High altitude and its effect on lung

26-8-16

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Pulmonary medicine

- High Altitude physiology
- Acute high altitude illness
- Chronic high altitude illness
- High altitude in pre-existing lung disease

HIGH ALTITUDE PHYSIOLOGY

High altitude

	High altitude	Very high altitude	Extreme altitude
Ht (m)	1500 - 3500 m	3500 - 5500 m	5500 - 8500 m
PaO2 (mm Hg)	55 -75	40-60	28 -40
SpO2 (%)	Atleast 90	75 -85	58 -75
High altitude illness	>2500 m	HAI	Severe HAI
Physiology	Increased ventilation prevents hypoxia	Extreme hypoxia during sleep, exercise	Progressive deterioration of physiologic functions

Hackett, PH, Roach, RC. High-Altitude Medicine. In: Wilderness Medicine, 5th ed

High altitude

- Hypobaric hypoxia
- Low environmental temperature
  - temperature falls by 1ºC per 150m gain in altitude
- Low absolute humidity
  - increases the insensible water loss from the body
  - predispose to dehydration
- Increased solar and ionizing radiation
  - harmful effects especially in the eye and skin

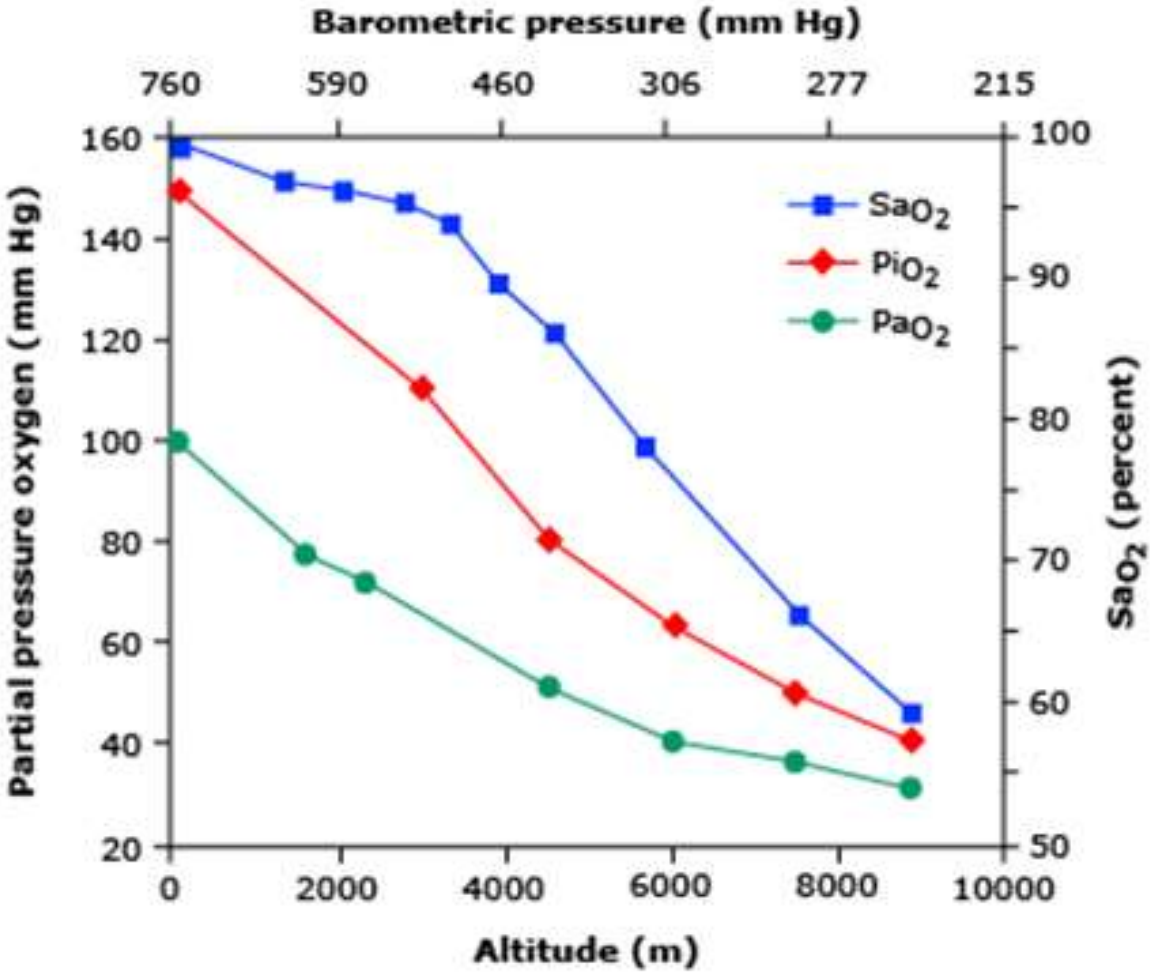
A.M. Luks and E.R. Swenson, ERJ 2007

Hypoxia at high altitude

Altitude, *m (ft)*	Barometric Pressure, *mm Hg*	Inspired Po_2, *mm Hg (% of sea level)*
0 (0)	760	149 (100)
1000 (3281)	679	132 (89)
2000 (6562)	604	117 (79)
3000 (9843)	537	103 (69)
4000 (13 123)	475	90 (60)
5000 (16 404)	420	78 (52)
8848 (29 028)	253	43 (29)

John B West, Ann Intern Med 2004

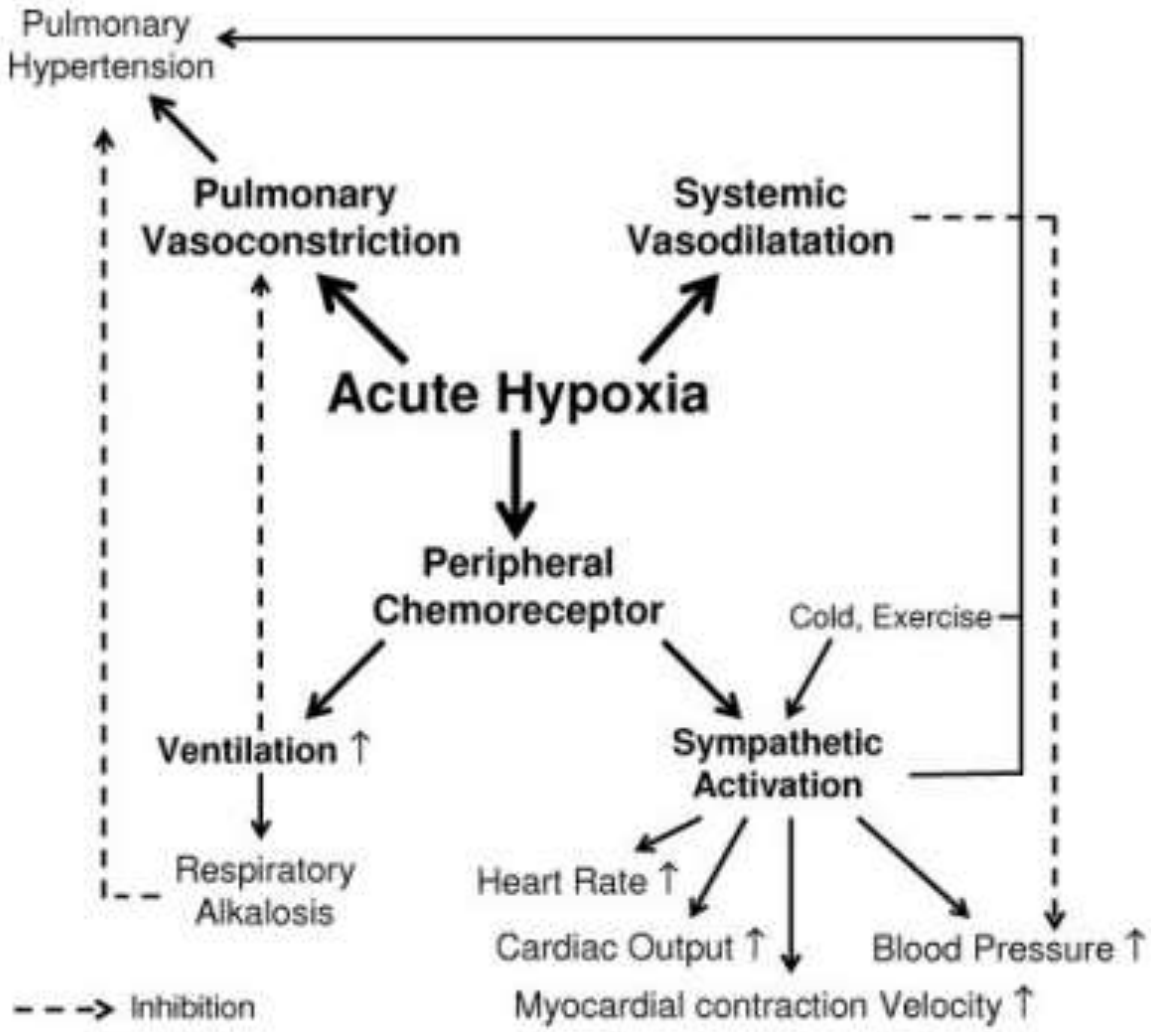
High altitude



Hackett, PH, Roach, RC. High-Altitude Medicine. In: Wilderness Medicine, 5th ed

Oxygen cascade

- O2 diminishes as oxygen moves from air to the tissues.
- *Ventilation*
- *Regional matching of ventilation and blood flow*
- *Diffusion of oxygen from the air to the blood*
- *Transport within the circulation*
- *Diffusion of oxygen from the blood into the tissue*
- *Metabolism in the mitochondria*



