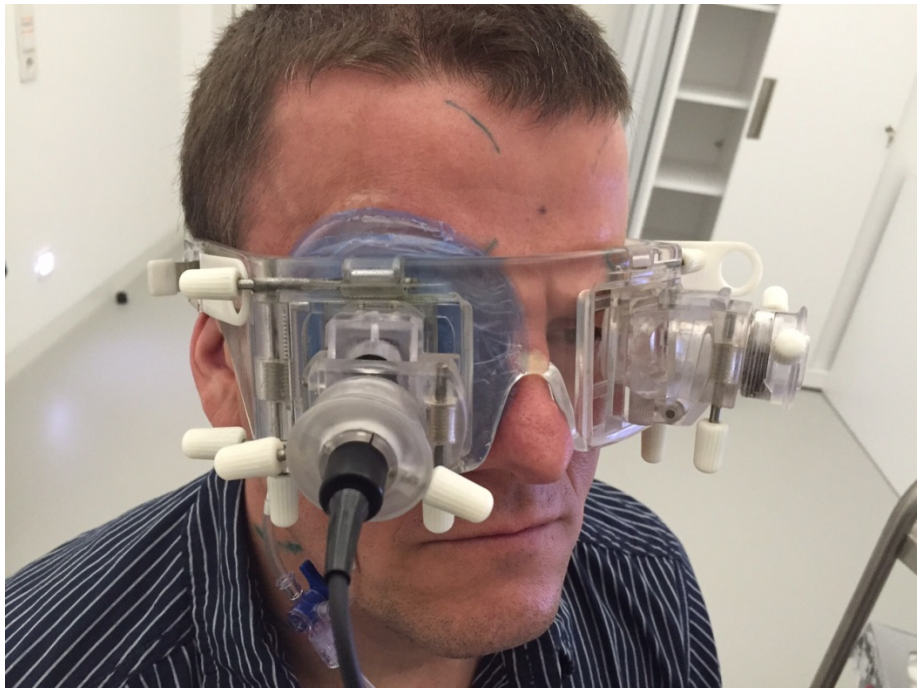
study day	HDT1	HDT1	HDT1
Condition	atmosphere #1	atmosphere #1	atmosphere #1
wake-up order	1	2	3
subject	D	E	F
6:30	Temp, BP, HR	Temp, BP, HR	Temp, BP, HR
6:45	Urine 2, BW	Urine 2, BW	Urine 2, BW
7:00	BD	BD	BD
7:15			
7:30	Breakfast/Drink		
7:45			
8:00	seated spiro/CO/ETCO2 Phono / BGA	Breakfast/Drink	Breakfast/Drink
8:15			
8:30	supine spiro/CO/ETCO2 Phono / BGA		
8:45			
9:00	Puffy face	seated spiro/CO/ETCO2 Phono / BGA	Cognition / NIRS seated
9:15			
9:30	Cognition / NIRS seated	supine spiro/CO/ETCO2 Phono / BGA	
9:45			
10:00		Puffy face	seated spiro/CO/ETCO2 Phono / BGA
10:15	Urine 3	Cognition / NIRS seated	
10:30	START Condition #1 and -12° HDT		supine spiro/CO/ETCO2 Phono / BGA
10:45			Puffy face
11:00	Cognition / NIRS		
11:15		Urine 3	
11:30	TCD / Finometer	START Condition #1 and -12° HDT	
11:45			
12:00	Cflow / Fino / BGA	Cognition / NIRS	
12:15	Cerebrotech / Fino / BGA		Urine 3
12:30	IOP and OCT	TCD / Finometer	START Condition #1 and -12° HDT
12:45			
13:00	Lunch/Drink	Cflow / Fino / BGA	Cognition / NIRS
13:15		Cerebrotech / Fino / BGA	
13:30	Vittamed	IOP and OCT	TCD / Finometer
13:45			
14:00		Lunch/Drink	Cflow / Fino / BGA
14:15	Sniffin' Sticks		Cerebrotech / Fino / BGA
14:30	spirometry/CO/ETCO2 Phono / BGA	Vittamed	IOP and OCT
14:45			
15:00			Lunch/Drink
15:15		Sniffin' Sticks	
15:30	URINE 4 + BD	spirometry/CO/ETCO2 Phono / BGA	Vittamed
15:45	Puffy face		
16:00	Cognition / NIRS		
16:15			Sniffin' Sticks
16:30	TCD / Finometer	URINE 4 + BD	spirometry/CO/ETCO2 Phono / BGA
16:45		Puffy face	
17:00	Cflow / Fino / BGA	Cognition / NIRS	
17:15	Cerebrotech / Fino / BGA		
17:30	IOP and OCT	TCD / Finometer	URINE 4 + BD
17:45			Puffy face
18:00	Vittamed	Cflow / Fino / BGA	Cognition / NIRS
18:15		Cerebrotech / Fino / BGA	
18:30		IOP and OCT	TCD / Finometer
18:45	Sniffin' Sticks		Cflow / Fino / BGA
19:00	Dinner	Vittamed	Cerebrotech / Fino / BGA
19:15			IOP and OCT
19:30		Sniffin' Sticks	
19:45			Vittamed
20:00	spirometry/CO/ETCO2 Phono / BGA	Dinner	
20:15			Sniffin' Sticks
20:30		spirometry/CO/ETCO2 Phono / BGA	Dinner
20:45	Headache questionnaire		
21:00		Headache questionnaire	spirometry/CO/ETCO2 Phono / BGA
21:15			
21:30	Drink	Drink	Headache questionnaire
21:45	LOG	LOG	LOG
22:00			Drink
22:15	Bedtime	Bedtime	Bedtime
22:30			
22:45			

