CEREBRAL HYPOXIA: ITS ROLE IN AGE-RELATED CHRONIC AND ACUTE COGNITIVE DYSFUNCTION

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Geriatric Anesthesia

NARRATIVE REVIEW ARTICLE

Cerebral Hypoxia: Its Role in Age-Related Chronic and Acute Cognitive Dysfunction

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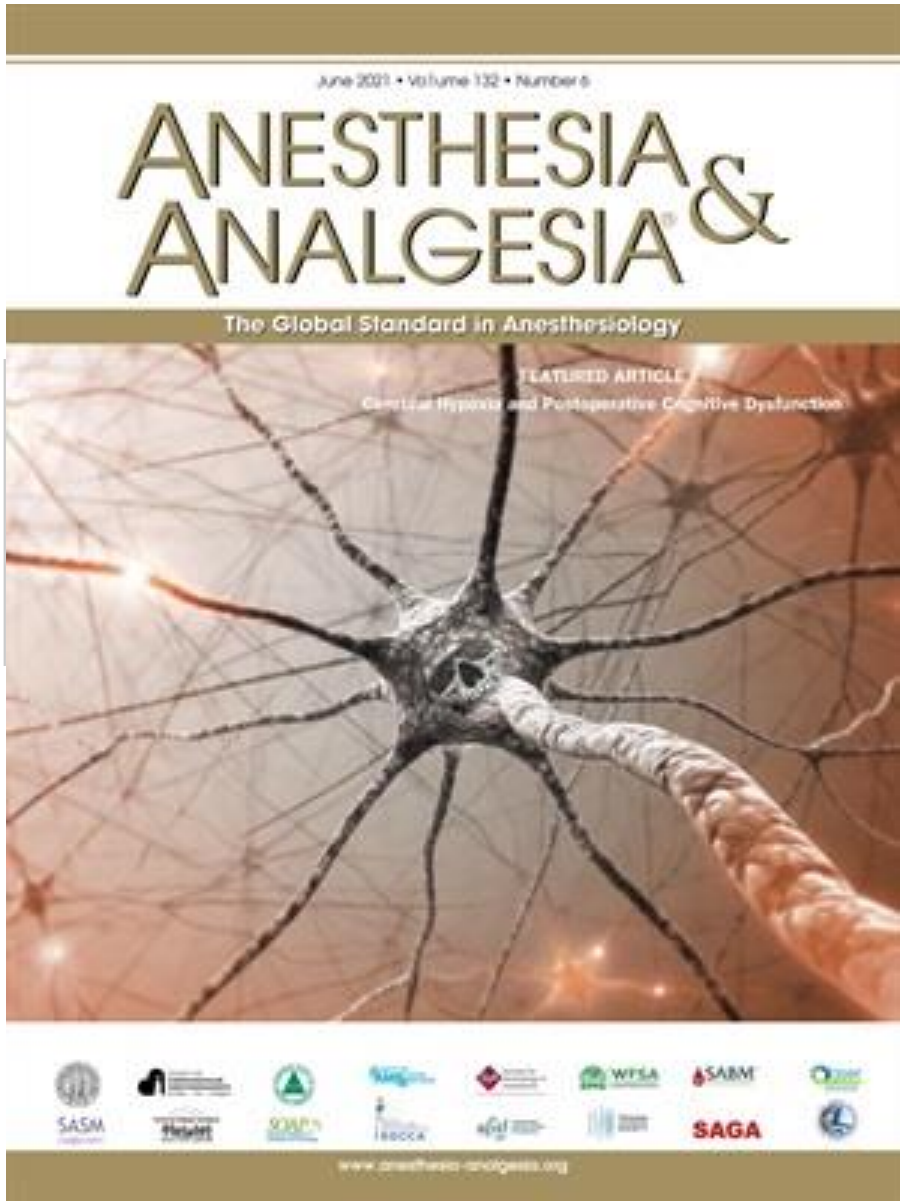


POSTOPERATIVE COGNITIVE DYSFUNCTION (POCD)

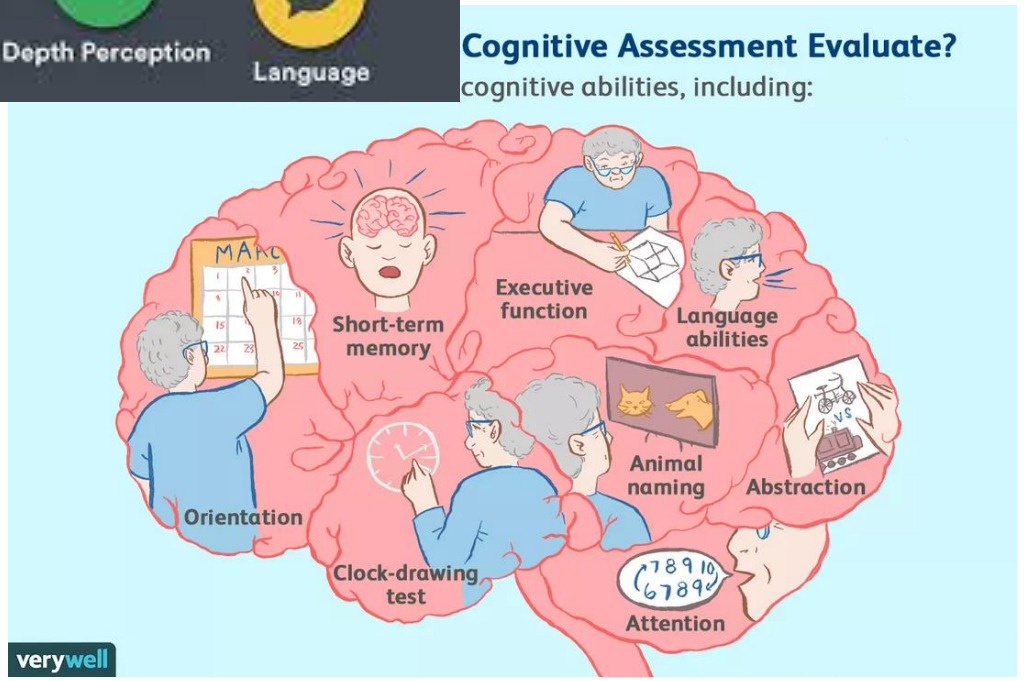
POCD is a syndrome defined by worsening performance on neuropsychologic tests postoperatively compared to a perioperative baseline.

POCD resolves within months of both cardiac and noncardiac surgery; however, individual patients may follow different trajectories with declines remaining up to 5 years or longer.