Peter Bärtsch et al; Circulation. 2007;116:2191-2202

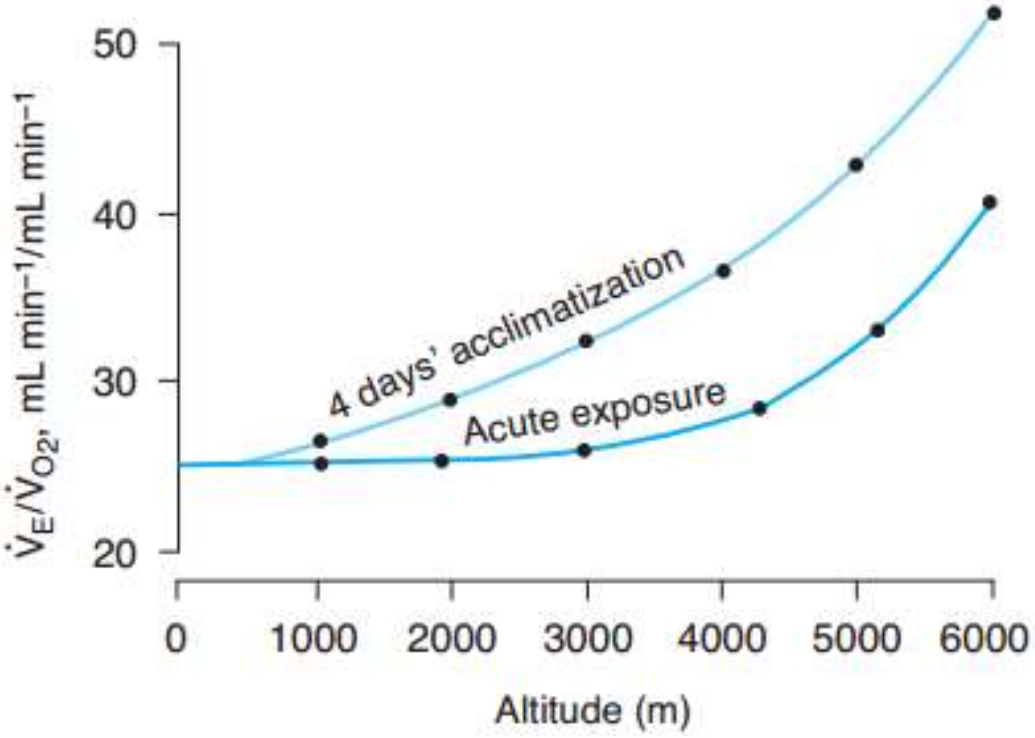
Hypoxic ventilatory response

- Hypoxic stimulation of the peripheral chemoreceptors
- Genetically determined and quite variable
- Correlate positively with physical performance at high altitude and inversely with the susceptibility to AMS
- Extrinsic factors
  - respiratory depressants (alcohol and sedative/hypnotics)
  - fragmented sleep
  - respiratory stimulants (progesterone) and sympathomimetics (coca, caffeine)

Hypoxic ventilatory response

- Respiratory alkalosis blunts the HVR by acting on central medullary chemoreceptors
- However ventilation gradually increase – '*ventilatory acclimatization*'
  - compensatory metabolic acidosis by kidney
  - Movement of HCO_3 out of CSF
  - increased sensitivity of carotid body
  - erythropoietin signalling in brain

Hypoxic ventilatory response



Lenfant C, Sullivan K: Adaptation to high altitude; NEJM 1971;284:1298

Blood gases at 8848 m

Barometric pressure, mm Hg	Inspired PO_2, mm Hg	PA O_2 mm Hg	PaO_2 mm Hg	Pa CO_2 mm Hg	pH
253	43	35	28	7.5	> 7.7
760	149	100	95	40	7.4

West JB. Science, 1984

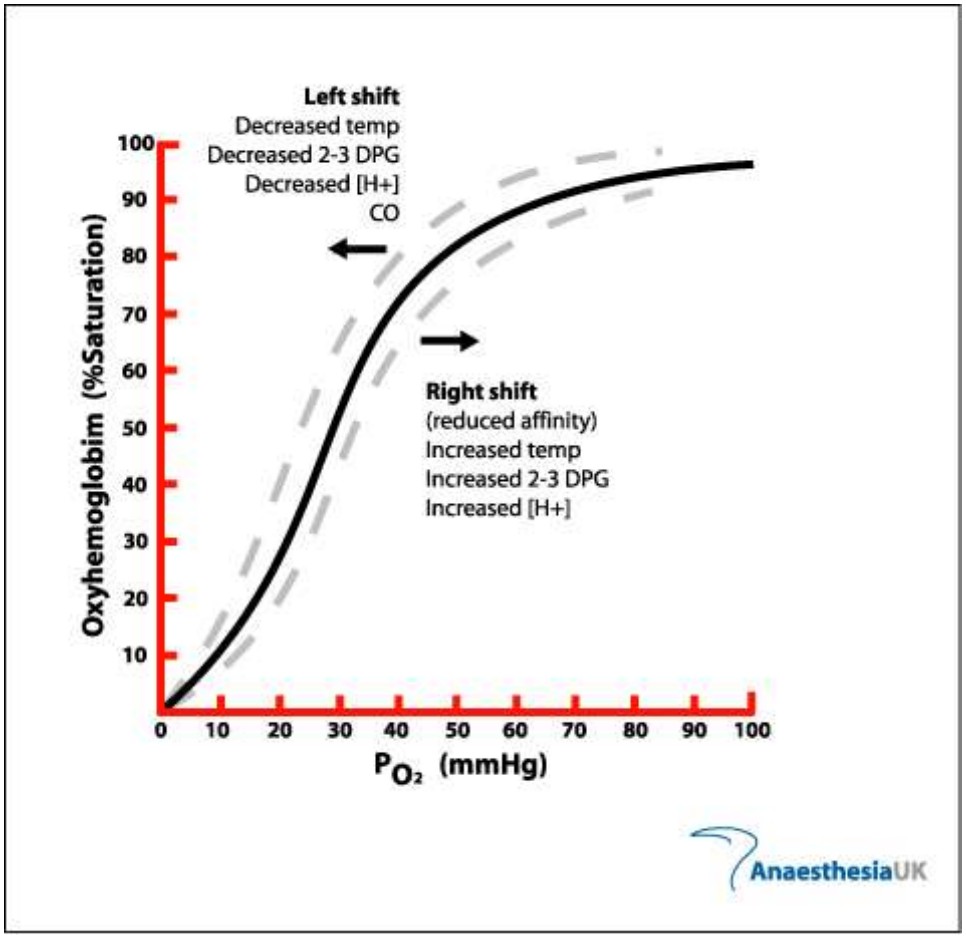
Gas exchange

Decrease O_2 delivery	Increase O_2 delivery
Low alveolar – arterial oxygen gradient	Haemoconcentration by a mild diuretic effect of hypoxia
Effective diffusion limitation during exercise (↑CO ↓capillary transit time)	Hypoxia-mediated EPO secretion - increased RBC production
Increased extravascular lung water	

Gas exchange

Intra erythrocytic alkalosis

↑alkalosis
very high altitudes
(>5000 m)



Increased
2, 3 DPG

Pulmonary mechanics

- Fall in vital capacity
  - pulmonary vascular engorgement
  - subclinical interstitial oedema
  - increased abdominal distension
  - decreased respiratory muscle strength
- No change in FEV1
- Increase in PEFR
  - decreased air density

Mason et al; High Alt Med Biol 2000 Fall;1(3):185-95.

Hypoxic pulmonary vasoconstriction

- Small pulmonary arterioles and veins with a diameter of < 900 µm
- Venous changes -~20% of the total increase in pulmonary vascular resistance
- Intrinsic to muscle cells of pulmonary arteries
- Endothelin and sympathetic activation

Peter Bärtsch et al; Circulation. 2007;116:2191-2202

Hypoxic pulmonary vasoconstriction

- Normally inhomogenous
  - baseline ventilation-perfusion ratio (V/Q) inhomogeneity
  - regional differences in endothelial release of NO
  - uneven distribution of smooth muscle cells in pulmonary arterioles
- Inhomogenecity increases with the magnitude of HPV
- Exaggerated HPV – risk of HAPE

Peter Bärtsch et al; Circulation. 2007;116:2191-2202

Cardiovascular response

- Unchanged or slightly decreased systemic BP
  - hypoxic vasodilation
- BP and SVR rise over at least 3 to 4 weeks
  - increasing sympathetic activity
  - reduced tissue hypoxia a/w acclimatization
- ↑ HR (both at rest and on exercise), myocardial contractility & ↑ cardiac output

Peter Bärtsch et al; Circulation. 2007;116:2191-2202

Hematologic response

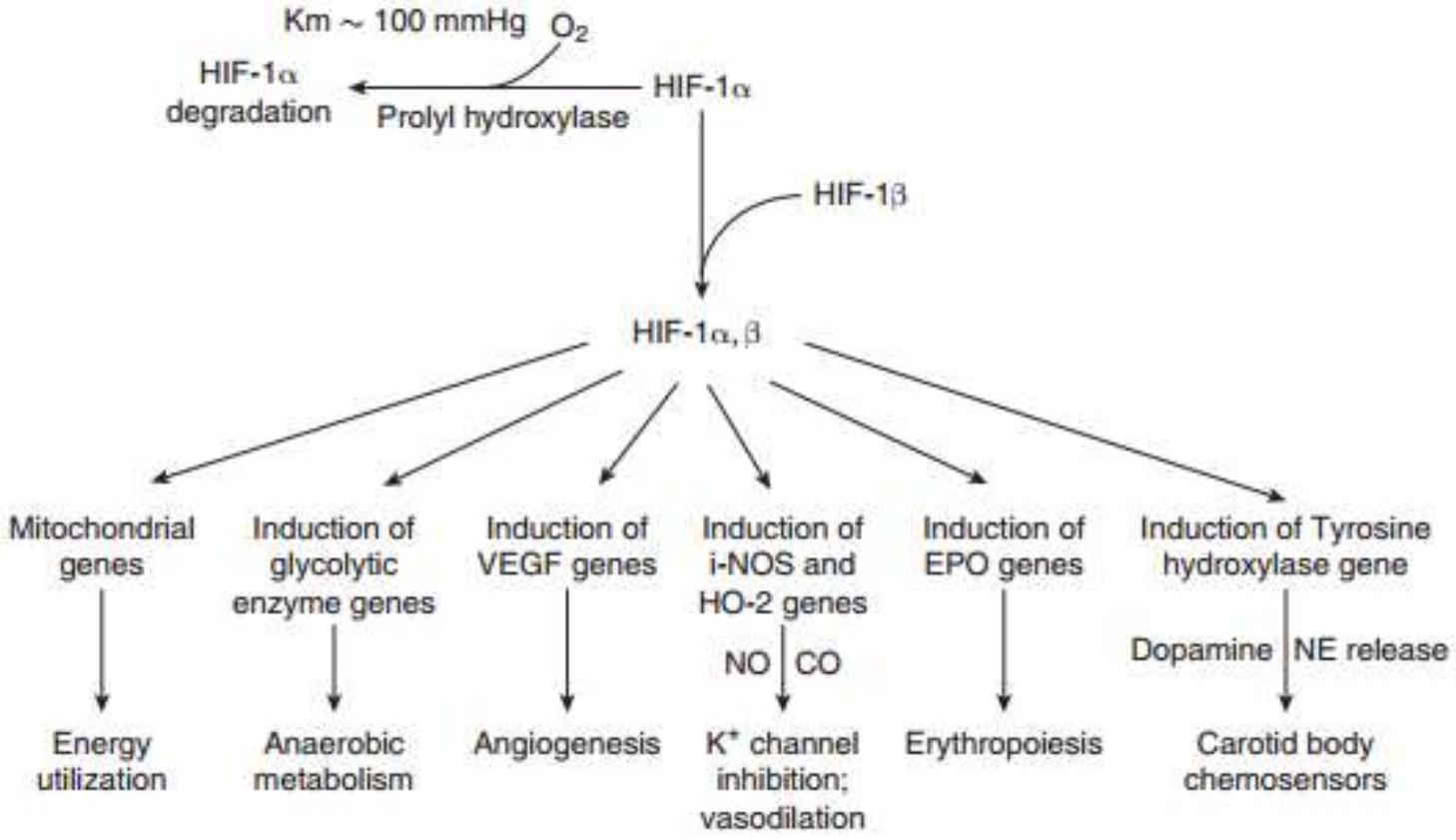
- Hb % increases within 1 to 2 days of ascent and continue to increase
- Initially – hemoconcentration
  - great insensible fluid loss by large ventilation of cold dry air
  - hormonal effects
- Later – EPO production (within 24 -48 hrs starts raising)
- Increased viscosity sufficiently impair cardiac output and limit microvasculature perfusion