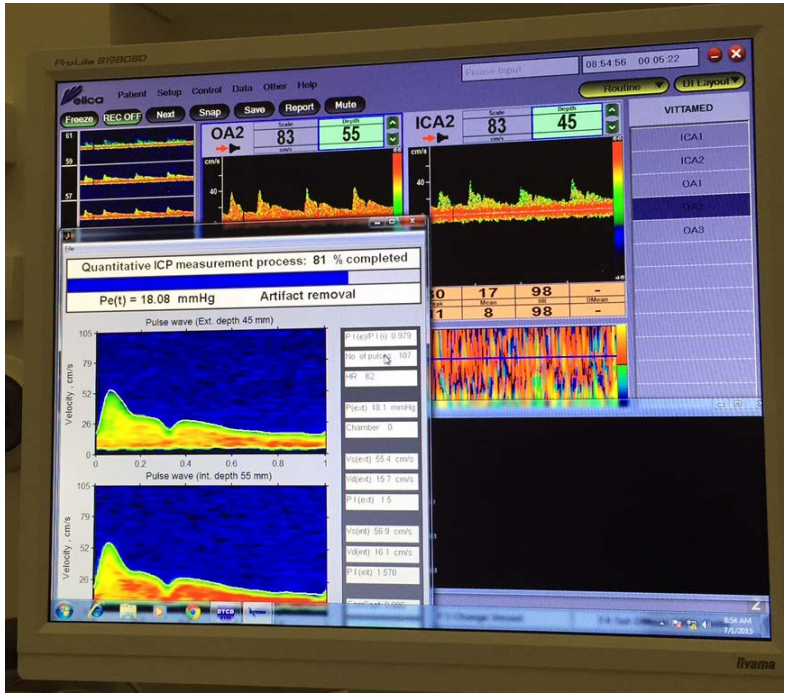
Thursday, June 18 2015

study day	R+0	R+0	R+0	study day
Condition	atmosphere #1	atmosphere #1	atmosphere #1	Condition
wake-up order	1	2	3	wake-up order
subject	A	B	C	subject
6:30	Temp, BP, HR	Temp, BP, HR	Temp, BP, HR	6:30
6:45	Urine 4, BW	Urine 4, BW	Urine 4, BW	6:45
7:00	Breakfast/Drink			7:00
7:15		Breakfast/Drink	Breakfast/Drink	7:15
7:30	spirometry/CO/ETCO2 Phono / BGA			7:30
7:45				7:45
8:00	Cognition / NIRS			8:00
8:15				8:15
8:30	Vittamed	spirometry/CO/ETCO2 Phono / BGA		8:30
8:45				8:45
9:00		Cognition / NIRS		9:00
9:15	Sniffin' Sticks			9:15
9:30	IOP and OCT	Vittamed	spirometry/CO/ETCO2 Phono / BGA	9:30
9:45				9:45
10:00	TCD / Finometer	Sniffin' Sticks	Cognition / NIRS	10:00
10:15				10:15
10:30	Cflow / Fino / BGA	IOP and OCT	Vittamed	10:30
10:45	Cerebrotech / Fino / BGA			10:45
11:00	URINE 4 + BD	TCD / Finometer		11:00
11:15			Sniffin' Sticks	11:15
11:30	MRI	Cflow / Fino / BGA	IOP and OCT	11:30
11:45		Cerebrotech / Fino / BGA		11:45
12:00		URINE 4 + BD	TCD / Finometer	12:00
12:15				12:15
12:30	FMD, puffy face	MRI	Cflow / Fino / BGA	12:30
12:45			Cerebrotech / Fino / BGA	12:45
13:00	Lunch/Drink		URINE 4 + BD	13:00
13:15	Urine 5	FMD, puffy face		13:15
13:30	START of 3% CO2		MRI	13:30
13:45	TCD / Cflow / Finometer	Lunch/Drink		13:45
14:00				14:00
14:15	IOP / ETCO2 / BGA	Urine 5		14:15
14:30		START of 3% CO2	FMD, puffy face	14:30
14:45	Cerebro / Finometer	TCD / Cflow / Finometer		14:45
15:00			Lunch/Drink	15:00
15:15	MRI	IOP / ETCO2 / BGA	Urine 5	15:15
15:30			START of 3% CO2	15:30
15:45	BD	Cerebro / Finometer	TCD / Cflow / Finometer	15:45
16:00	FMD, puffy face			16:00
16:15	END of 3% CO2	MRI	IOP / ETCO2 / BGA	16:15
16:30			Cerebro / Finometer	16:30
16:45	Tilt Table + Echocardiography	BD		16:45
17:00		FMD, puffy face	MRI	17:00
17:15		END of 3% CO2		17:15
17:30	Urine 6, BW			17:30
17:45	spirometry/CO/ETCO2 Phono / BGA	Tilt Table + Echocardiography	BD	17:45
18:00			FMD, puffy face	18:00
18:15			END of 3% CO2	18:15
18:30	PANAS/GHQ-28/ Headache SCOT survey	Urine 6, BW	Tilt Table + Echocardiography	18:30
18:45		spirometry/CO/ETCO2 Phono / BGA		18:45
19:00	Dinner		Urine 6, BW	19:00
19:15			spirometry/CO/ETCO2 Phono / BGA	19:15
19:30	LOG	PANAS/GHQ-28/ Headache SCOT survey		19:30
19:45	Departure DLR			19:45
20:00		Dinner	PANAS/GHQ-28/ Headache SCOT survey	20:00
20:15				20:15
20:30		LOG	Dinner	20:30
20:45		Departure DLR		20:45
21:00			LOG	21:00
21:15			Departure DLR	21:15
21:30				21:30
21:45				21:45
22:00				22:00
22:15				22:15
22:30				22:30
22:45				22:45