POSTOPERATIVE COGNITIVE DYSFUNCTION (POCD)

Cognitive domains

- Learning and memory
- Executive function
- Complex attention
- Perceptual-motor
- Social cognition



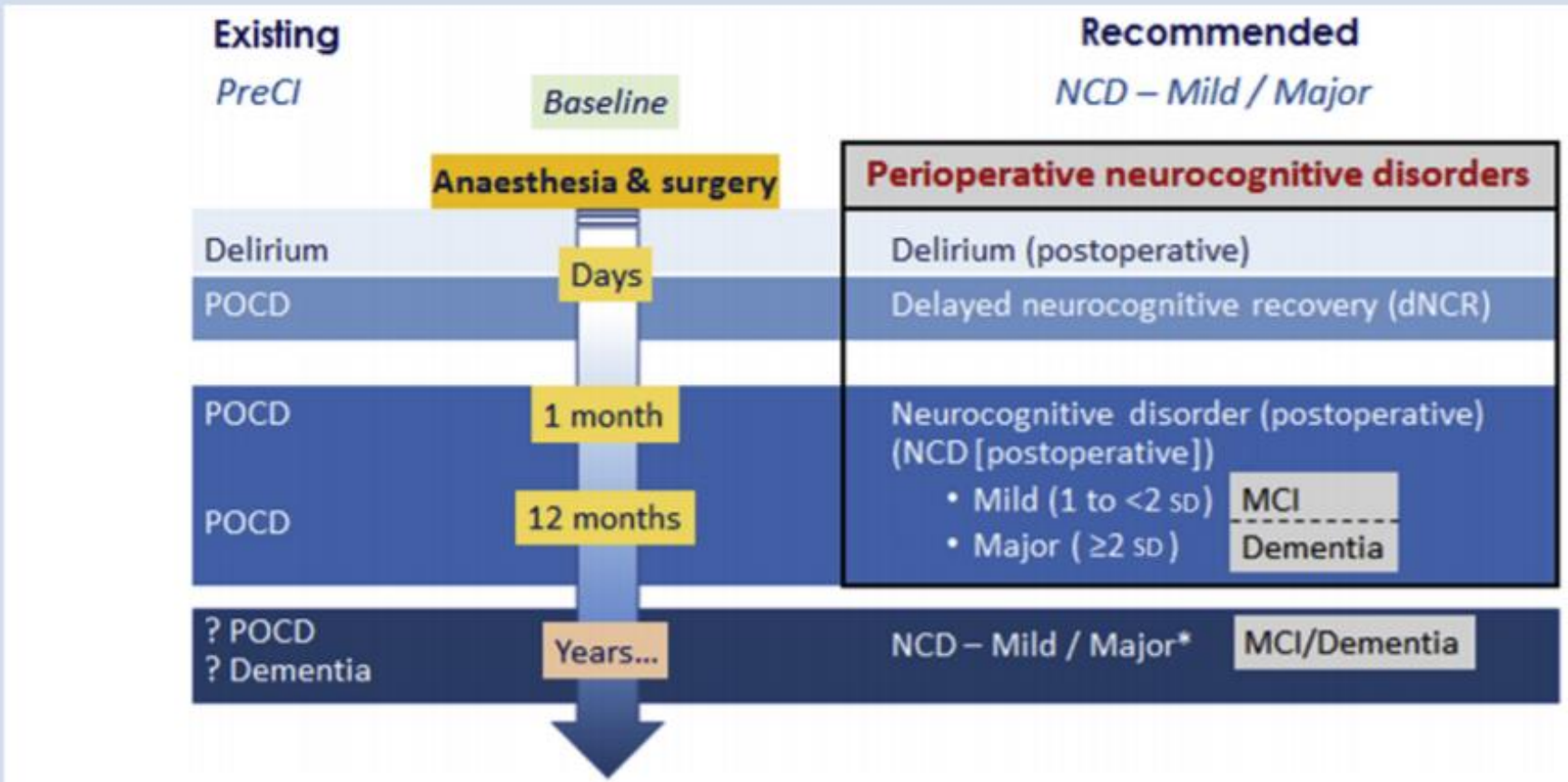


Fig 1. Postoperative cognitive dysfunction and neurocognitive disorders, a crosswalk. MCI, mild cognitive impairment; POCD, postoperative cognitive dysfunction.* Where a new diagnosis is made after 12 months.[20]

TABLE 82.1 Constructs Previously Used to Define Cognitive Change Associated with the Perioperative Period and the Recommended New Nomenclature

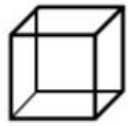
Time Period	Previous Nomenclature	Old Criteria	New Nomenclature	New Criteria
OVERARCHING TERM: PERIOPERATIVE NEUROCOGNITIVE DISORDERS (PND)				
Preoperative Baseline	Preexisting cognitive impairment (PreCI)	≥2 SD below norms on ≥2 tests	Mild/Major NCD	NCD criteria, DSM-5: 1 to <2 SD (mild) or ≥2SD (major) below norms or controls in ≥1 cognitive domain *Plus:* Subjective complaint, *and* IADLs (preserved for mild NCD and declined for Major NCD)
Acute postoperative	Postoperative delirium (POD)	DSM-5	Delirium (postoperative) (POD)	DSM-5
1-30 days postoperatively	Postoperative cognitive dysfunction (POCD)	≥1.96 SD below controls on ≥2 tests	Delayed neurocognitive recovery	NCD criteria, DSM-5
30 days-12 months postoperatively	Postoperative cognitive dysfunction (POCD)	≥1.96 SD below controls on ≥2 tests	Mild NCD (postoperative) Major NCD (postoperative)	NCD criteria, DSM-5
New diagnosis beyond 12 months postoperatively	Postoperative cognitive dysfunction (POCD)	≥1.96 SD below controls on ≥2 tests	Mild NCD Major NCD (unless not a new diagnosis)	NCD criteria, DSM-5

IADLs, Instrumental Activities of Daily Living; *NCD*, neurocognitive disorder.

OBJECTIVE TESTING

	TMSE	MMSE-Thai 2002	MOCA-T
Orientation	(6) Time - วัน วันที่ เดือน เวลา Place - สถานที่ Person – คน	(10) Time - วัน วันที่ เดือน ปี ฤดู Place - สถานที่ ชั้น อำเภอ จังหวัด ภาค หรือ Place – สถานที่และบ้านเลขที่ หมู่บ้าน อำเภอ จังหวัด ภาค	(6) Time - วัน วันที่ เดือน ปี Place – สถานที่ จังหวัด
Attention	(5) บอกชื่อวันย้อนหลัง	(5) สะกดคำย้อนหลัง	(3) Digit forward Digit backward Vigilance
Calculation	(3) Serial 7s บอกตัวตั้งต้น	(5) Serial 7s ไม่บอกตัวตั้งต้น	(3) Serial 7s ไม่บอกตัวตั้งต้น
Registration	(3) ของ 3 อย่าง	(3) ของ 3 อย่าง	(0) คำ 5 คำ
Recall	(3) Free recall	(3) Free recall	(5) Free recall Cued recall

OBJECTIVE TESTING

	TMSE	MMSE-Thai 2002	MOCA-T
Language	(7) Naming Repetition 3-step verbal command Written command	(8) Naming Repetition 3-step verbal command Written command Writing	(6) Naming Repetition Verbal fluency (letter)
Visuoconstruction skills	(2) 	(1) 	(4)  Clock drawing test
Executive function	-	-	(1) Alternative trail making
Abstraction	(1)	-	(2)

OBJECTIVE TESTING

	Cut-off point	Sensitivity	Specificity
TMSE	≤ 23	NA	NA
MMSE-Thai 2002	≤ 22	92	92.6
MOCA-T	≤ 24	100	98

Train the brain forum committee 1993
Folstein et al. 1975
Tangwongchai et al. 2009