Tissue adaptation

- Diminished muscle fiber size
- Increased myoglobin concentration
- Increased activity of enzymes in oxidative metabolism
- Up regulation of cytoglobins (heme proteins similar to myoglobin)

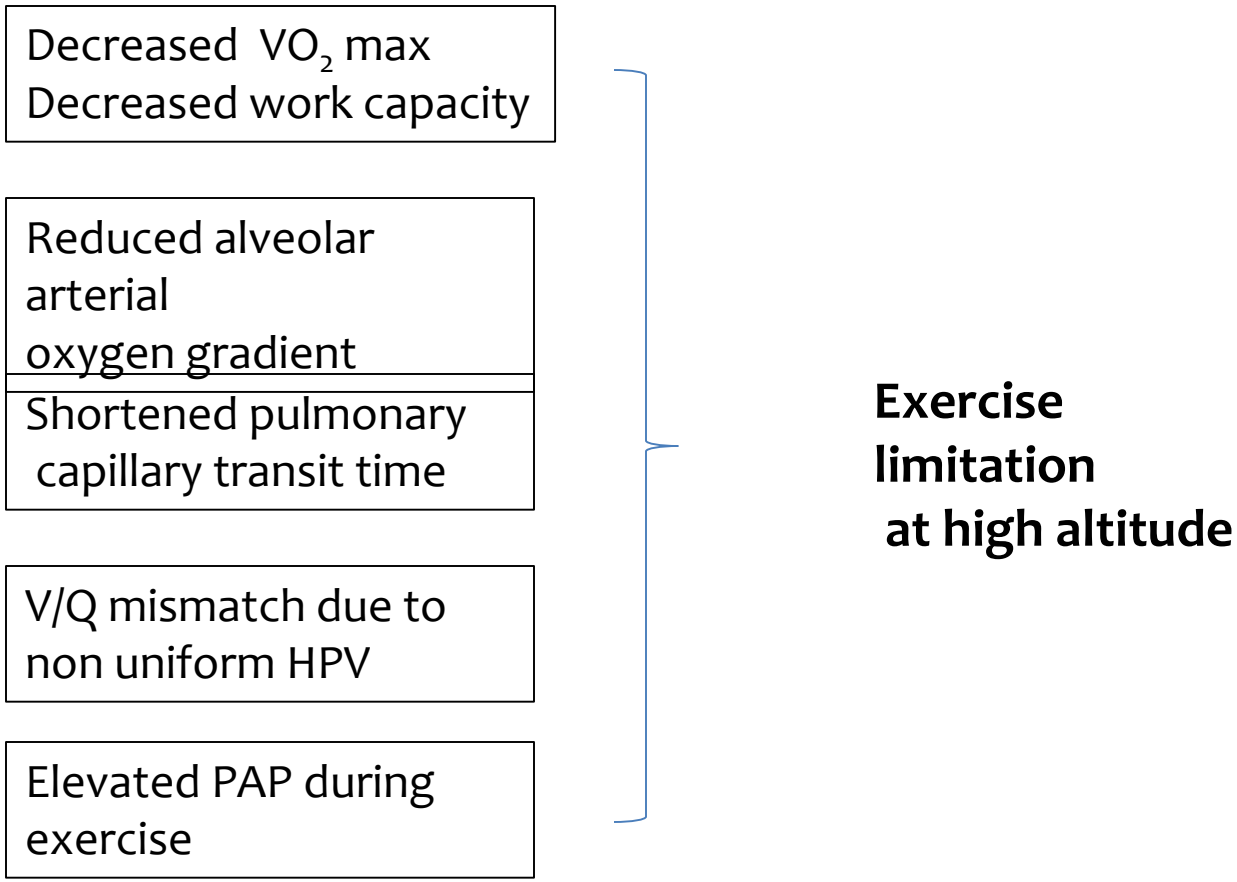
HIF

Cellular adaptation to hypoxia



Wilson DF, Roy A, Lahiri S: High Altitude Med Biol 6:97–111, 2005

Physical performance



John B West, Ann Intern Med 2004

Mental performance

- At an altitude above 4000 m people experience
  - an increased arithmetic errors
  - reduced attention span
  - increased mental fatigue
  - decision making

John B West, Ann Intern Med 2004

Sleep

- Subjective features
  - poor quality with sensation of occasional awakenings
  - sense of suffocation
  - restless sleep on awakening
- Objective features
  - shift from deeper to lighter sleep stages
  - fragmentation of sleep (frequency of arousals)
  - periodic breathing
  - duration of sleep maintained

John V Weil , High Alt Med Biol 2004

Periodic breathing

- Waxing and waning breathing pattern in sleep
- Instability in the control system
- Stimulation by hypoxia alternates with inhibition by hypocapnic alkalosis
- Declines during acclimatization at moderate altitude (< 4500 m)

John V Weil , High Alt Med Biol 2004

Periodic breathing

- Acetazolamide – reduction of alkalosis and possible lowering of apneic threshold

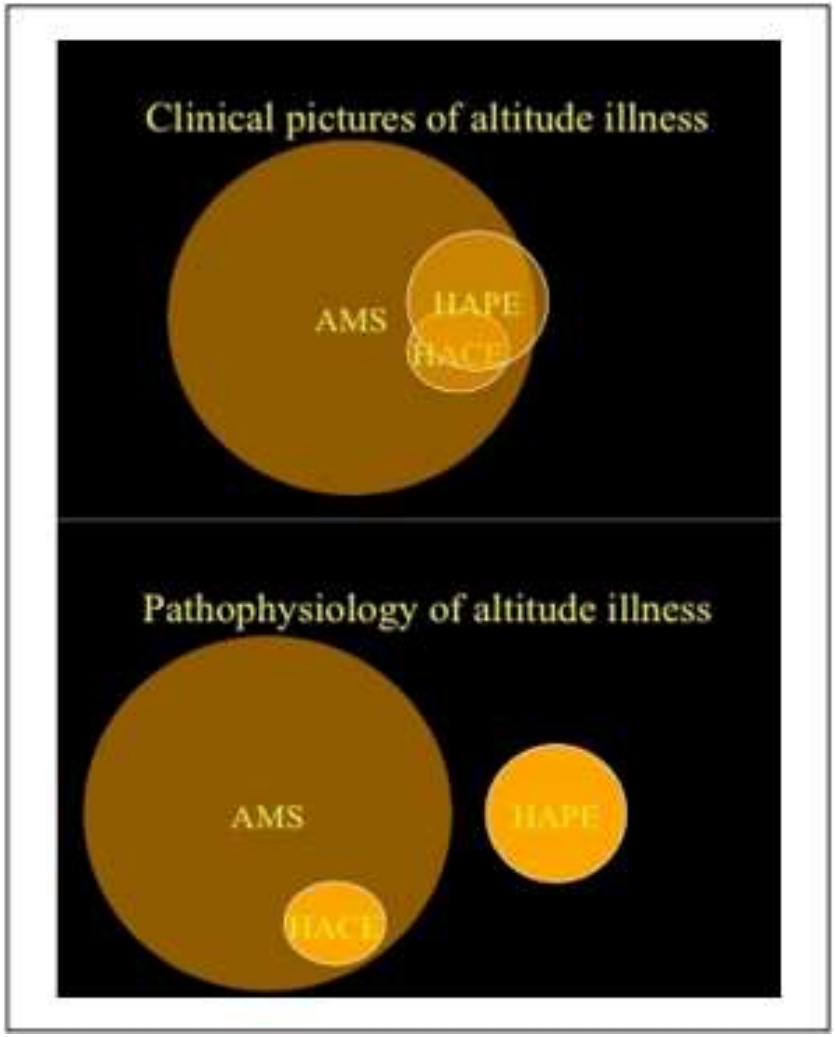
- Low doses of BZDs - shortened sleep latency, decreased arousals, increased sleep efficiency, increased REM, and produced subjectively better sleep

John V Weil , High Alt Med Biol 2004

ACUTE HIGH ALTITUDE ILLNESS

Acute high altitude illness

- Acute mountain sickness (AMS)
- High altitude cerebral edema (HACE)
- High altitude pulmonary edema (HAPE)



Tom Smedley & Michael PW Grocott, British J pain 2013

Epidemiology of HAI

- Up to 50–70% of mountaineers develop symptoms of AMS
- HACE and HAPE - incidence of 0.1–4%
- AMS > 2500 m
  HAPO > 3000 m
  HACO > 4000–5000 m
- Susceptible individuals can be affected below these altitudes also

Tom Smedley & Michael PW Grocott, British J pain 2013

Risk factors HAI

- Genetic susceptibility
- Degree of hypoxic stress
  - Rate of ascent
  - Elevation attained
  - Lack of acclimatisation
  - Vigorous exertion or substance consumption
- *Occur in any subject if the altitude is sufficiently high or the rate of ascent is sufficiently rapid, regardless of the person's capacity to acclimatize*

Tom Smedley & Michael PW Grocott, British J pain 2013

HAPE – susceptibility

- Susceptible individuals
  - abnormal increase in pulmonary artery pressure (PAP) during brief or prolonged hypoxic exposure
  - Greater PAP rise during exercise in normoxia
- Polymorphisms of RAAS pathway, the nitric oxide pathway and the hypoxia inducible factor pathway

Risk factors HAI (HAPE)

- Cold ambient temperature
- Respiratory tract infection
- Preexisting abnormalities with ↑ pulmonary blood flow - predispose to HAPE, even at altitudes below 2500 m
  - Primary pulmonary hypertension
  - Congenital absence of one pulmonary artery
  - Left-to-right intra cardiac shunts

Joshua O. Stream et al; Wilderness & environmental medicine, Dec 2008 : Vol. 19

Risk factors HAI (HAPE)

- PFO - reverses the direction of blood flow, shunting blood from right to left and further
- Larger PFOs correlate directly with increased arterial hypoxemia, and a increased risk of developing HAPE