Study procedures:
Non-Invasive ICP Meter (Vittamed, Lithuania)

Non-invasive measurement of intracranial pressure



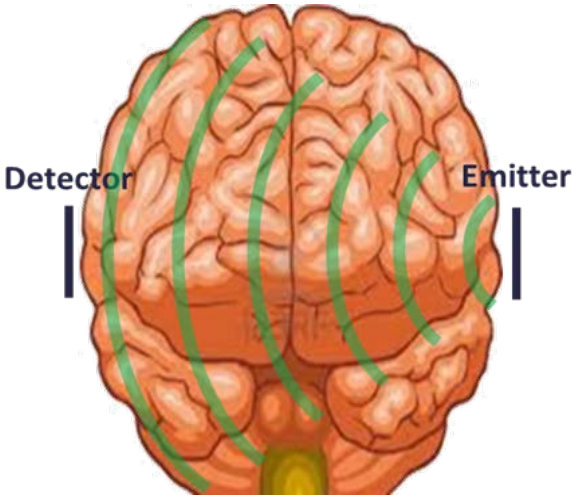


Study procedures:
CBF monitor (cFLOW, Ornim, Israel)

Non-invasive continuous measurements of brain blood flow rate

Volume Integral Phase Shift Spectroscopy (Cerebrotech, Pleasanton, CA)

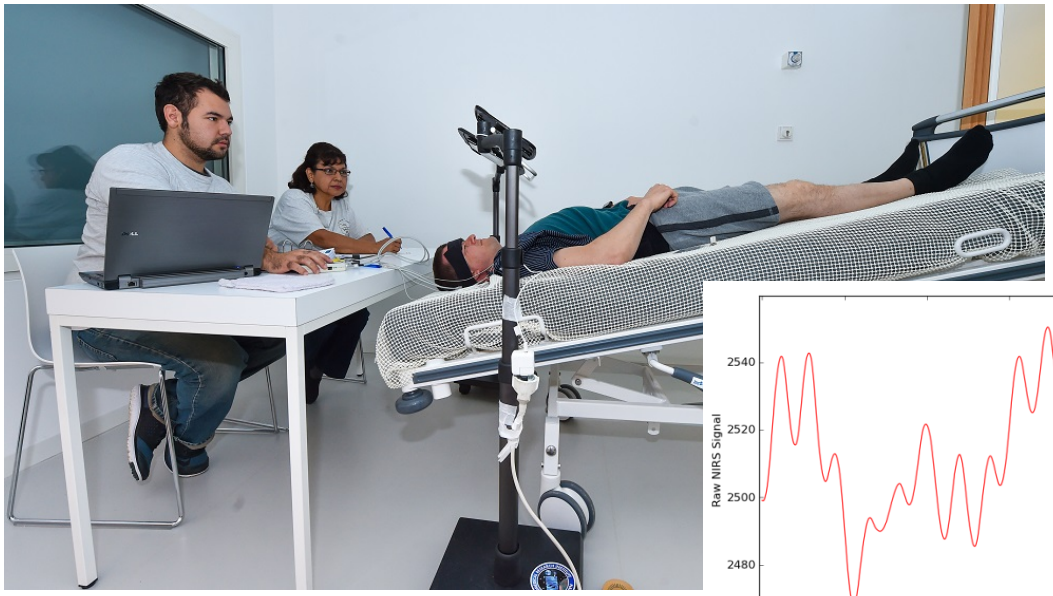
Non-invasive continuous measurements of brain fluid volume (blood, CSF)



Courtesy of Chethan Venkatasubba Rao, MD

Near infrared spectroscopy combined with Cognition

Non-invasive continuous measurements of brain blood oxygenation with concurrent cognitive functional assessment