แบบทดสอบสภาพสมองเบื้องต้นฉบับภาษาไทย

MMSE – Thai 2002

ในกรณีที่ผู้ถูกทดสอบอ่านไม่ออกเขียนไม่ได้ ไม่ต้องทำข้อ 4, 9 และ 10

	บันทึกคำตอบไว้ทุกครั้ง (ทั้งคำตอบที่ถูกและผิด)	คะแนน
1. Orientation for time (5 คะแนน)		
(ตอบถูกข้อละ 1 คะแนน)		
1.1 วันนี้วันที่เท่าไร	.....	☐
1.2 วันนี้วันอะไร	.....	☐
1.3 เดือนนี้เดือนอะไร	.....	☐
1.4 ปีนี้ ปีอะไร	.....	☐
1.5 ฤดูนี้ฤดูอะไร	.....	☐
2. Orientation for place (5 คะแนน) (ให้เลือกทำข้อใดข้อหนึ่ง)		
(ตอบถูกข้อละ 1 คะแนน)		
2.1 กรณีอยู่ที่สถานพยาบาล		
2.1.1 สถานที่ตรงนี้เรียกว่า อะไร และ....ชื่อว่าอะไร	.....	☐
2.1.2 ขณะนี้อยู่ที่ชั้นเท่าไรของตัวอาคาร	.....	☐
2.1.3 ที่นี่อยู่ในอำเภอ-เขตอะไร	.....	☐
2.1.4 ที่นี่จังหวัดอะไร	.....	☐
2.1.5 ที่นี่ภาคอะไร	.....	☐
2.2 กรณีอยู่ที่บ้านของผู้ถูกทดสอบ		
2.2.1 สถานที่ตรงนี้เรียกว่าอะไร และบ้านเลขที่เท่าไร	.....	☐
2.2.2 ที่นี่หมู่บ้าน หรือละแวก/ตุ้ม/ย่าน/ถนนอะไร	.....	☐
2.2.3 ที่นี่อยู่ในอำเภอ/เขตอะไร	.....	☐
2.2.4 ที่นี่จังหวัดอะไร	.....	☐
2.2.5 ที่นี่ภาคอะไร	.....	☐

3. Registration (3 คะแนน) **คะแนน**

ต่อไปนี้เป็นการทดสอบความจำ ผม (ดิฉัน) จะบอกชื่อของ 3 อย่าง คุณ (ตา,ยาย,...) ตั้งใจฟังให้ดีนะ เพราะจะบอกเพียงครั้งเดียว ไม่มีการบอกซ้ำอีก เมื่อผม(ดิฉัน)พูดจบ ให้ คุณ (ตา,ยาย,...) พูดทบทวนตามที่ได้ยิน ให้ครบทั้ง 3 ชื่อ แล้วพยายามจำไว้ให้ดีเดี๋ยวดิฉันถามซ้ำ

* การบอกชื่อแต่ละคำให้ห่างกันประมาณหนึ่งวินาที ต้องไม่ช้าหรือเร็วเกินไป

(ตอบถูก 1 คำ ได้ 1 คะแนน)

○ ดอกไม้ ○ แม่น้ำ ○ รถไฟ ..... ☐

ในกรณีที่ทำแบบทดสอบซ้ำภายใน 2 เดือน ให้ใช้คำว่า

○ ต้นไม้ ○ ทะเล ○ รถยนต์ ..... ☐

4. Attention/Calculation (5 คะแนน) (ให้เลือกทำข้อใดข้อหนึ่ง)

ข้อนี้เป็นการคิดเลขในใจเพื่อทดสอบสมาธิ คุณ (ตา,ยาย,...) คิดเลขในใจเป็นไหม?

ถ้าตอบผิดคิดเป็นให้ทำข้อ 4.1 ถ้าตอบคิดไม่เป็นหรือไม่ตอบให้ทำข้อ 4.2

4.1 "ข้อนี้คิดในใจเอา 100 ตั้ง ลบออกทีละ 7

ไปเรื่อยๆ ได้ผลลัพธ์เท่าไรบอกมา" .... ☐

บันทึกคำตอบตัวเลขไว้ทุกครั้ง (ทั้งคำตอบที่ถูกและผิด) ทำทั้งหมด 5 ครั้ง

ถ้าลบได้ 1,2, หรือ 3แล้วตอบไม่ได้ ก็คิดคะแนนเท่าที่ทำได้ ไม่ต้องย้ายไปทำข้อ 4.2

4.2 "ผม (ดิฉัน) จะสะกดคำว่า มะนาว ให้คุณ(ตา,ยาย,...) ฟังแล้วให้คุณ(ตา,ยาย,...) สะกดถอยหลังจากพยัญชนะตัวหลังไปตัวแรก คำว่ามะนาว สะกดว่า มอม้า-สระอะ นอหนู-สระอา-วอแหวน ไหนคุณ(ตา,ยาย,...) สะกดถอยหลังให้ฟังซิ" .... ☐

ว า น ะ ม

5. Recall (3 คะแนน)

"เมื่อสักครู่ที่ให้จำของ 3 อย่าง จำได้ไหมมีอะไรบ้าง" (ตอบถูก 1 คำได้ 1 คะแนน)

○ ดอกไม้ ○ แม่น้ำ ○ รถไฟ ..... ☐

ในกรณีที่ทำแบบทดสอบซ้ำภายใน 2 เดือน ให้ใช้คำว่า

○ ต้นไม้ ○ ทะเล ○ รถยนต์ ..... ☐

จัดทำโดย คณะกรรมการจัดทำแบบทดสอบสภาพสมองเบื้องต้นฉบับภาษาไทย พ.ศ.2542 ขอเอกสาร และรายละเอียดเพิ่มเติมที่ สถาบันเวชศาสตร์ผู้สูงอายุ โทร. 0-2590-6229-30

6. Naming (2 คะแนน)

6.1 ยื่นดินสอให้ผู้ถูกทดสอบดูและถามว่า

"ของสิ่งนี้เรียกว่าอะไร" ..... ☐

6.2 ชี้นาฬิกาข้อมือให้ผู้ถูกทดสอบดูและถามว่า

"ของสิ่งนี้เรียกว่าอะไร" ..... ☐

7. Repetition (1 คะแนน)

(พูดตามได้ถูกต้องได้ 1 คะแนน)

"ตั้งใจฟังผม (ดิฉัน) นะ เมื่อผม (ดิฉัน) พูดข้อความนี้

แล้วให้คุณ (ตา,ยาย,...) พูดตาม ผม (ดิฉัน) จะบอกเพียงเที่ยวเดียว"

"ใครใคร่ขายไข่ไก่" ..... ☐

8. Verbal command (3 คะแนน)

"ฟังดีๆ นะเดี๋ยวผม (ดิฉัน) จะส่งกระดาษให้ แล้วให้คุณ (ตา,ยาย,...)