	HAPE-Susceptible Participants (n = 16)	HAPE-Resistant Participants (n = 19)	*P* Value (Odds Ratio [95% CI])
Frequency of PFO, No. (%)			
At 550 m	9/16 (56)	2/19 (11)	.004 (10.9 [1.9-64.0])*
At 4559 m	11/16 (69)	3/19 (16)	.001 (11.7 [2.3-59.5])*
P value (550 vs 4559 m)†	.16	.32	
Frequency of HAPE, No. (%)			
At 4559 m	8/16 (50)	0/19 (0)	.001*

Yves Allemann et al; JAMA, Dec 2006

Risk factors HAI

RF	Odds ratio	CI
Prior h/o HAI	12.82	6.95 -23.66
Ascent > 400 m/day	5.89	3.78-9.16
Migraine	2.28	1.28-4.07
Low Ventilatory response to hypoxia at exercise	6.68	3.83–11.63
Desaturation at exercise in hypoxia ≥ 22%	2.50	1.52–4.11;

Jean-Paul Richalet et al; Am J Respir Crit Care Med 2012

Pathophysiology – AMS/HACE

- Cerebral edema
  - *Vasogenic edema* - increase in permeability of BBB due to increase in intravascular pressures or the effect of hypoxemia per se
- MRI showed intense T2 signals in the white matter, particularly in the splenium and corpus callosum with no gray matter edema*
  - *Cytotoxic edema* - rare
  - Increased CBF and the loss of autoregulation of ICP
  - Chemical factors (VEGF, NO & cytokines) alter the endothelial permeability

Hackett PH et al; JAMA 1998

Pathophysiology – AMS/HACE

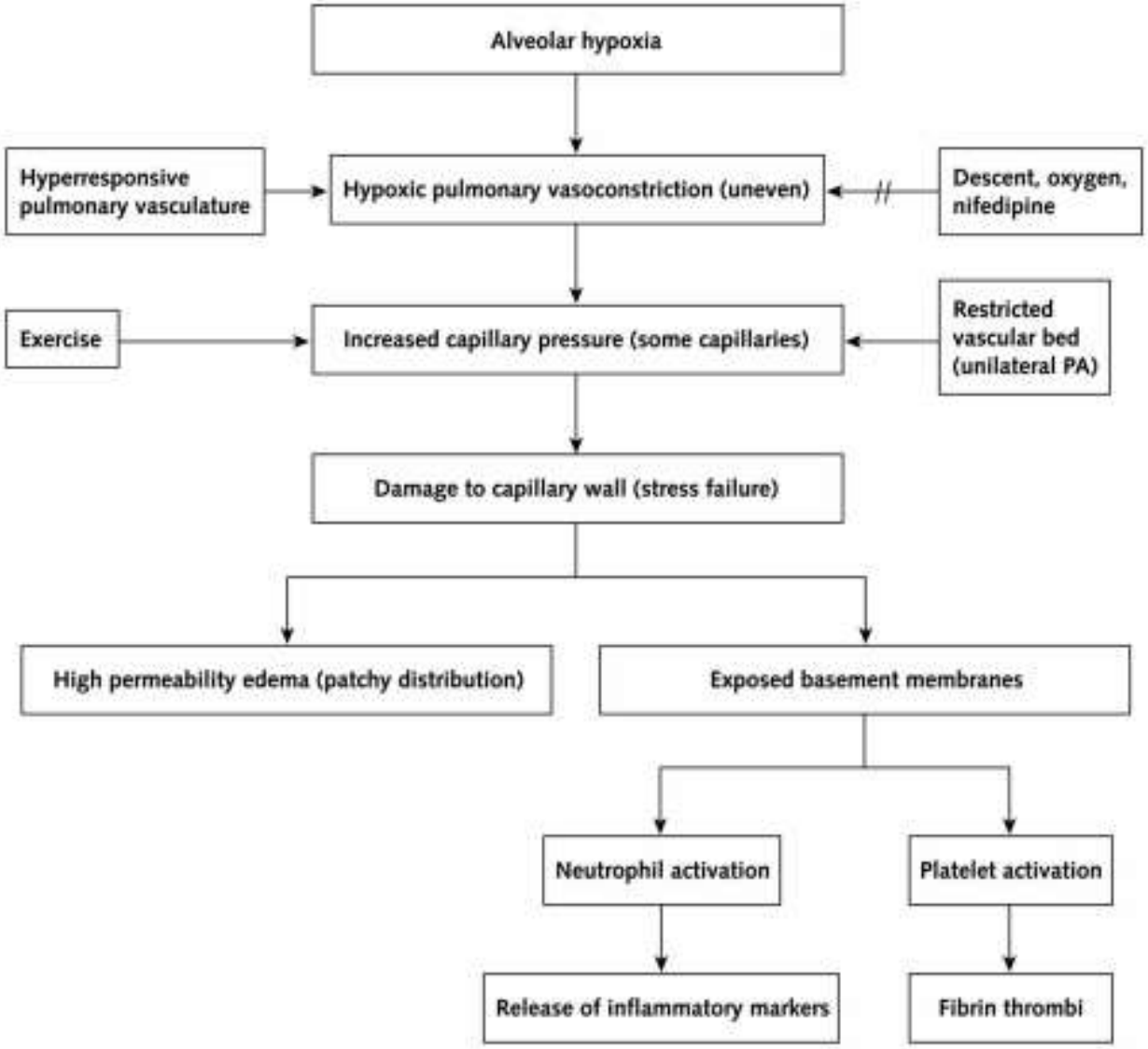
- Tight fit hypothesis
  - not the amount of swelling that matters
  - person's ability to tolerate such swelling
  - Individuals with a greater brain to cranial vault ratio become more symptomatic than individuals with a smaller ratio but with the same degree of cerebral edema

Pathophysiology - HAPE

Maladaptive responses to the hypoxia

- *Exaggerated and uneven pulmonary vasoconstriction*
- Poor ventilatory response
- Increased sympathetic tone
- Hypoxia induced endothelial dysfunction (↓NO & ↑ endothelin)

Joshua O. Stream et al; Wilderness & environmental medicine, Dec 2008 : Vol. 19



John B West, Ann Intern Med 2004

Criteria for HAI

Condition	*Criteria**
Acute mountain sickness	Headache and at least one of the following symptoms: fatigue or weakness; dizziness or lightheadedness; gastrointestinal symptoms (nausea or vomiting, anorexia); difficulty sleeping
High-altitude cerebral edema	Change in mental status *or* ataxia in a person with acute mountain sickness, or change in mental status *and* ataxia in a person without acute mountain sickness
High-altitude pulmonary edema	At least two of the following symptoms: dyspnea at rest; cough; weakness or decreased exercise performance; chest tightness or congestion *and* At least two of the following signs: crackles or wheezing in at least one lung field; central cyanosis; tachypnea; tachycardia

High Altitude Medicine Guide. The Lake Louise consensus on the definition of altitude illness. http://www. high-altitude-medicine.com/AMS-LakeLouise.html.

Risk assessment HAI

Low	Moderate	High
Slow ascent (≤500 m/day above 2500 m) and taking 1 day for acclimatisation for every addnl 1000m ascent	Fast ascent (>500 m/day above 2500 m) & taking 1 day for acclimatisation for every addnl 1000 m ascent	Fast ascent (>500 m/day above 2500 m) without a extra day for acclimatisation
No h/o high altitude illness with previous exposure to similar altitude		History of high altitude illness with previous exposure to similar high altitude
Fast ascent (>500 m/day above 2500 m) for persons who are partially acclimatized		Ascent > 3000 m in less than 2 days

Peter Bärtsch; Acute high altitudinal illnesses; NEJM 2013

AMS

- Head ache - cardinal symptom
- Anorexia, nausea, dizziness, malaise, sleep disturbances or combination of these
- Sense of oppression in the chest
- Delayed for 6 to 12 hours following arrival at high altitude

Peter Bärtsch; Acute high altitudinal illnesses; NEJM 2013

AMS

- Within 6 to 12 hours after ascent to 2500 m or more
- Resolve in one day if there is no further ascent, and do not recur at the same altitude
- Prevalence and severity increase with increasing altitude
  - 10 to 25% of who ascend to 2500 m
  - 50 to 85% of who ascend to 4500 to 5500 m

Peter Bärtsch; Acute high altitudinal illnesses; NEJM 2013

D/D - AMS

- Clinical history
- No confirmatory laboratory tests
- Supplemental oxygen may be used to support the clinical diagnosis
- Differentials :
  - dehydration
  - hypothermia
  - exhaustion
  - alcohol hangover
  - carbon monoxide poisoning
  - respiratory or cerebral infections

Peter Bärtsch; Acute high altitudinal illnesses; NEJM 2013

HACE

- Truncal ataxia
- Progressive decline of mental function & consciousness
- Coma followed by death from brain herniation within 24 hours
- After at least 2 days at altitudes above 4000 m
- 0.5 to 1.0% among persons at 4000 to 5000 m
- *Headache not responding to NSAIDs and associated vomitings indicates probable progression of AMS to HACE*

Peter Bärtsch; Acute high altitudinal illnesses; NEJM 2013

Lake Louise Score for the Dx of AMS

Symptoms	Severity	Score
1. Headache	None	0
	Mild	1
	Moderate	2
	Severe/incapacitating	3
2. Gastrointestinal	None	0
	Poor appetite or nausea	1
	Moderate nausea or vomiting	2
	Severe nausea or vomiting/ incapacitating	3
3. Fatigue/weakness	None	0
	Mild	1
	Moderate	2
	Severe/incapacitating	3
4. Dizziness/lightheaded	None	0
	Mild	1
	Moderate	2
	Severe/incapacitating	3
5. Difficulty sleeping	None	0
	Not as well as usual	1
	Poor night's sleep	2
	Unable to sleep	3
A diagnosis of acute mountain sickness (AMS) requires (a) score > 3, (b) presence of headache and (c) recent ascent.		
High-altitude cerebral oedema	**With AMS**	Altered mental status *or/and* ataxia
	Without AMS	Altered mental status *and* ataxia

Treatment

	AMS	HACE
Descent	Not mandatory except in the setting of intractable symptoms or suspicion that illness is progressing	*Immediate descent at first suspicion is crucial*
Supplemental O_2	Can serve as an alternative to descent	Not definite therapy
Hyperbaric therapy	Effective temporizing measure awaiting descent or benefits of medical therapy Practically challenging for use in patients with severe nausea, vomiting or decreased conscious level	
Drugs Rx	Acetazolamide Dexamethasone – severe AMS	*Dexamethasone (administered immediately upon first suspicion of HACE)*

Tom Smedley & Michael PW Grocott, British J pain 2013

Descent

- Descent remains the single best treatment for AMS and HACE
- Should descend until symptoms resolve
- Symptoms resolve following descent of 300 to 1000 m
- Required descent vary between persons

Tom Smedley & Michael PW Grocott, British J pain 2013

Acetazolamide

- 125 to 250 mg orally every 12 hours
- Continue for 24 hours after symptoms resolve or descent accomplished
- Relieves symptoms, improves arterial oxygenation, and prevents further impairment of pulmonary gas exchange
- Accelerates acclimatisation process

Grissom CK et al; Ann Intern Med. 1992;116 (6):461.