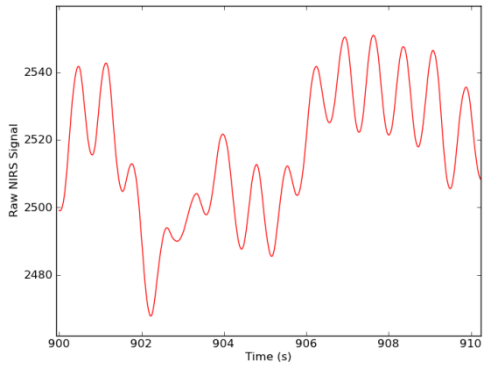
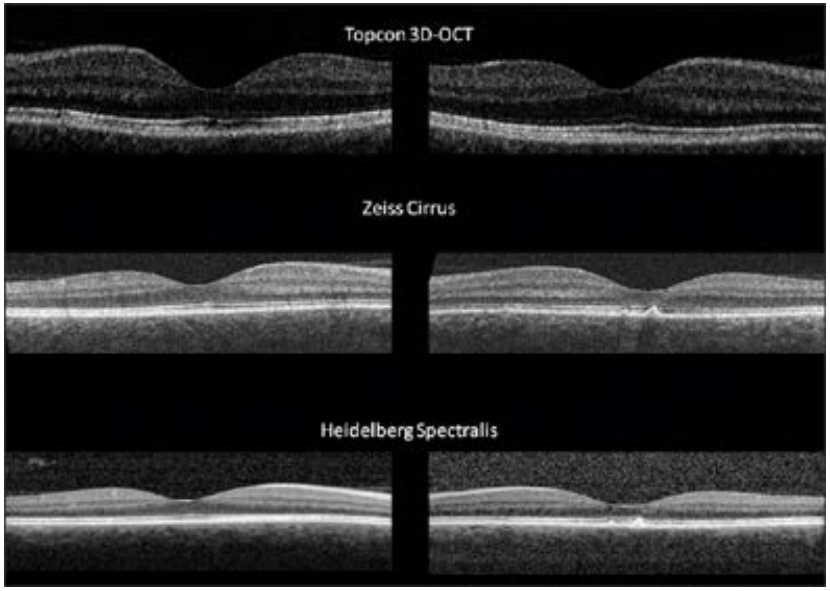


Figure 5. NINscan 4a, with 2 source colors (in a single laserdiode canister), 2 photodetectors, 3 ECG leads, and a 3-axis accelerometer.

Courtesy of Gary Strangman

Optical Coherence Tomography

Non-invasive high resolution measurements of ocular structures



MRI brain (maintained CO_2 and HDT)

Imaging of the brain and ocular structures

Results: Baseline demographics

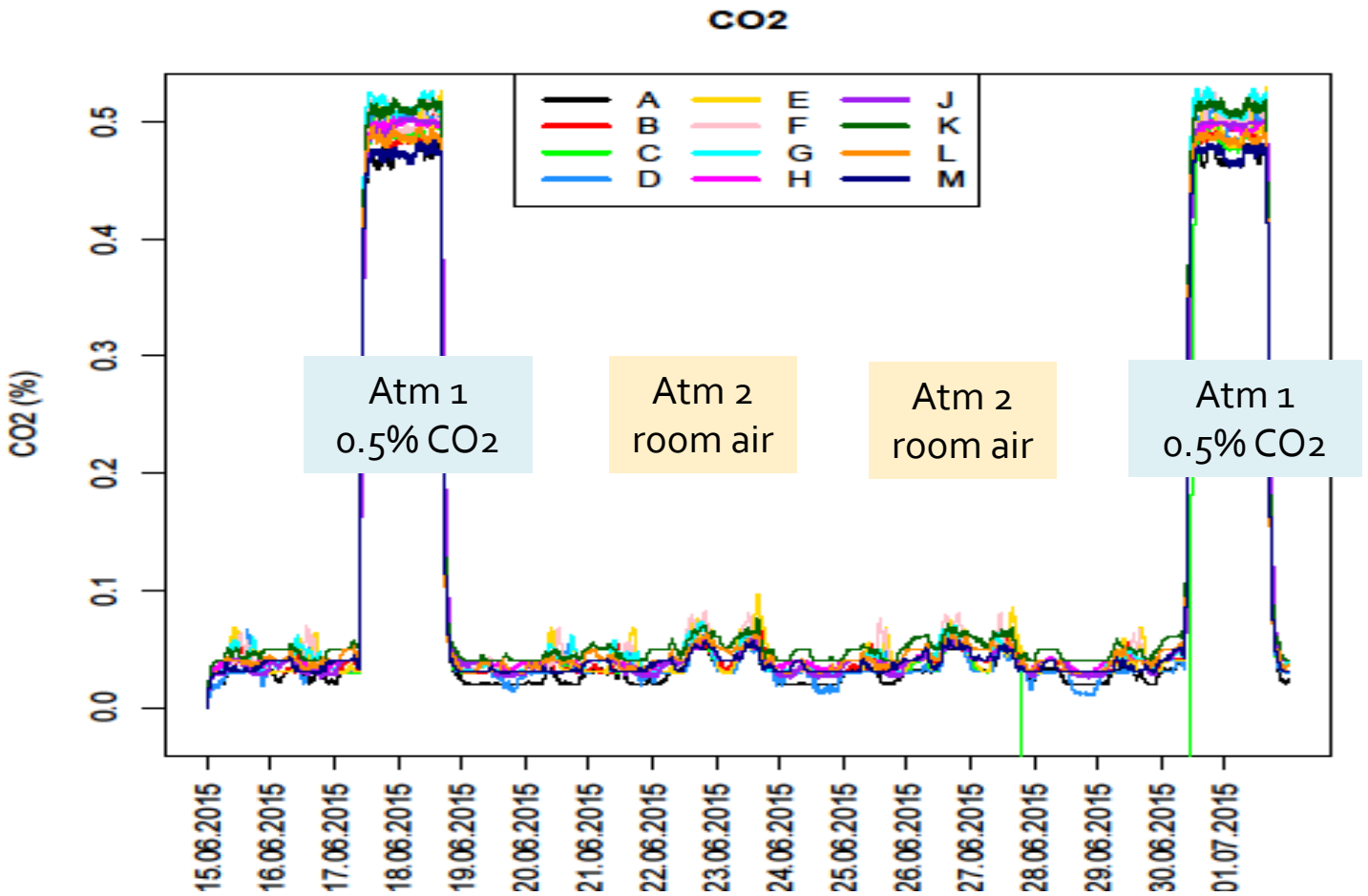
Subjects simulate astronaut demographics