รับด้วยมือขวา พับครึ่ง แล้ววางไว้ที่....."(พื้น, โต๊ะ, เตียง)

ผู้ทดสอบแสดงกระดาษเปล่าขนาดประมาณ เอ-4

ไม่มีรอยพับ ให้ผู้ถูกทดสอบ

○ รับด้วยมือขวา ○ พับครึ่ง ○ วางไว้ที่ (พื้น,โต๊ะ,เตียง) ..... ☐

9.Written command (1 คะแนน)

ต่อไปนี้เป็นคำสั่งที่เขียนเป็นตัวหนังสือ ต้องการให้คุณ (ตา,ยาย,...) อ่าน

แล้วทำตามคุณ (ตา,ยาย,...) จะอ่านออกเสียงหรืออ่านในใจก็ได้

ผู้ถูกทดสอบแสดงกระดาษที่เขียนว่า "หลับตา" ○ หลับตาได้ ..... ☐

10. Writing (1 คะแนน)

ข้อนี้เป็นคำสั่ง "ให้คุณ (ตา,ยาย,...) เขียนข้อความอะไรก็ได้ที่อ่านแล้วรู้เรื่อง

หรือมีความหมายมา 1 ประโยค

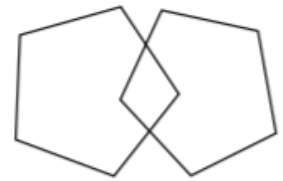
..... ☐

○ ประโยคมีความหมาย

11. Visuoconstruction (1 คะแนน) **คะแนน**

ข้อนี้เป็นคำสั่ง "จงวาดภาพให้เหมือนภาพตัวอย่าง" ☐

(ในที่ว่างด้านข้างของภาพตัวอย่าง)



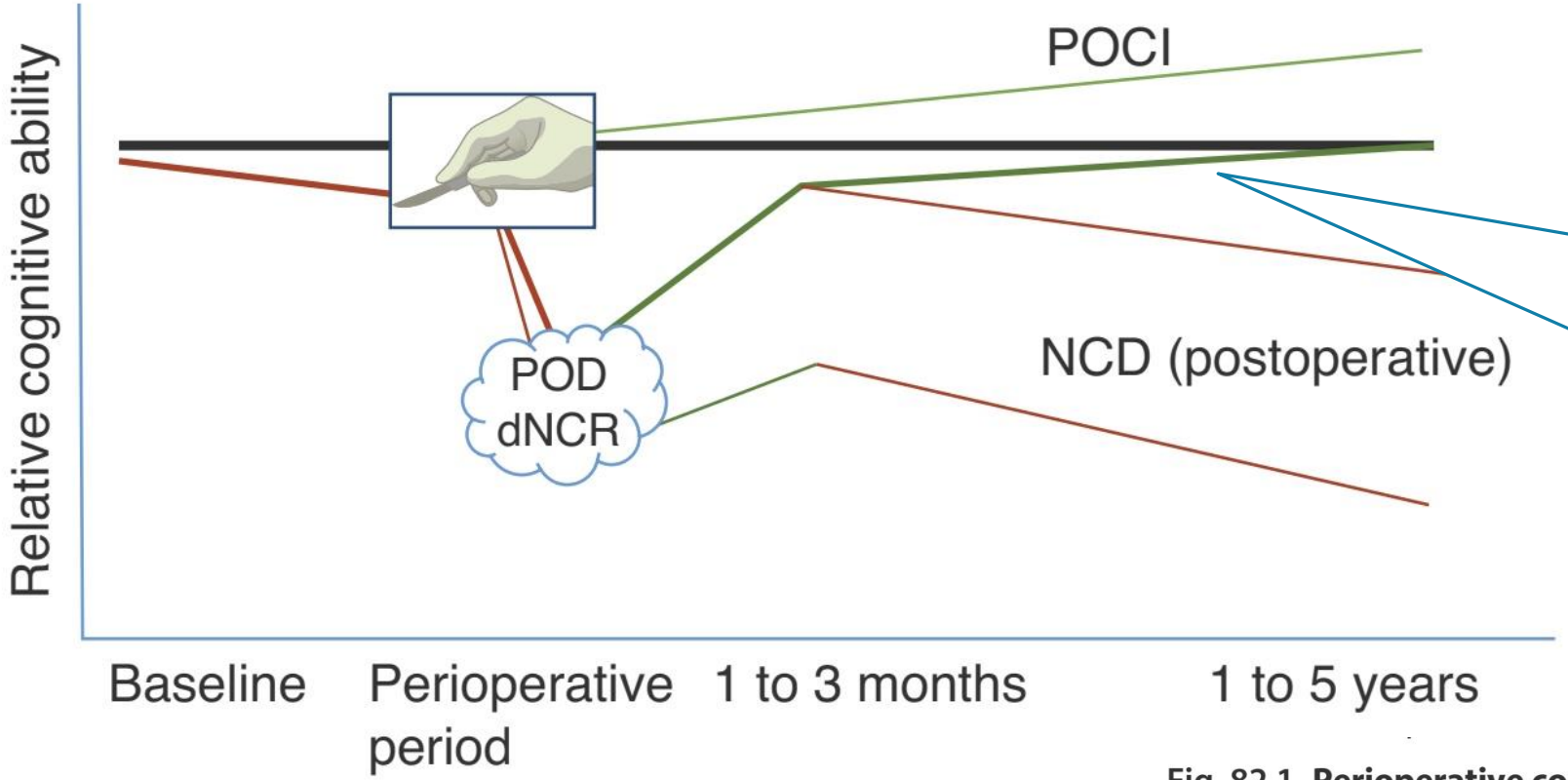
คะแนนรวม.....

ลงชื่อผู้ทำการทดสอบ.....วันที่.....เดือน.....พ.ศ.....

จุดตัด (cut-off point) สำหรับคะแนนที่สงสัยสภาวะสมองเสื่อม (cognitive impairment)

ระดับการศึกษา	คะแนน	
	จุดตัด	เต็ม
ผู้สูงอายุปกติไม่ได้เรียนหนังสือ (อ่านไม่ออก-เขียนไม่ได้)	☐ 14	23 (ไม่ต้องทำ 4,9,10)
ผู้สูงอายุปกติเรียนระดับประถมศึกษา	☐ 17	30
ผู้สูงอายุปกติเรียนระดับสูงกว่าประถมศึกษา	☐ 22	30

หลับตา



Correction of underlying pathology and improve function e.g. reduction in pain, improved mobility, improved ADL

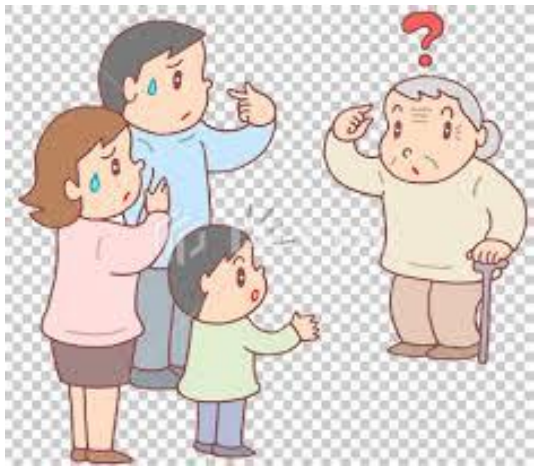


Fig. 82.1 Perioperative cognitive trajectories. Perioperative patients come into surgery having either a stable *(black)* or declining trajectory of cognition *(red)*. After surgery, the majority are unchanged *(black)*, with a small fraction showing postoperative cognitive improvement (*POCI*, *green*). Some postoperative patients have an acute decline into POD or dNCR, from which most recover *(green)*. A fraction of these will decline again later, perhaps matching their preoperative trajectory. The bottom red trajectory is meant to indicate that a very small fraction of perioperative patients never fully recover, and assume a steeper downward trajectory than if they had not had surgery. Thickness of line is intended as a rough reflection of probability of following the indicated trajectory. Other trajectories are possible. *dNCR*, Delayed neurocognitive recovery; *NCD*, neurocognitive disorder; *POD*, postoperative delirium.

POSTOPERATIVE COGNITIVE DYSFUNCTION (POCD)

Risk factors normally predispose to cognitive impairment, such as

- ApoE allelic expression
- Reduced cerebrovascular reserve
- Increased vascular burden

(presence of factors known to impair vascular structure and function)

eg, atherosclerosis, diabetes, hypertension, smoking, obesity, hypercholesterolemia, and lack of physical activity

POSTOPERATIVE COGNITIVE DYSFUNCTION (POCD)

Anesthetic exposure and neuroinflammatory processes continue to be frequently investigated as mechanisms for POCD.