Dexamethasone

- Does not facilitate acclimatization and further ascent should be delayed until the patient is asymptomatic while off the medication
- 8-mg dose (IM/IV/PO) followed by 4 mg q6h until symptoms resolve
- False sense of security when symptoms diminish

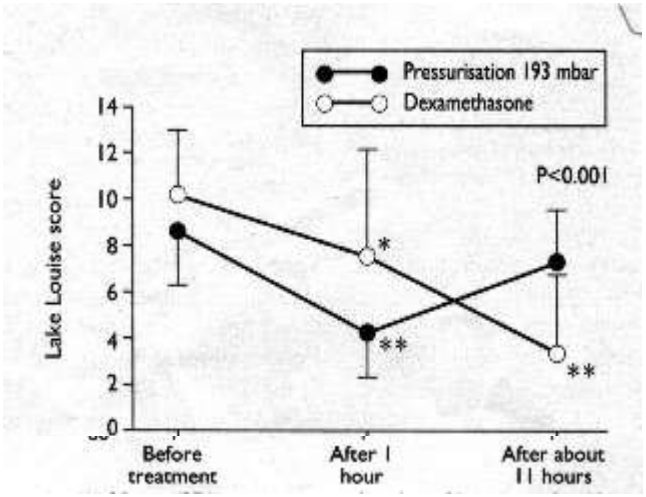
Tom Smedley & Michael PW Grocott, British J pain 2013

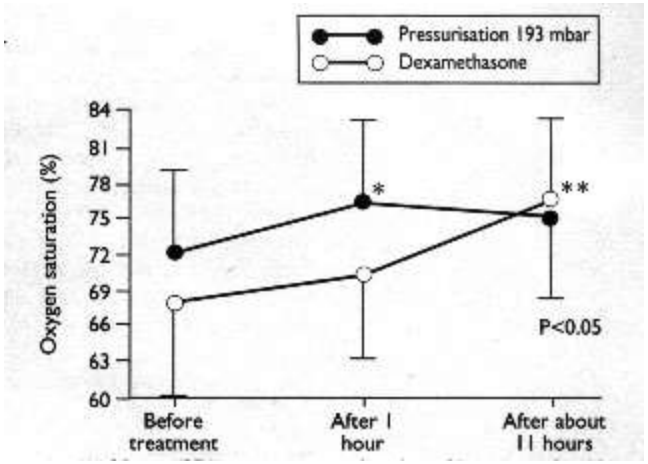
Dexamethasone

Study	n	Methods	Assessment AMS	Results
Levine et al; NEJM 1989 RCT	6	Simulated altitude of 3700m for 48 hrs *4 mg PO/IM q6h*	Symptom score	Reduction of symptoms by 63 %
Hackett et al; Aviat space Environ Med 1988	11	4400 m after 1 hr flight *4 mg PO/IM q6h*	Symptom score	Improvement at 12 hrs in symptom score
Ferrazini et al; BMJ 1987 RCT	35	altitude of 4559m above sea level Placebo (18) vs Dexa(17)	Symptom score O2 saturation FEV1 & FVC Resting MV	No change in MV , rest all improved in dexa group

Dexamethasone vs hyperbaric chamber

- Randomised trial among AMS subjects (n =31)
- Altitude of 4559m above sea level





Keller HR et al; BMJ 1995

Prevention

High Altitude acclimatization	
International Society of Mountain Medicine	• Once above 3000m, sleeping altitude should not increase by more than 500m per day • One day of rest should be catered after every 3-4 days of ascent
Wilderness Medical Society	• First night at altitude should be spent below an altitude of 2400m • Once above 2400m, sleeping altitude should not increase by more than 600m per day

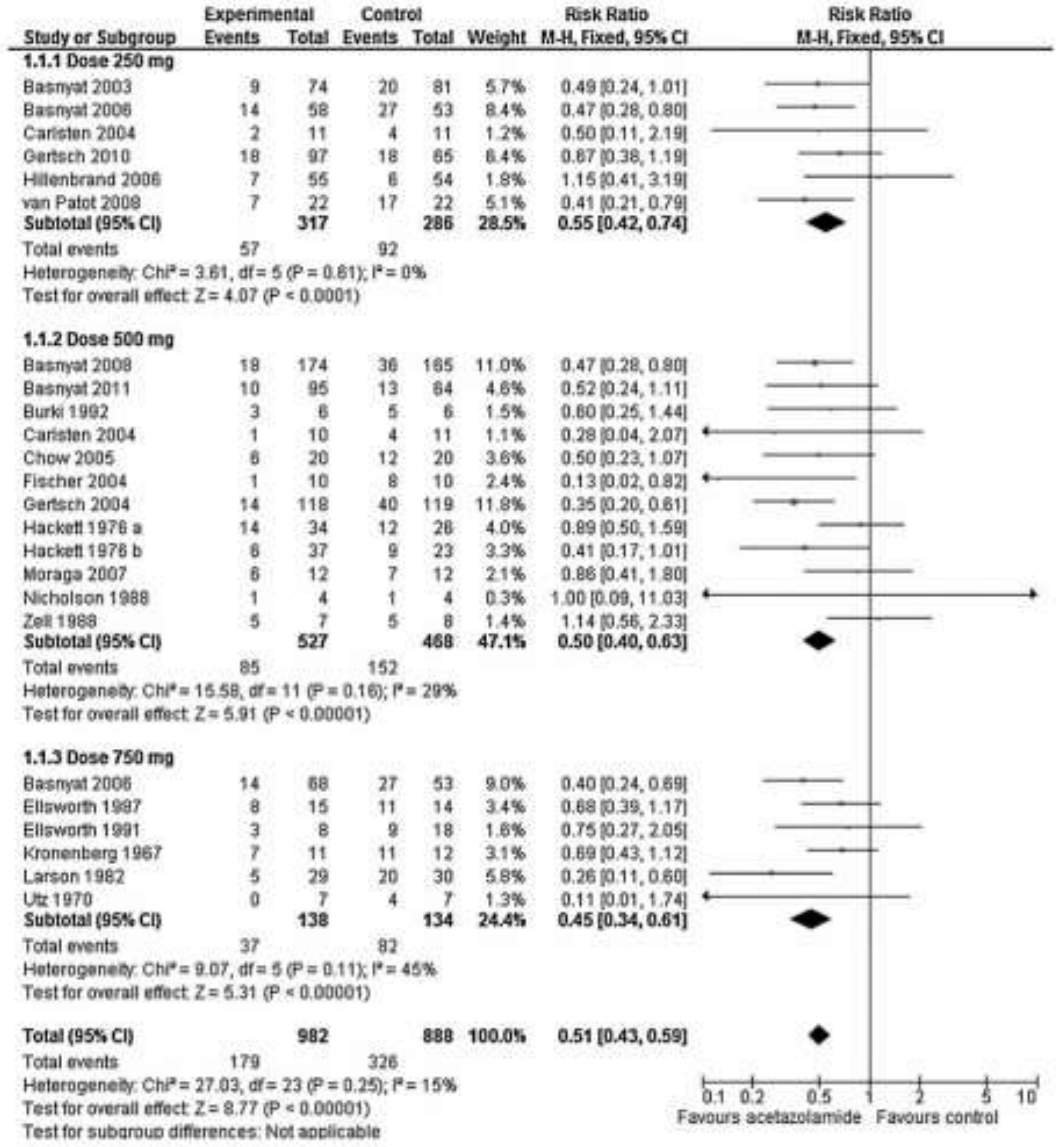
Prevention of AMS

- Acetazolamide
- Dexamethasone
  - prior h/o intolerance
  - allergic reaction to acetazolamide
  - rapid ascent higher than 3000 m
- Acetazolamide & dexamethasone – very rapid ascent
- Gingko biloba
- NSAIDs

✓ Prophylaxis may be stopped after 2 to 3 days at the target altitude, if stays for several days

✓ Should be stopped once descent is initiated

Prevention of AMS by Acz



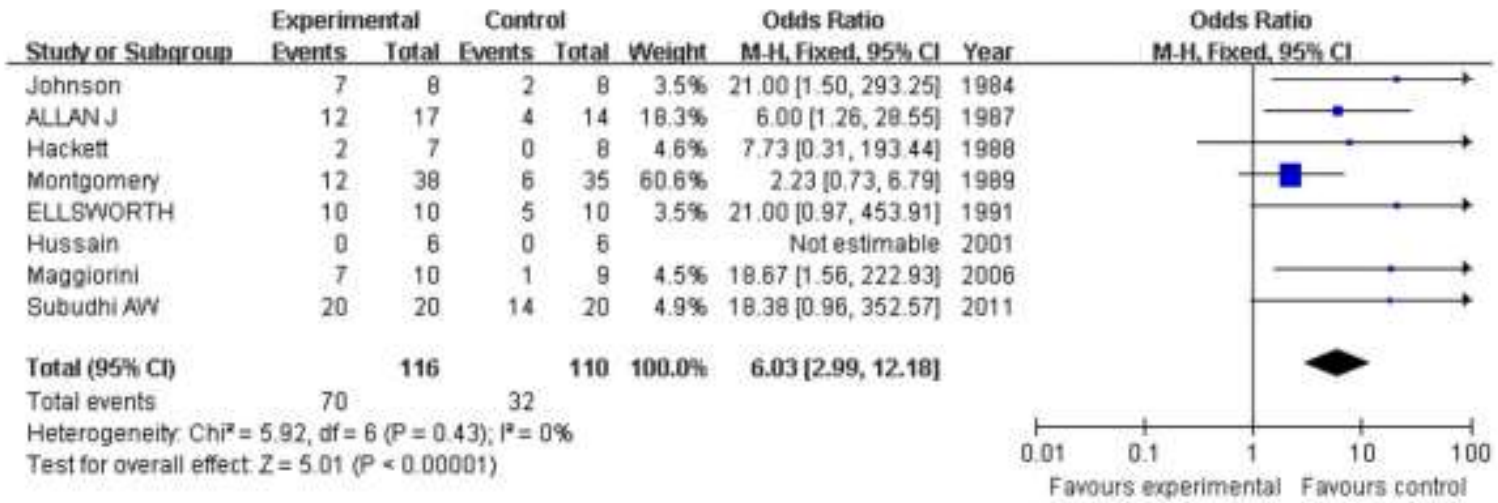
Kayser B, High Alt Med Biol. 2012 Jun;13(2):82-92.