Subject	Age	Sex	Weight (kg)	Weight (lbs)	Height (cm)	Height (inch)	BMI (nl 18.5-24.9)
A	47	M	82.5	181.5	174	68.5	27.2
B	43	M	91.5	201.7	182.5	72	27.4
C	39	M	68.8	151.7	174.5	69	22.6
D	33	M	80.1	176.6	177.5	70	25.4
E	39	M	85.0	187.4	180	71	26.2
F	43	M	84.5	186.3	173	68	28.2

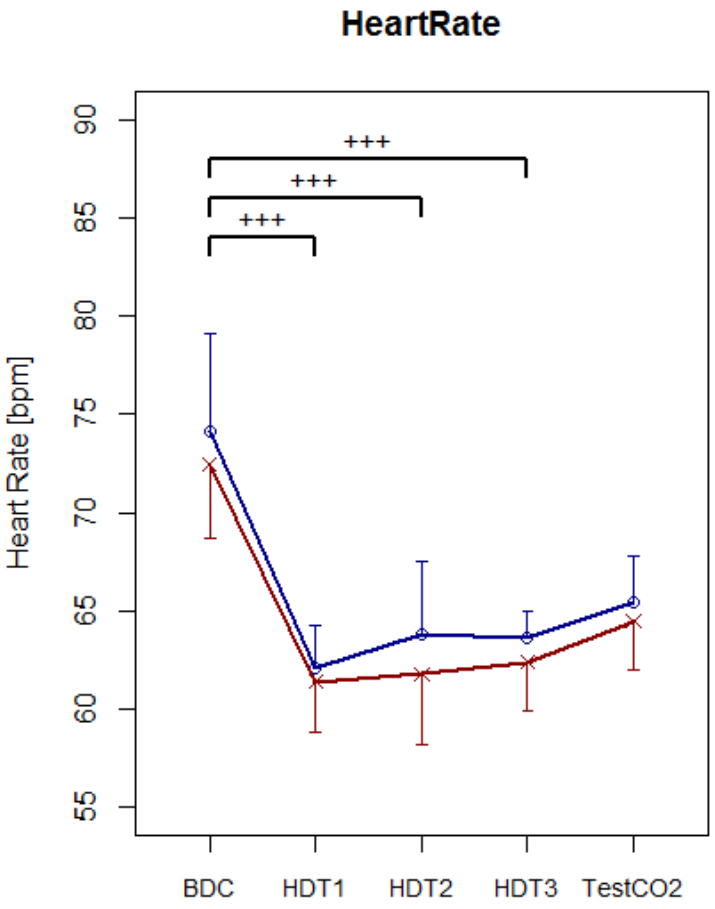
All subjects had back pain related to 12 degree HDT positioning

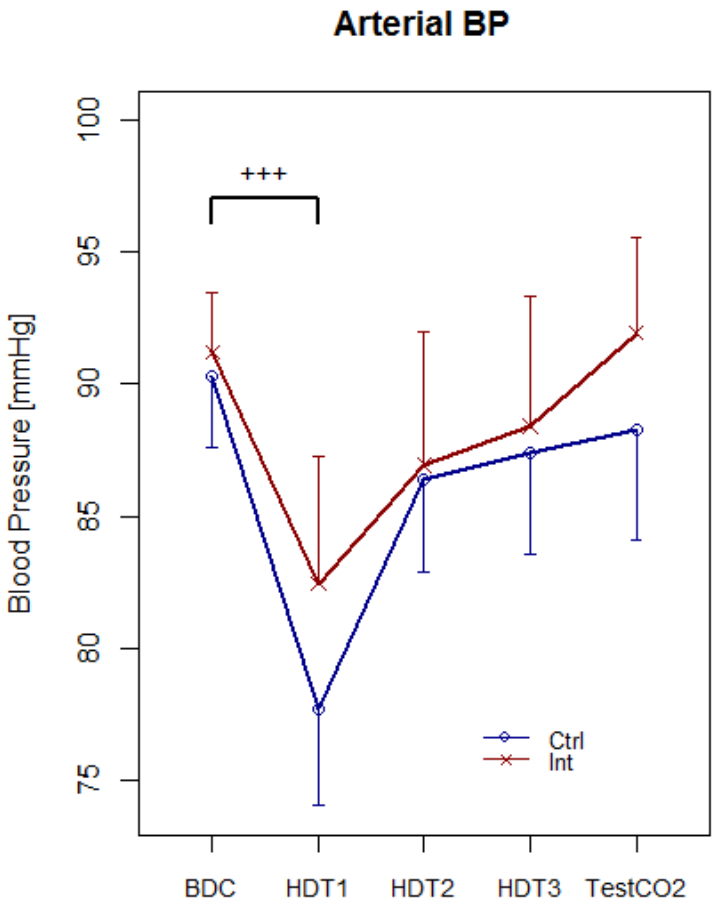
- All subjects had varying degrees of back pain moderate to severe, alleviated with pharmacological or mechanical methods
- One subject with severe urinary retention in first HDT campaign
- Good tolerance with atmospheres
- Good tolerance with study procedures