Coincident cerebral hypoxia is a mechanism common to many medical comorbidities of aging and has been implicated as a risk factor for cognitive decline outside the surgical arena.

PERIOPERATIVE HYPOXIA AND POCD

Intraoperative hypoxemia and postoperative hypoxemia occur with a frequency previously unrecognized.

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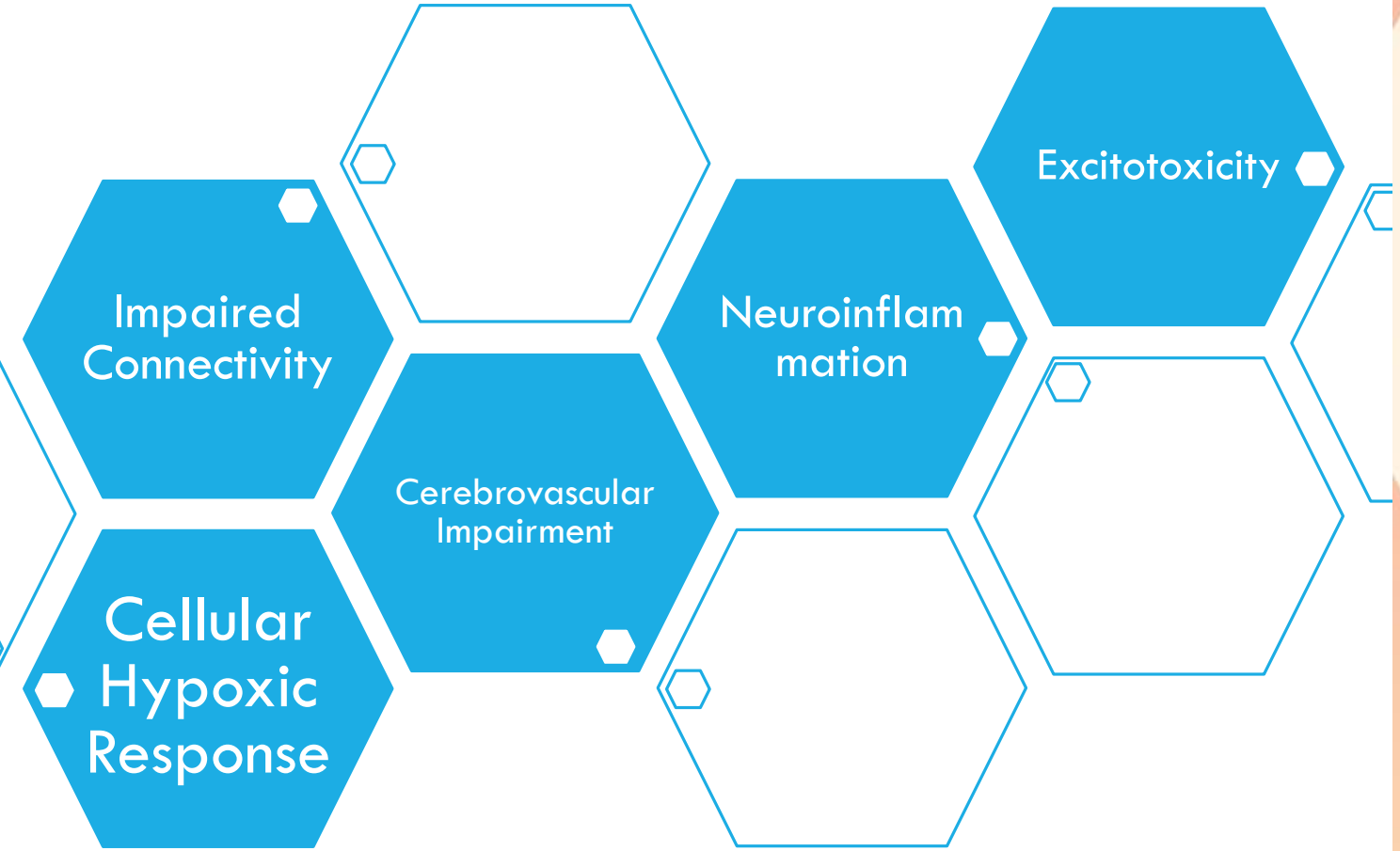
Anesth Analg. 2015 September ; 121(3): 709–715. doi:10.1213/ANE.0000000000000836.

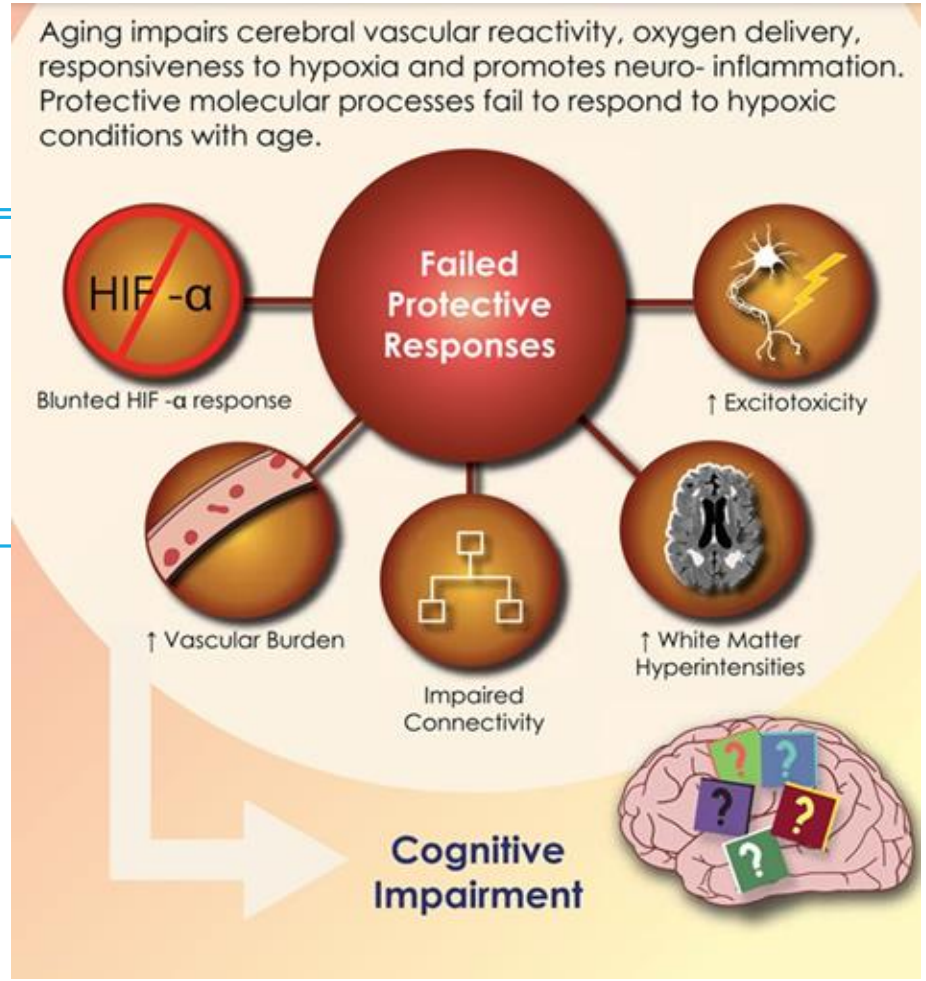
Postoperative Hypoxemia Is Common and Persistent: A Prospective Blinded Observational Study

Pulse oximetry was recorded continuously in 1500 patients (mean age = 64 years) for 3 consecutive days postoperatively.