Prevention of AMS by Acz

		Paresthesia		*Polyuria*		*Taste disturbance*	
Regimen	*Number of subjects*	*Acetazolamide*	*Placebo*	*Acetazolamide*	*Placebo*	*Acetazolamide*	*Placebo*
250 mg day^{-1}	No. with event/ total No. (%)	130/191 (68.1)	40/186 (21.5)	34/62 (54.8)	28/53 (52.8)	2/57 (3.5)	2/49 (4.1)
	Risk ratio [95% CI]	3.04 [2.31 to 4.01]		1.04 [0.74 to 1.46]		0.86 [0.13 to 5.88]	
500 mg day^{-1}	No. with event/ total No. (%)	113/187 (60.4)	17/190 (8.9)	14/138 (10.1)	9/139 (6.5)	16/145 (11.0)	5/147 (3.4)
	Risk ratio [95% CI]	6.44 [4.09 to 10.1]		1.56 [0.72 to 3.40]		3.05 [1.19 to 7.78]	
750 mg day^{-1}	No. events/ total No. (%)	76/84 (90.5)	16/58 (27.6)	66/136 (48.5)	32/117 (27.4)	9/65 (13.8)	2/49 (4.1)
	Risk ratio [95% CI]	3.15 [2.09 to 4.75]		1.59 [1.18 to 2.14]		3.39 [0.77 to 15.0]	

Kayser B, High Alt Med Biol. 2012 Jun;13(2):82-92.

Prevention of AMS by Dexa



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Johnson	7	8	2	8	3.5%	21.00 [1.50, 293.25]	1984
ALLAN J	12	17	4	14	18.3%	6.00 [1.26, 28.55]	1987
Hackett	2	7	0	8	4.6%	7.73 [0.31, 193.44]	1988
Montgomery	12	38	6	35	60.6%	2.23 [0.73, 6.79]	1989
ELLSWORTH	10	10	5	10	3.5%	21.00 [0.97, 453.91]	1991
Hussain	0	6	0	6		Not estimable	2001
Maggiorini	7	10	1	9	4.5%	18.67 [1.56, 222.93]	2006
Subudhi AW	20	20	14	20	4.9%	18.38 [0.96, 352.57]	2011
Total (95% CI)		**116**		**110**	**100.0%**	**6.03 [2.99, 12.18]**	
Total events	70		32				

Heterogeneity: Chi² = 5.92, df = 6 (P = 0.43); I² = 0%
Test for overall effect: Z = 5.01 (P < 0.00001)

Enjie Tang et al; International Journal of Cardiology 2014

NSAIDS - AMS

Study	Lipman et al, 2012, California	Gerstch et al, 2012, Mt Everest, Nepal
Participants	86 participants Ascending from 1,240 m to 3,810 m	294 trekkers 4280 or 4358m (183 completed)
Methods	Ibuprofen 600 mg or placebo TID, starting 6 hours before ascent	Ibuprofen 600 mg or placebo TID, before ascent to 4928 m
Comparator	44 ibuprofen, 42 placebo	232 ITT (123 vs 109) 183 APP (110 vs 73)
Outcome (study vs control)	AMS 43 % Vs 69 % (***OR 0.3***, 95% CI 0.1 to 0.8) AMS severity also lower in NSAID group	(ITT) AMS (24.4% vs 40.4%; *P* = 0.01) (APP) AMS (32.9% vs 22.7%; *P* =0 .129) (ITT) Severity (8.9% vs 11.9%; *P* =0.45) (APP) Severity (9.6% vs 8.2%; *P* =0.74)

Lipman et al; Annals of Emergency Medicine 2012
Gerstch et al, Wilderness & environmental medicine,2012

NSAIDs

- Aspirin or ibuprofen may be useful for preventing the headache associated with AMS
- Role in high risk situation is unclear
- The limitations of trials involving NSAIDs make such determinations difficult

Gingko biloba

	Chow T et al; 2005, California	Moraga FA et al, 2007, Ollague, Chile
Participants	57 subjects Elevated to 3800 m to 24 hrs	36 subjects Elevated to 3696 m
Methods	LLS used for AMS Dx 120 mg BD G biloba 250 mg BD ACZ 5 days before the ascent	G biloba 80 mg/12 h ACZ 250 mg/12 h or Placebo 24 hours before ascent and during their 3-day stay
Comparator	20 acetazolamide 17 Ginkgo biloba 20 placebo	12 G biloba 12 ACZ 12 placebo
Outcome AMS incidence	30 % ACZ 65 % G biloba 60 % placebo	36 % ACZ 0 % G biloba 56 % placebo
Conclusion	No benefit of G Biloba	Support the use of G Biloba

Tony Chow et al; Ann Intern Med 2005
Moraga FA et al, Wilderness and Environmental Medicine, 18, 251 257 (2007)

Gingko biloba

Gertsch et al; Prevention of HAI trial, Mt Everest Himalayas, Nepal	
Participants	487 healthy trekkers assigned to receive ginkgo, acetazolamide, combined acetazolamide and ginkgo, or placebo, initially taking at least three or four doses before continued ascent
Methods	randomised in a double blind fashion to receive twice daily either ginkgo 120 mg, acetazolamide 250 mg, combined ginkgo 120 mg and acetazolamide 250 mg, or placebo
Outcome measure	Incidence of AMS by LLS
Results	14 (12 %) ACZ 43 (35 %) G biloba 18 (14 %) ACZ + biloba 40 (34 %) placebo
Conclusion	When compared with placebo, ginkgo is not effective at preventing AMS. Acz 250 mg twice daily afforded robust protection against symptoms of AMS

Gertsch et al; BMJ 2004

Clinical features HAPE

- Usually 2 - 4 days after arrival at a new altitude
- Subtle, non productive cough → pink, frothy sputum to frank blood
- Dyspnea on exertion and difficulty walking uphill with early progression to dyspnea at rest
- Restricted exercise tolerance
- Deterioration in gas exchange also increases the risk of high-altitude cerebral edema

Peter Bartsch et al; N Engl J Med 2013;368:2294-302

Clinical features HAPE

- Inspiratory crackles
- *Appears better than expected for the severity of hypoxemia*
- *Rapid correction of the SpO2 and clinical status with supplemental O2 in the setting of a severe infiltrative lung process seen on radiograph is virtually pathognomonic for HAPE*

Peter Bartsch et al; N Engl J Med 2013;368:2294-302

Diagnosis HAPE

- History and physical examination
- CXR - patchy alveolar infiltrates, predominantly in the right central hemithorax, which become more confluent and bilateral as the illness progresses
- USG – Ultrasound lung comets caused by air fluid interface in the presence of EVLW
- Differentiating HAPE from ADHF or pneumonia can be difficult, particularly in older patients with comorbidities

Wimalasena Y et al; Wilderness Environ Med, 2013

Oxygen therapy

- Supplemental O_2 and rest while remaining at high altitude are sufficient treatment for mild to moderate HAPE
- Supplemental O_2 is *first-line therapy*
  - reduces pulmonary artery (PA) pressure
  - reverses capillary leak
  - reduces both the heart and respiratory rates

Descent / Hyperbaric chamber

- Atleast 500 to 1000 m
- Passive descent recommended
- Also treats acute mountain sickness
- Portable hyperbaric chamber
  - good temporizing measure before definitive therapy
  - if oxygen is not available
  - descent is unsafe or impossible

PAP therapy

- Improves gas exchange by providing positive airway pressure
- Temporary measure
- Considered as an adjunct to O_2 administration
- No studies have established its role in HAPE

Larson EB; Lancet 1985; 1(8425):371-3

Pharmacologic therapy

- Nifedipine
- PDE5 inhibitors
  - Sildenafil
  - Tadalafil
  - Strong physiologic rationale present, but no studies have evaluated therapeutic benefit

Nifedipine - HAPE

- Decreased systolic PAP
- Narrows the alveolar-arterial oxygen gradient
- Improves radiographic scores of PE
- 30 mg SR formulation every 12 hours
- Unlikely to cause significant hypotension in previously healthy persons
- Should not be relied on as the sole therapy unless descent is impossible and access to supplemental oxygen or portable hyperbaric therapy cannot be arranged

Oelz O etal; Lancet 1989 Nov 25;2(8674):1241-4

Nifedipine - HAPE

- Prospective study among 110 patients in a military hospital in Sikkim
- Alternately received nifedipine or placebo along with reduction of altitude, bed rest and nasal oxygen therapy
- Nifedipine appears to provide no additional benefit in the resolution of HAPE

Rajesh Deshwal et al; Wilderness Environ Med. 2012 Mar;23(1):7-10

Nifedipine – prevention HAPE

Nifedipine Vs placebo in prevention of HAPE
20 mg SR Nifedipine every 8 hrly during the ascent and following 3 days at high altitude

	Nifedipine (n =10)	Placebo (n= 11)	*P*
Pulmonary edema	1	7	0.01
Systolic PAP (mm Hg)	41 ± 8	53 ± 6	0.01
A-a O2 gradient	6.6 ± 3.8	11.8 ± 4.4	<0.01

Bärtsch P et al:NEJM 1991;325(18):1284

Prevention HAPE

- RCT of 29 adult with previous HAPE
- 4559 m within 2 days ascent

	Placebo (n=9)	Tadalafil (n=10)	Dexamethasone (n=10)
AMS	8	7	3
Mean sPAP	28 mm Hg	13 mm Hg P=0.005	16 mm Hg P =0.012

Both dexamethasone and tadalafil decrease systolic PAP
May reduce the incidence of HAPE in adults with a history of HAPE

Maggiorini M et al; Ann Intern Med 2006

Prevention HAPE

Salmeterol 125 mcg vs placebo
Beta agonists up regulate clearance of alveolar fluid

VARIABLE	SALMETEROL GROUP	PLACEBO GROUP	P VALUE
Age (yr)	49.6±10.2	46.0±12.6	NS
Sex (no.)			NS
Male	13	15	
Female	5	4	
No. of previous episodes†	2.4±1.0	1.9±1.1	NS
Heart rate (beats/min)	94.1±11.1	89.1±13.5	NS
Systolic pulmonary-artery pressure (mm Hg)	60.9±15.5	63.6±13.9	NS
Arterial oxygen saturation (%)	73.5±11.5	67.0±7.9	0.03
Partial pressure of arterial oxygen (mm Hg)	33.9±7.3	30.0±5.1	0.04

Incidence of HAPE
74 % (placebo) vs 33 % (Rx)
P = 0.02

Satori et al; NEJM 2002

CHRONIC HIGH ALTITUDE ILLNESS

CMS

- Maladaptation among high altitude residents
- Altitudes above 2500 m
- First described by Carlos Monge 1928 in Peru

CMS

- Excessive erythrocytosis

  (> 2 SD above the mean Hb % of the population at altitude of residence)
- Severe hypoxemia
- Moderate to severe PH
- Gradually disappears after descent to low altitude & reappears after return to high altitude

Léon-Velarde et al; High Alt Med Biol Vol 6, 2005

CMS

Blunted HVR

Relative hypoventilation

More HPV

Exaggerated hematopoietic response

Polycythemia blunting ventilatory response

CMS - prevalence

- 83 individuals
- Eight towns across the HP districts (mean altitude 3281 m)
- Overall prevalence of CMS – 6.17 %