Atmospheric CO_2 levels were well maintained at desired targets



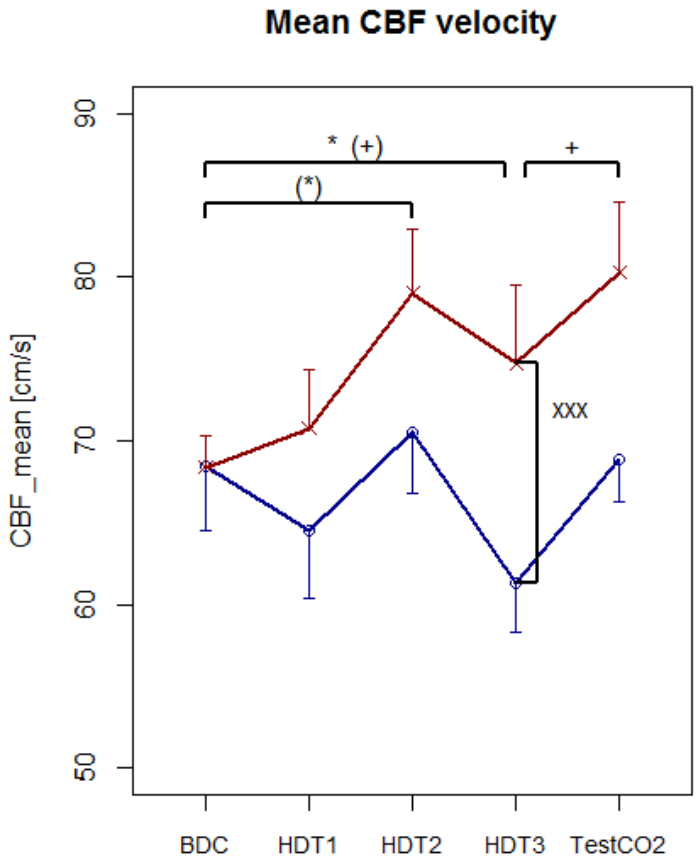
12 degree HDT significantly decreased heart rate and blood pressure





Slide courtesy of J. Rittweger, H. Stetefeld et al.

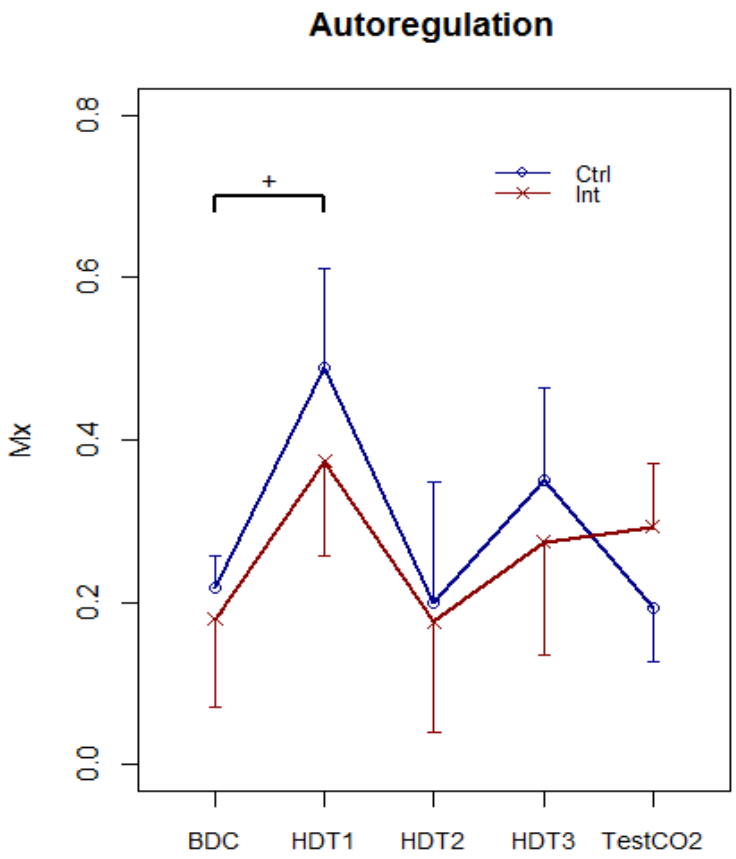
CO_2 increased cerebral blood flow velocities (TCD)



Red = HDT + 0.5% co2; blue = HDT + room air, test CO_2 = 3% CO_2

Slide courtesy of: J. Rittweger, H. Stetefeld et al.