- 21% experienced hypoxemia for at least 10 min/h
- 8% experienced hypoxemia for at least 20 min/h
- 8% experienced severe hypoxemia (arterial hemoglobin oxygen saturation [Sao_2])

MECHANISMS OF COGNITIVE DECLINE ASSOCIATED WITH CHRONIC AND ACUTE HYPOXIA OR HYPOXEMIA





MECHANISMS OF COGNITIVE DECLINE ASSOCIATED WITH HYPOXIA :CELLULAR HYPOXIC RESPONSE

Hypoxia immediately stabilizes the various isoforms of hypoxia-inducible factor alpha (HIFα) to regulate acute and chronic responses to hypoxia.

HIF-α controls expression of over 600 genes including

EPO
vascular endothelial growth factor (VEGF)
metabolic switching proteins like glucose transporter-1
lactate dehydrogenase-A
vasoactive nitric oxide
reactive oxygen species (ROS)
nicotinamide adenine dinucleotide phosphate oxidase (NOX).

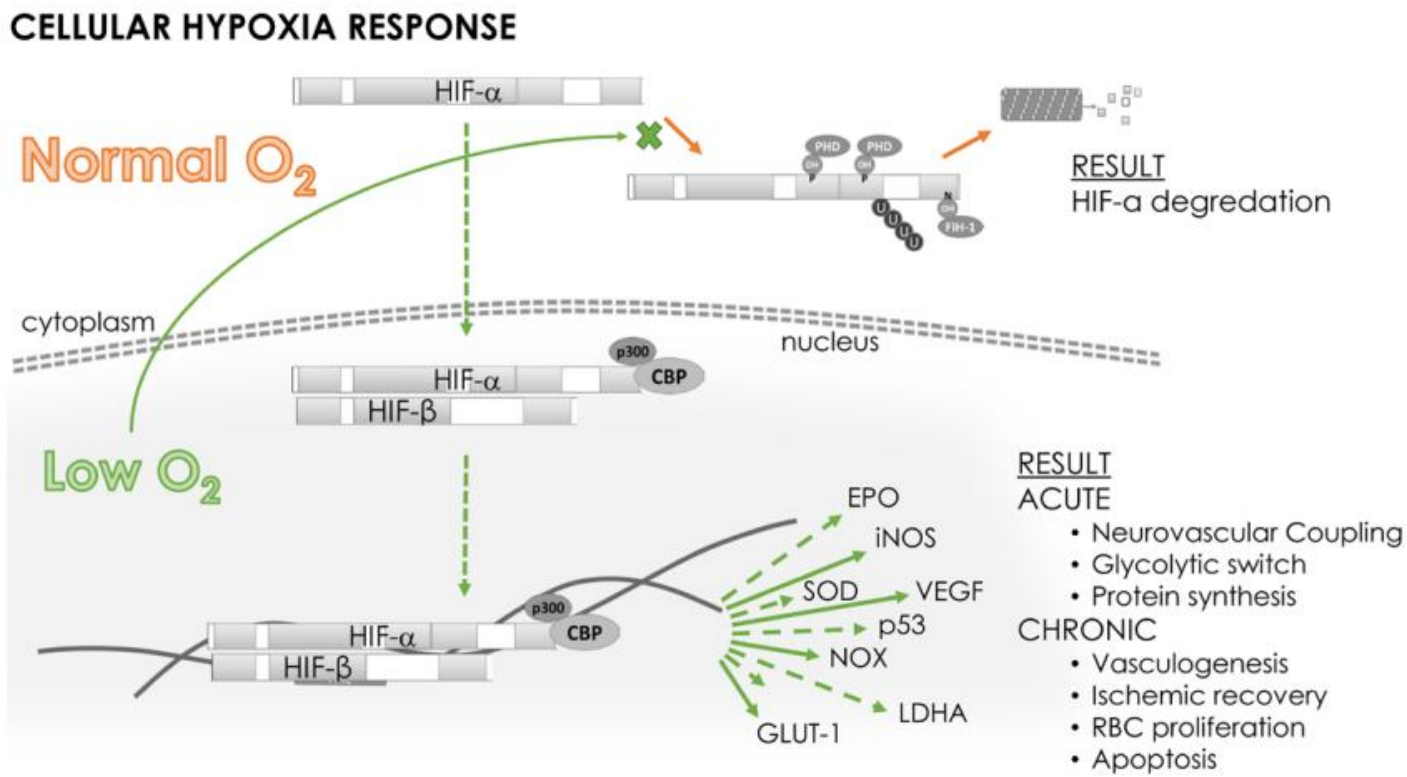
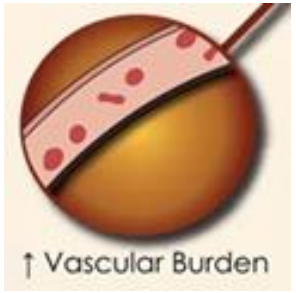


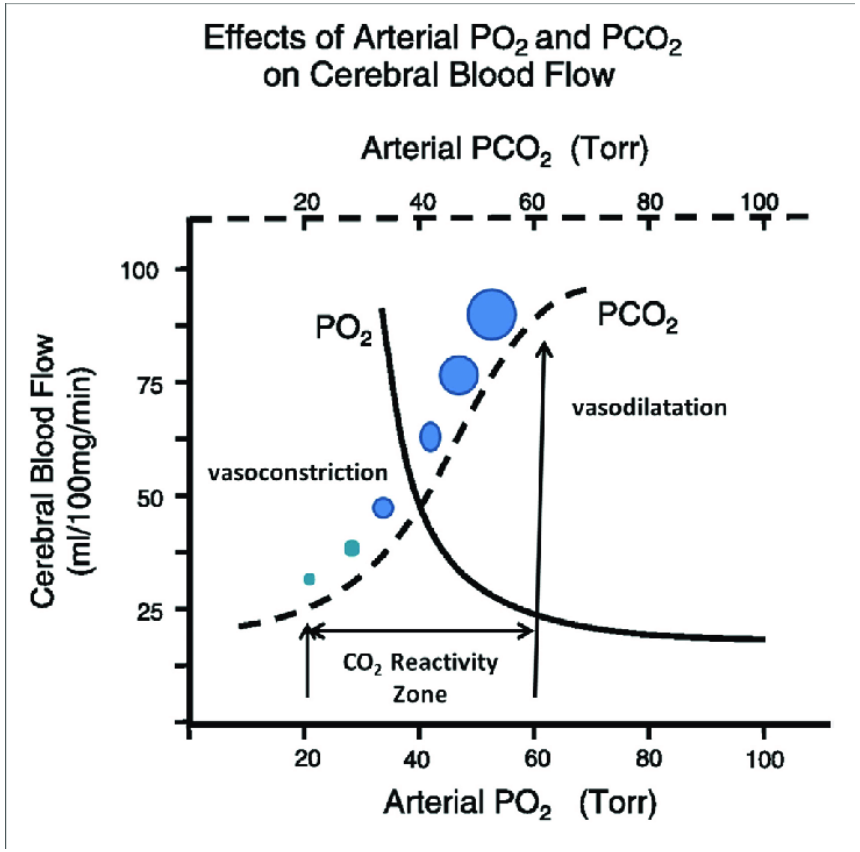
Figure 1. Cellular hypoxic response in healthy cells. HIF-α is targeted to degradation under normal oxygenation by PHD and FIH-1. However, hypoxia prevents hydroxylation and stabilizes HIF-α, allowing it to enter the nucleus and bind with coactivators (p300 and CBP) to initiate expression of gene products that improve oxygenation and promote cell survival. Representative gene transcription initiated by HIF-α includes EPO, iNOS, SOD, VEGF, NOX, LDHA, and GLUT-1. CBP indicates creb-binding protein; EPO, erythropoietin; FIH-1, factor-inhibiting hypoxia-inducible factor protein; GLUT-1, glucose transporter-1; HIF, hypoxia-inducible factor; HIF-α, hypoxia-inducible factor alpha; HIF-β, hypoxia-inducible factor beta; iNOS, inducible nitric oxide synthase; LDHA, lactose dehydrogenase-A; NOX, nicotinamide adenine dinucleotide phosphate oxidase; OH, hydroxide; PHD, prolyl hydroxylases; RBC, red blood cell; SOD, superoxide dismutase; VEGF, vascular endothelial growth factor.