Altitude group (m)	N	CMS score	prevalence
< 3000	31	1.03 ± 0.20	0 %
≥ 3000	50	1.85 ± 0.25	13.73 %

Sahota and Panwar, IJOEM Dec 2013; Vol 17

CMS

- Headache, tinnitus, vertigo, dizziness, lethargy, impaired memory and mentation
- Burning in the palms and soles
- Dilatation of veins
- Plethoric appearance with ↑hematocrit & Hb
- Normal respiratory function confirmed by lung function tests

CMS

- Erythrocytosis
  - Increased production of pro-inflammatory markers
  - oxidative stress
  - damage to the vascular endothelium
  - development of atherosclerosis
  - consequent increment in the risk of cardiovascular events such as vascular occlusion, myocardial ischemia and stroke

The Qinghai CMS score

- *Breathlessness and/or palpitations*
- *Sleep disturbance*
- *Cyanosis*
- *Dilatation of veins*
- *Paresthesias*
- *Headaches and*
- *Tinnitus*
- *Hb Males: 18 - 21 g/dl (0), ≥ 21 g/dl (3)*
  Females: 16 - 19 g/dl (0), ≥ 19 g/dl (3)

- Value of 0, 1, 2, and 3 (absent, mild, moderate, and severe respectively)
- Absent Score 0 - 5
  Mild Score 6 - 10
  Moderate Score 11 - 14
  Severe Score > 15

Léon-Velarde et al; High Alt Med Biol Vol 6, 2005

CMS - therapy

- Periodic travel to low altitude levels
- Severe cases – to be shifted permanently
- Phlebotomy with / without isovolumic hemodilution
  - reduces hematocrit
  - improves oxygenation
  - relief of symptoms
- Safety and efficacy not established

Francisco C Villafuerte & Noemi Corante; High Altitude medicine & Biology 2016

CMS - therapy

- Iron deficiency – leading to increased pulmonary artery pressures and aggravation of PH
- Rebound rise if the person continue to stay at high altitude
- Subjects concern on blood letting

Francisco C Villafuerte & Noemi Corante; High Altitude medicine & Biology 2016

CMS - therapy

- Physical exercise – non pharmacological Rx
- Aerobic exercise might play a beneficial role in decreasing the erythrocytic mass and in reducing CMS symptoms
- Exercise has to be performed with care due to the development of severe PH
- Reduction of Hb concentration is consequence of improved oxygenation due to training & increased exercise-related hemolysis

Francisco C Villafuerte & Noemi Corante; High Altitude medicine & Biology 2016

CMS - therapy

- Respiratory stimulants
  - Medroxy progestero
  - Almitrine
- ACE Inhibitors
  - Enalaprilat
- Adrenergic blockers
- Safety and efficacy not established

Peripheral stimulant for ventilation
1.5 mg/kg/day
Decrease in Hct, CMS symptoms

Increased renal blood flow, oxygen availability, suppressing EPO, direct antagonism also

Reduced renal nerve activity
Reduced hypoxia mediated sympathetic stimulation

Mariia Rivera-Ch et al; Respirol Physiol Neurobiol 2007 ;158(2-3):251-65

CMS - therapy

- **Acetazolamide**
  - decreased serum erythropoietin
  - decreased hematocrit
  - decreased serum soluble transferrin receptors
  - increased arterial pO_2
  - reduced the number of apnea–hypopnea episodes and pulmonary vascular resistance

- Prolonged treatment with 250 mg acetazolamide (6 months) is well tolerated and efficient for CMS

Mariıa Rivera-Ch et al; Respirol Physiol Neurobiol 2007
Richalet et al,Am J Respir Crit Care Med, 2008

Location	*Altitude*	N *of cases*	*Disease*	*TX*	*Target*	*Outcome*	*Level of evidence*	*Ref.*
China	3008–4888	13	CMS	Isovolemic hemodilution	Decrease Hct	Improved signs and symptoms	NR controlled single group	Wu, 1979
USA	3100	5	CMS	Medroxy-progesterone	Improve oxygenation, decrease Hct	Decreased Hct	P–D double-blind crossover trial	Kryger et al., 1978b
China	3300	129	CMS	*Rhodiola*, a Tibetan herb	Decrease erythrocyte deformability and lipid peroxidation	Improved signs and symptoms	P–D double-blind controlled R-trial	Xi et al., 2000
Bolivia	3600	31	CMS and HAPH	Nifedipine	Decrease HAPH (D.E.)	Decrease >20% in Ppa in 2/3 of the subjects	NR case-control series	Antezana et al., 1998
Bolivia	3600	40	CMS	Almitrine	Increase ventilation, decrease Hct	Increased Pa_{O_2}, decreased Pa_{CO_2}	P–D double-blind controlled R-trial	Villena et al., 1985
Bolivia	3600	8	CMS	Isovolemic hemodilution	Increase C.O. and ventilation, decrease Hct, decrease HAPH (H.C.)	Decreased VE/Q m, improved Pa_{O_2}	NR controlled single group	Manier et al., 1988

Léon-Velarde et al; High Alt Med Biol Vol 6, 2005

Location	*Altitude*	N *of cases*	*Disease*	*TX*	*Target*	*Outcome*	*Level of evidence*	*Ref.*
China	3658	60	CMS	Medroxy-progesterone	Improve oxygenation, decrease Hct	Improved signs and symptoms	NR controlled single group	Zhou et al., 1983
Perú	3700	155	CMS	Bloodletting	Decrease Hct	Improved signs and symptoms	NR controlled single group	Sedano et al., 1988b
Perú	3700	36	CMS	Isovolemic hemodilution	Decrease Hct	Improved signs and symptoms	NR controlled single group	Sedano and Zaravia, 1988
Perú	4430	1	CMS	Isovolemic hemodilution	Decrease Hct	Improved oxygen transport	NR prepost series	Winslow et al., 1985
Perú	4430	10	CMS	O_2 supplementation and breathing technique	Improve oxygenation, decrease Hct	Improved signs and symptoms	NR case-control series	Bernardi et al., 2003
Perú	4430	10	CMS	Acetazolamide	Increase ventilation, decrease Hct	Increased Sa_{O_2}, decreased Hct	P–D double-blind controlled R-trial	Richalet et al., 2004

Léon-Velarde et al; High Alt Med Biol Vol 6, 2005

HAPH

- Subset of CMS (*PH and Cor pulmonale without polycythemia)*
- Mean PAP > 30 mm Hg or Systolic PAP > 50 mmHg measured at the altitude of residence
- Right ventricular hypertrophy, heart failure, moderate hypoxemia
- Absence of excessive erythrocytosis

Léon-Velarde et al; High Alt Med Biol Vol 6, 2005

HAPH

- Reduction of NO production
- Vascular remodelling of pulmonary arterioles
  - endothelial dysfunction
  - smooth muscle proliferation
  - adventitial thickening
- Hypoxia associated smooth muscle proliferation in originally weakly muscularised arterioles and normally non-muscular pulmonary vessels

X-Q. Xu and Z-C. Jing; Eur Respir Rev 2009; 18: 111, 13–17

HAPH

- Non specific presentation
- Exertional dyspnea – m/c
- Signs related to right heart failure
- Echocardiography – screening tool
- Right heart catheterisation – gold standard

X-Q. Xu and Z-C. Jing; Eur Respir Rev 2009; 18: 111, 13–17

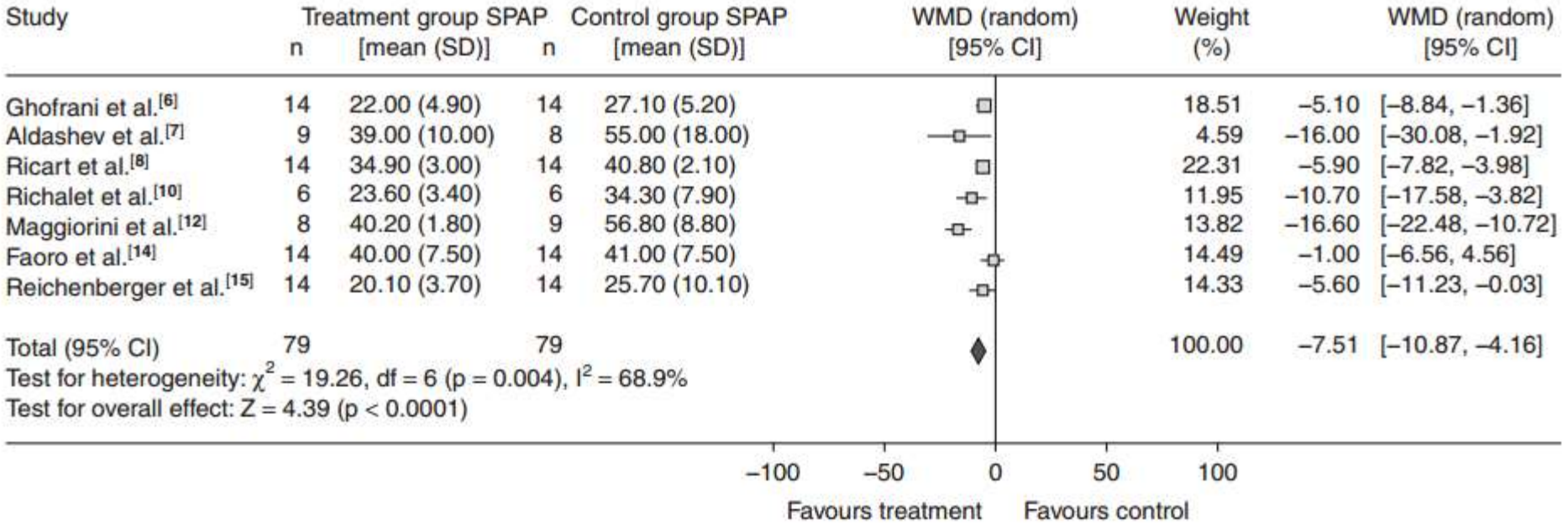
HAPH

- Ideal management for HAPH is migration to low altitude
- PDE 5 Inhibitors – relatively selective pulmonary vasodilatation with little systemic hypotension
- Endothelin antagonists
- Rho kinase inhibitor fasudil