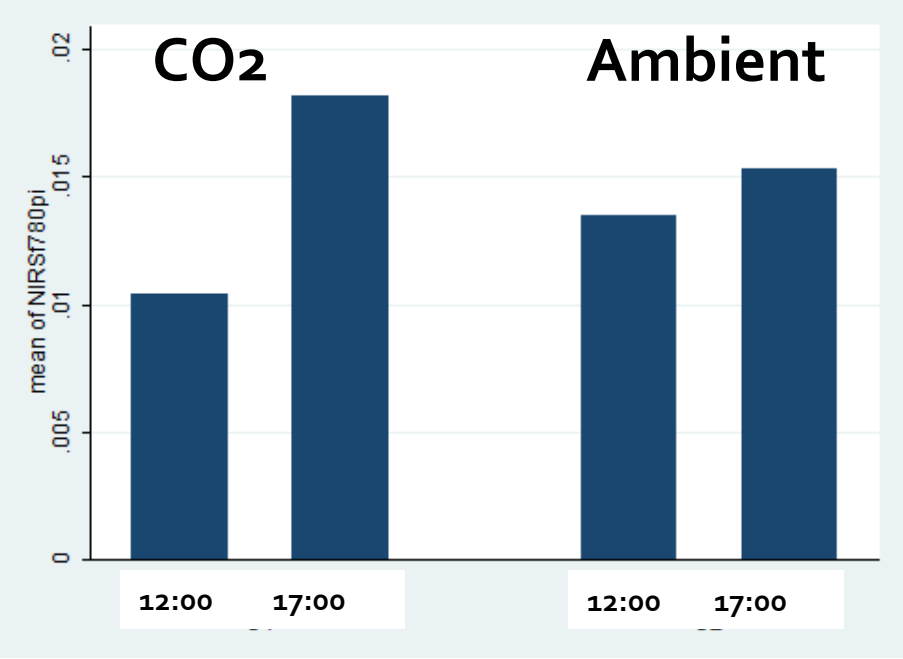
12 degree HDT transiently impaired cerebral autoregulation



Slide courtesy of J. Rittweger, H. Stetefeld et al.

CO_2 significantly increased cerebral arterial blood pulsatility (near infrared spectroscopy)

- Mixed-effects regression (random=subj)
  - Significant:
    - Pulsatility ≈ condition +time +condition*time