MECHANISMS OF COGNITIVE DECLINE ASSOCIATED WITH HYPOXIA
:EFFECT OF CEREBROVASCULAR IMPAIRMENT



The cerebrovascular response to hypoxemia is vasodilation to increase cerebral blood flow (CBF) and oxygen delivery.

In the case of anemia, the marked increase in CBF is driven primarily by cerebral oxygen demand.



MECHANISMS OF COGNITIVE DECLINE ASSOCIATED WITH HYPOXIA
:EFFECT OF CEREBROVASCULAR IMPAIRMENT

Progressive cognitive decline is observed as a consequence of chronic cerebral hypoperfusion, even in the absence of acute stroke/TIA.

The effect of chronic diseases of the vasculature
- Small vessel disease
- Carotid disease
- Atherosclerosis
- Endothelial dysfunction
- Deficient cerebral autoregulation
- Amyloidosis
- Integrity of the blood brain barrier [BBB])

Neuroimaging (MRI) markers
- Small punctate lesions
- Microbleeds
- White matter hyperintensities (WMH, also called leukoaraiosis and lacunes)

MECHANISMS OF COGNITIVE DECLINE ASSOCIATED WITH HYPOXIA
:EFFECT OF CEREBROVASCULAR IMPAIRMENT

These observations have led to the development of the concept of

"vascular burden," A general term that refers to the cumulative effect of vascular disorders and risk factors including stroke, hypertension, white matter disease, diabetes mellitus, obesity, as well as vascular reactivity on the degree of cognitive impairment and age-related brain atrophy.

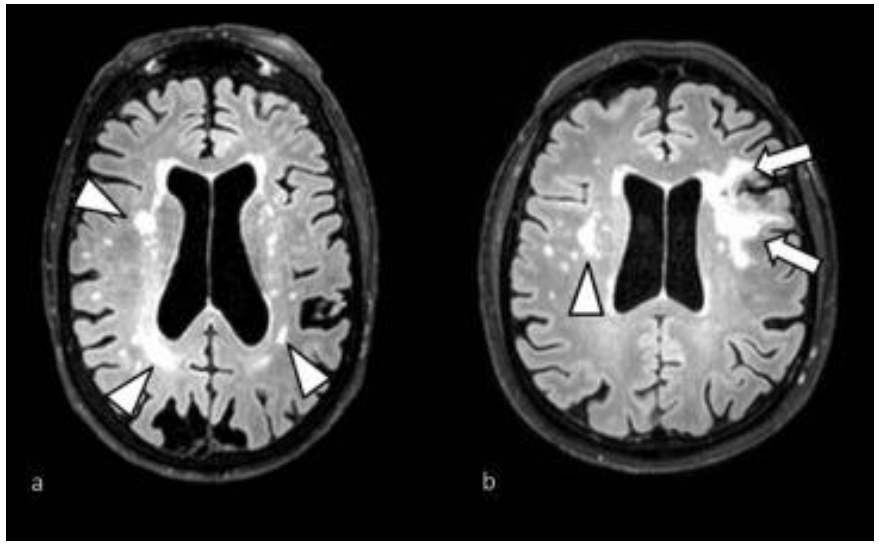
MECHANISMS OF COGNITIVE DECLINE ASSOCIATED WITH HYPOXIA
: IMPAIRED CONNECTIVITY

Accumulating evidence shows that presurgical neuroimaging markers of general vascular health, cerebral ischemia, and presurgical cognitive status are all strong predictors of POCD.

REGULAR RESEARCH ARTICLES

MRI Markers of Neurodegenerative and Neurovascular Changes in Relation to Postoperative Delirium and Postoperative Cognitive Decline

Ilse M.J. Kant, M.Sc., Jeroen de Bresser, M.D., Ph.D., Simone J.T. van Montfort, M.Sc., Arjen J.C. Slooter, M.D., Ph.D., Jeroen Hendrikse, M.D., Ph.D.



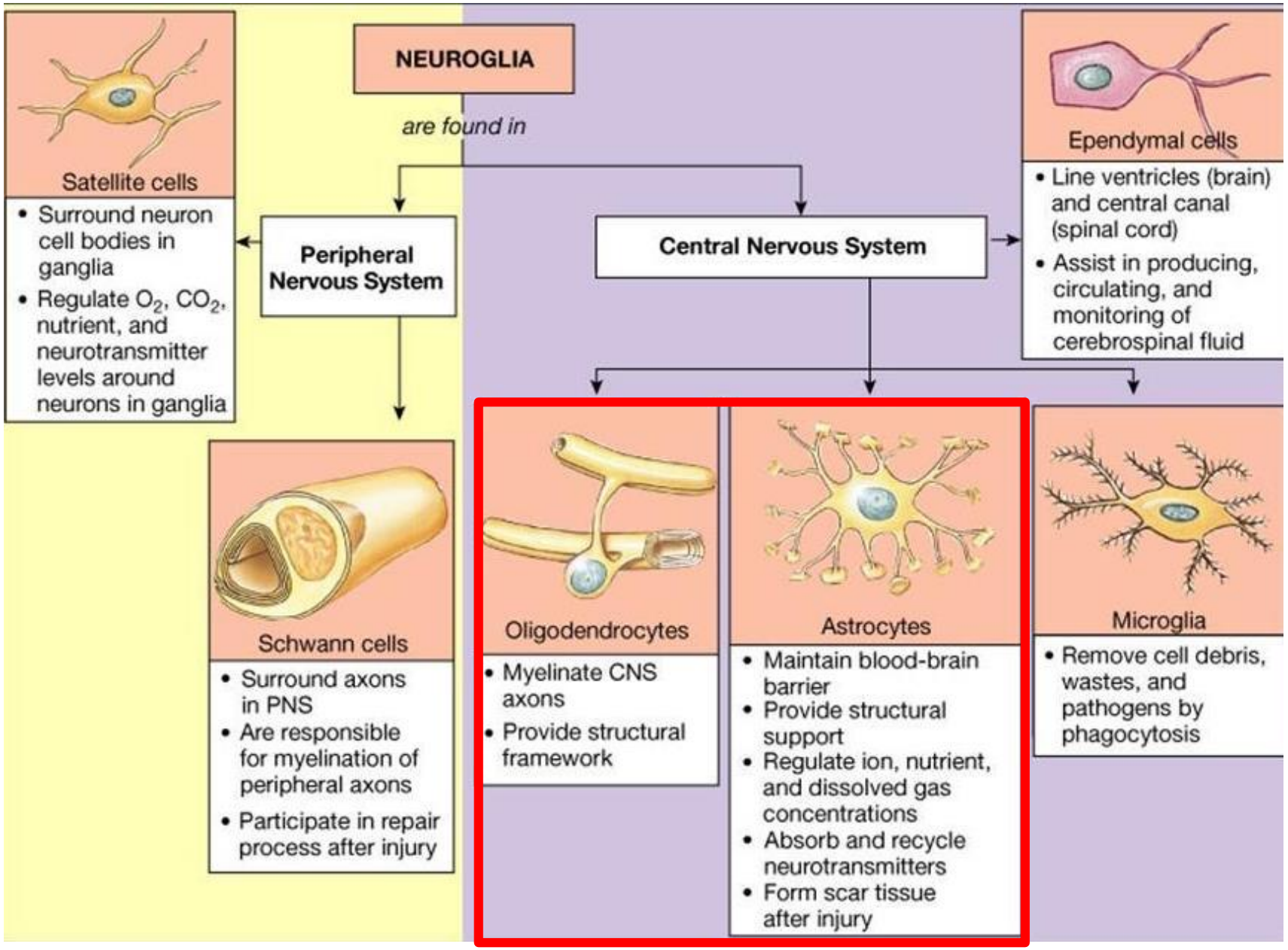
A recent systematic review of 15 neuroimaging (MRI) studies reported that POCD was more frequently associated with presurgical imaging markers of cerebrovascular ischemia (WMH) than neuroimaging markers of neurodegenerative changes (ie, global and regional brain volumes).