Aibek E. Mirrakhimov, The Open Cardiovascular Medicine Journal, 2016

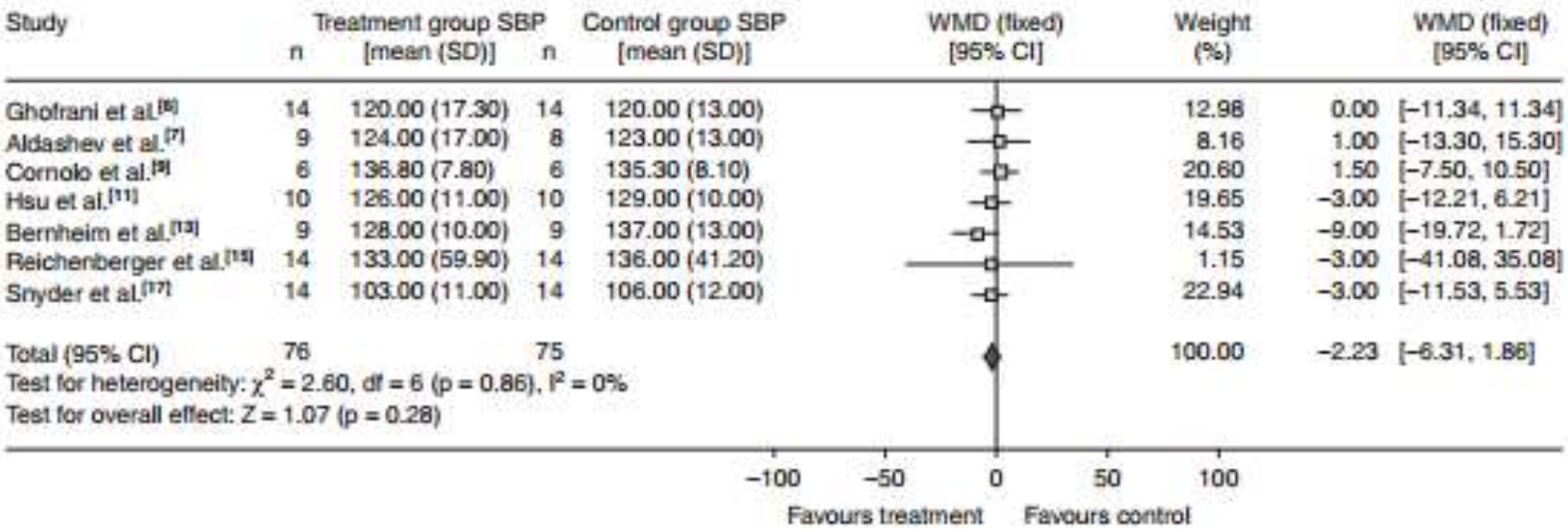
HAPH

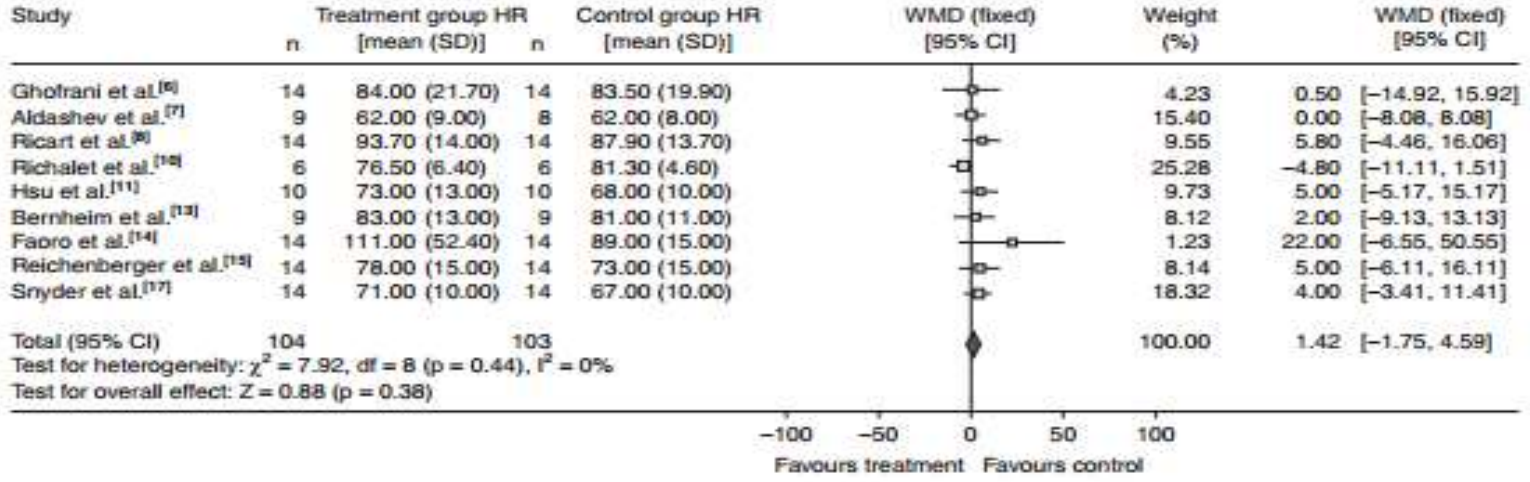
- PDE 5 inhibitors – meta analysis



Bo Jin et al; Clin Drug Investig 2010 30 (4): 259-265

HAPH





Bo Jin et al; Clin Drug Investig 2010 30 (4): 259-265

HAPH

Study	N	Methods	Outcome
Seheult RD et al,2009, RCT 3800m	8	Bosentan vs placebo 5 days before ascent and continued for 2 days at altitude	PASP increased in both the groups
Kozonazarov et al, 2012 3200–4000 m	15	sPAP before and 3 h after a single oral dose of bosentan (125 mg)	systolic PAP decreased from 46 ± 1.9 to 37 ± 2.2 mm Hg ($p < 0.01$)
Kozonazarov et al, 2012 3200-3500 m, RCT	19	Fasudil or placebo IV in a dose of 1 $mg \cdot min^{-1}$for the following 30 min (total dose of fasudil 30 mg) Continous echo monitoring	systolic P_{AP} by decreased by - 10.37 ± 0.97 mmHg ($p<0.001$) compared with placebo

HAPH

- No long-term data available on the management of HAPH
- All patients with HAPH should be advised to descend to a lower altitude
- Limitations of the data on pharmacological correction

Aibek E. Mirrakhimov, The Open Cardiovascular Medicine Journal, 2016

HIGH ALTITUDE ON PRE-EXISTING LUNG DISEASE

COPD

- Increased mortality and higher incidence of cor pulmonale among high altitude residents
- Impaired gas exchange with fall in PaO2 (difficult to predict the fall in paO2 in individuals)
- May not be symptomatic due to hypoxia due to partial acclimatization

AM Luks & Swenson, Eur Resp J 2007

COPD

- No studies in subjects with severe disease /resting hypercapnia or altitude above 3048 m
- Lower air density should improve airflow dynamics but effects in studies are variable
- At risk of HAPE and acute right heart failure if PH present

AM Luks & Swenson, Eur Resp J 2007

COPD

- Assess the need for supplemental O2 for patients with FEV1 < 1.5L
- Continue baseline medications and carry supply of rescue inhalers and prednisone for potential exacerbations
- Counsel patients with pre-existing PH against high-altitude travel
- Prophylaxis with nifedipine SR 20 mg bid if PH present
- Avoid travel till 2 wks after radiographic resolution in cases of spontaneous pneumothorax

AM Luks & Swenson, Eur Resp J 2007

Asthma

- Decreased allergen burden
- Exposure to cold air
- Variable effects of hypoxia and hypocapnia
- Reduced air density
- Variable response noted in different field studies

AM Luks & Swenson, Eur Resp J 2007

Asthma

- Mild intermittent or mild persistent disease may ascend to altitudes as high as 5000 m
- Caution in cases of more severe disease
- Continue baseline medications and carry peak flow meter and supply of rescue inhalers and prednisone for potential exacerbations
- Consider using balaclava or bandana over mouth to warm and humidify air

AM Luks & Swenson, Eur Resp J 2007

Pulmonary hypertension

- No systematic studies examining the outcomes in known PH
- Counsel patients about the risks, symptoms and signs of HAPE
- Administer supplemental oxygen for trips above 2000 m even in patients not on supplemental oxygen at baseline
- For patients not on pre-existing medical therapy, prophylaxis with nifedipine SR 20 mg BD

AM Luks & Swenson, Eur Resp J 2007

Pulmonary thromboembolic disease

- Prospective study of 20,257 hospital admissions

Low altitude (n= 18565)	High altitude (n = 1692)	*p*	*OR*
17	46	< 0.001	30.49 95% CI: 17.06-51.67

- Long term stay at high altitudes is associated with a 30 times higher risk of spontaneous vascular thrombosis

Anand et al, Natl Med J India, 2001

Pulmonary thromboembolic disease

- Conflicting results in literature about the effects of hypoxia on platelet function and coagulation parameters
- Many case reports which documented arterial or venous thromboembolic events at high altitude occurred in people with underlying coagulopathy
- Most marked rise in thrombin-antithrombin complexes during hypobaric hypoxic exposure was seen in those with the factor V Leiden mutation or oral contraceptive use

Schreijer AJ et al, Lancet 2006

Pulmonary thromboembolic disease

- Continue any pre-existing anticoagulation regimen during high-altitude sojourn with close follow-up of INR before and after trip
- Do not initiate new anticoagulation prescription in patients not on a pre-existing regimen
- Discontinue oral contraceptives in females with pre-existing coagulopathy
- Avoid immobility and dehydration

AM Luks & Swenson, Eur Resp J 2007

OHS

- Risk of right ventricular decompensation
- Avoid high-altitude travel
- Administer supplemental oxygen for day- and night-time use
- Prophylaxis with ACZ as they are at high risk for AMS
- Use CPAP unit and make necessary adjustments in set pressure for machines lacking pressure compensation

AM Luks & Swenson, Eur Resp J 2007

OSA

- Obstructive apneas markedly decreased
- Related to changes in air density, increased respiratory drive and upper airway tone
- May have increase in central apneas
- CPAP machine and make necessary adjustments in set pressure for machines lacking pressure compensation
- Acetazolamide therapy for central apneas

AM Luks & Swenson, Eur Resp J 2007

ILD

- Alteration in the gas exchange
- Assess need for supplemental oxygen and administer during stay at high altitude if predicted Pa O2 < 50–55 mmHg
- Screen for pre-existing PH and, if present administer supplemental oxygen and prophylax with nifedipine

AM Luks & Swenson, Eur Resp J 2007

Pneumothorax

- Bullae communicate with the airways to a greater extent than expected, allowing for pressure equalisation
- Patients with pneumothorax or recent chest surgery should wait 2–3 weeks after successful drainage of the pneumothorax prior to air travel
- With persistent pneumothorax or BPF, travel to altitude with chest tube or Heimlich valve in place
- Screening patients at high risk for SSP for the presence of occult pneumothorax with CXR / CT scan prior to travel

AM Luks & Swenson, Eur Resp J 2007

Take home message

- Prior h/o AHI - strong risk factor to develop AHI
- Descent - single best treatment for AHI
- Slow ascent < 500 m/day is preventive
- Acetazolamide – Rx of choice in AMS, CMS & sleep disordered breathing
- Oxygen therapy – Rx of choice for HAPE