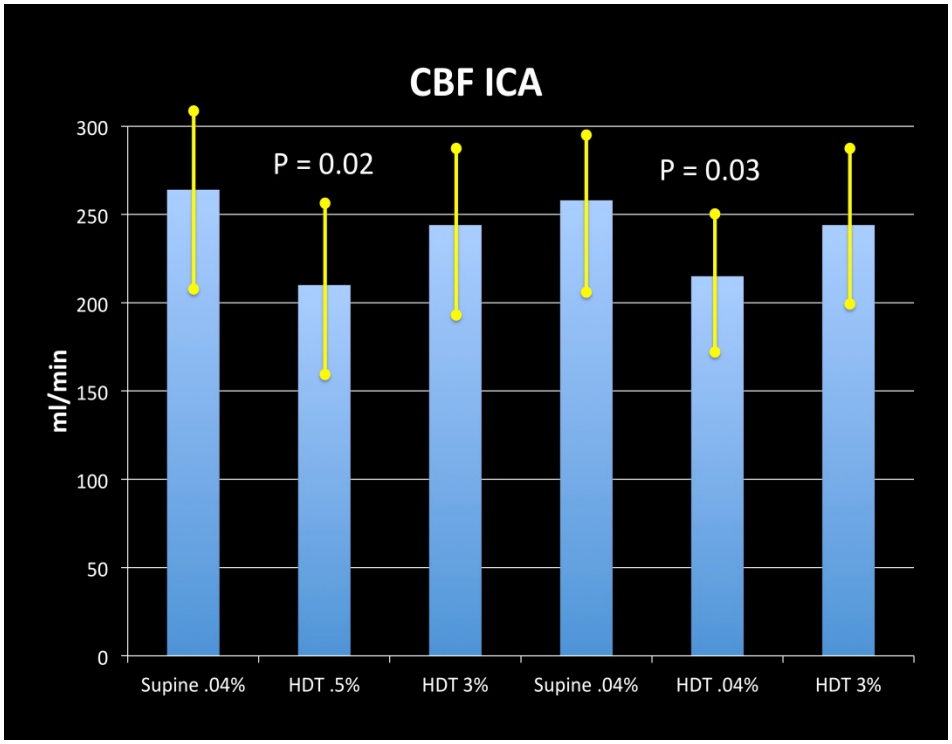


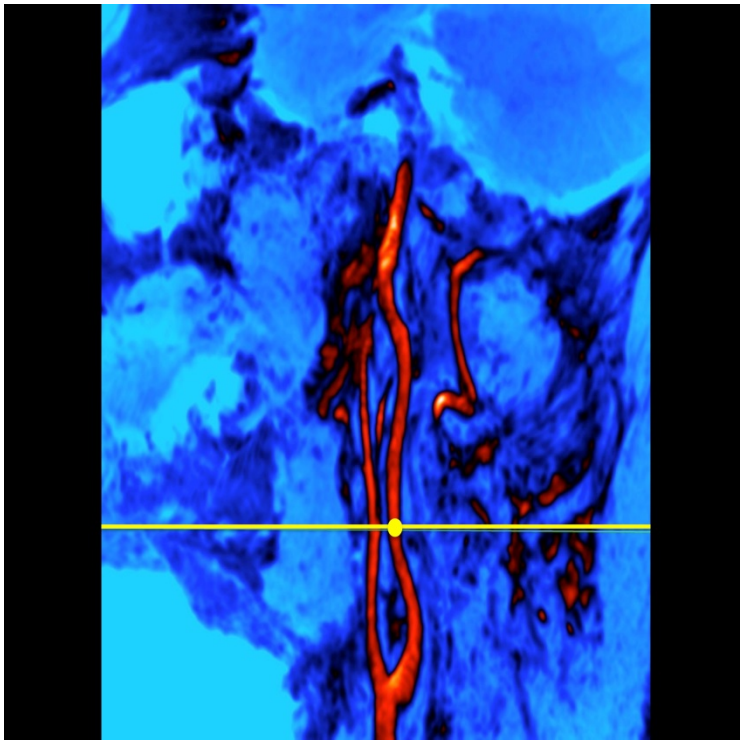
Sig. Interaction (p=0.002)

Holds when adjusting for near detector signal.

Courtesy of Gary Strangman

Head down tilt decreased cerebral blood flow compared to supine baseline





Courtesy of Larry Kramer, MD

Results Summary I

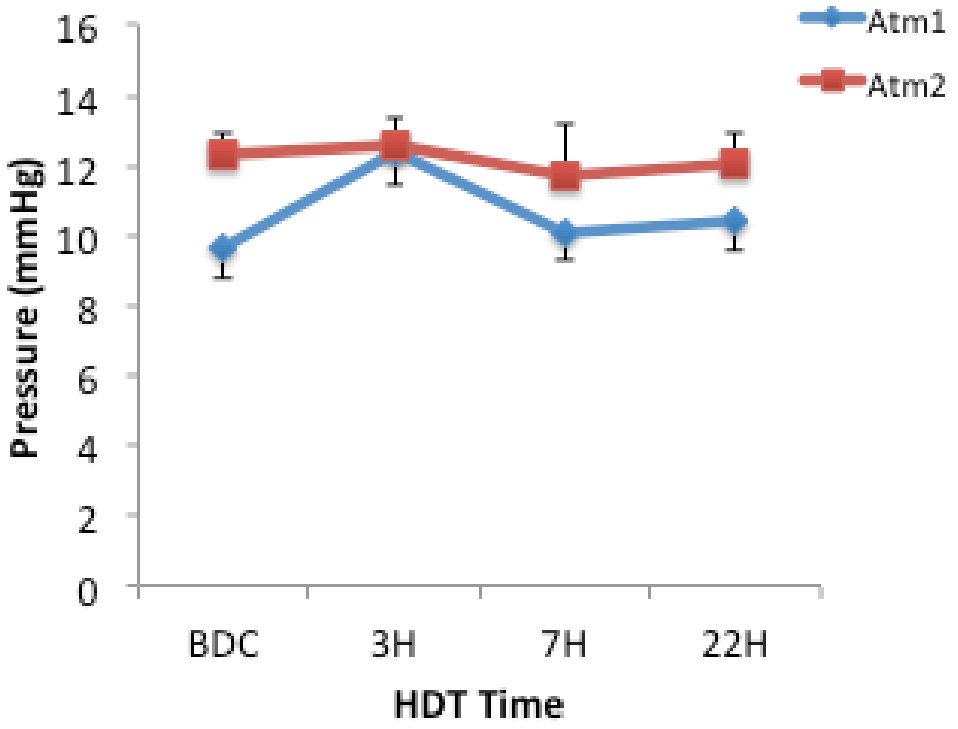
Task	HDT alone versus HDT+ 0.5% CO_2	Effect Size
VOLT	HDT faster response, more confident, but significantly less accurate than HDT + 0.5% CO_2 	Large
LOT	HDT faster, but less accurate than HDT + 0.5% CO_2	Medium
PVT	HDT alone slower, more lapses, and more false starts than HDT + 0.5% CO_2	Medium
2-Back	HDT alone less accurate, no difference in speed	Small
BART	HDT alone slower, no difference in risk taking	Small
ERT	HDT alone, no difference in accuracy	Small

No Difference between A1 and A2 for:

- Motor Praxis
- Digit Symbol Substitution
- Abstract Matching
- Matrix Reasoning

Courtesy of M. Basner, J. Nasrini

No significant increase in ICP with 12 degree HDT; Lower ICP with 0.5% CO_2



Courtesy of Karina Marshall-Goebel

Preliminary Summary of Findings

- Successfully conducted the first study and longest to date with 0.5% (atmospheric) CO_2 (combined with HDT)
- CBF velocities (TCD) increased with 0.5% CO_2, and further with 3% CO_2; no significant changes in CBF in HDT alone (compared to baseline)
- Decreased CBF on MRI in HDT compared to supine baseline; restored partially with 3% CO_2
- Contrary to expectations, non-invasive ICP lower in CO_2 condition, and no significant increases from upright baseline
- Contrary to expectations, in the HDT position, there was better cognitive function with atmospheric CO_2 present in some subtasks of the Cognition task (Visual object learning and psychomotor vigilance)

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