Therefore, mechanisms that hinder cerebral vascularization may be of particular interest in future investigations of POCD.

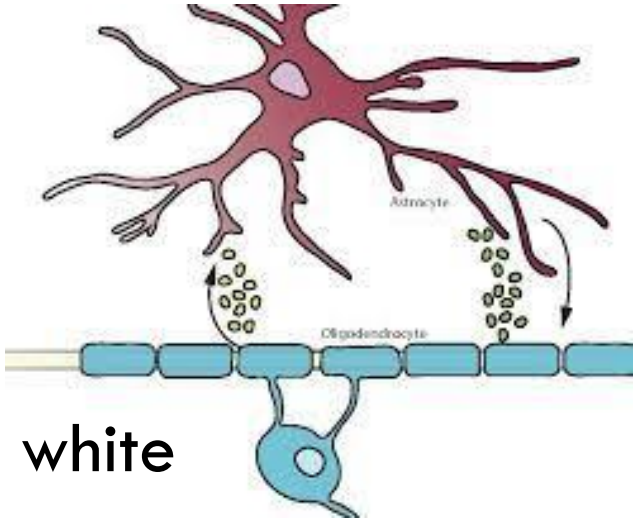
MECHANISMS OF COGNITIVE DECLINE ASSOCIATED WITH HYPOXIA
: IMPAIRED CONNECTIVITY

Disturbances indicated by white matter hyperintensities disrupt neuronal transmission and functional network connectivity, leading to widespread cerebral dysfunction and cognitive impairment.

Neurons have a high metabolic rate, resulting in a need for rapid and precise regulation of CBF and making them vulnerable to damage from both acute and chronic hypoxia.


NEUROGLIA
are found in
Peripheral Nervous System
Central Nervous System
Satellite cells
• Surround neuron cell bodies in ganglia
• Regulate O_2, CO_2, nutrient, and neurotransmitter levels around neurons in ganglia
Ependymal cells
• Line ventricles (brain) and central canal (spinal cord)
• Assist in producing, circulating, and monitoring of cerebrospinal fluid
Schwann cells
• Surround axons in PNS
• Are responsible for myelination of peripheral axons
• Participate in repair process after injury
Oligodendrocytes
• Myelinate CNS axons
• Provide structural framework
Astrocytes
• Maintain blood-brain barrier
• Provide structural support
• Regulate ion, nutrient, and dissolved gas concentrations
• Absorb and recycle neurotransmitters
• Form scar tissue after injury
Microglia
• Remove cell debris, wastes, and pathogens by phagocytosis

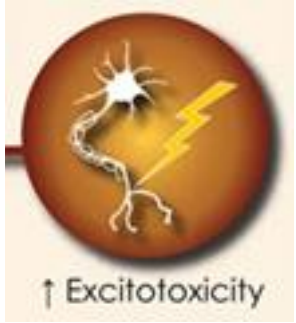
MECHANISMS OF COGNITIVE DECLINE ASSOCIATED WITH HYPOXIA
: IMPAIRED CONNECTIVITY



Oligodendrocytes, glial cells that compose the cerebral white matter, may be even more sensitive than neurons.

Astrocytes modulate synapses, neurovascular coupling, and transport of molecules across the BBB and are highly sensitive to hypoxia, altering glucose uptake and BBB integrity to fulfill energetic needs of neurons.

MECHANISMS OF COGNITIVE DECLINE ASSOCIATED WITH HYPOXIA :EXCITOTOXICITY

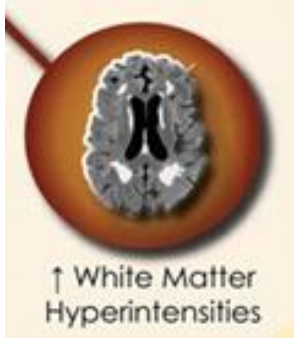


In the brainstem, cerebellar Purkinje neurons, and memory centers of the central nervous system (CNS)

Elevated ROS from hypoxia → Cytokine transcription and intracellular calcium → Postsynaptic excitatory inhibitory receptors → More frequent excitatory postsynaptic potentials and altered synaptic connectivity.

MECHANISMS OF COGNITIVE DECLINE ASSOCIATED WITH HYPOXIA

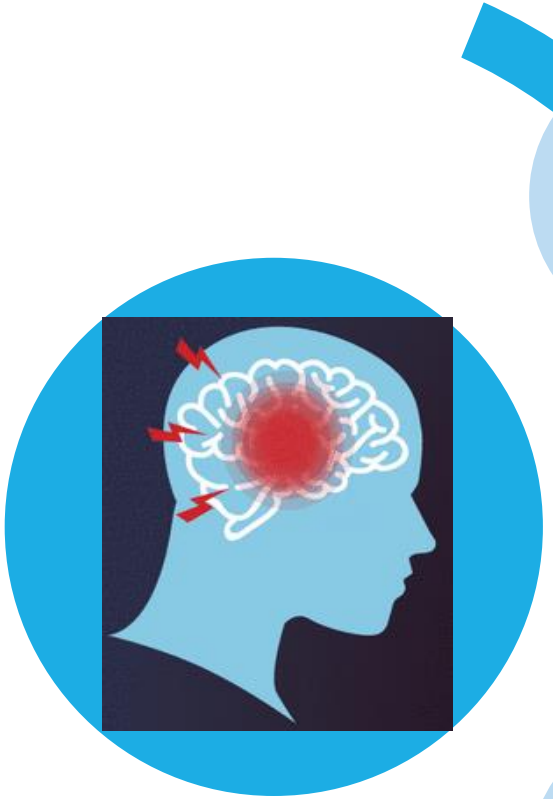
:NEUROINFLAMMATION



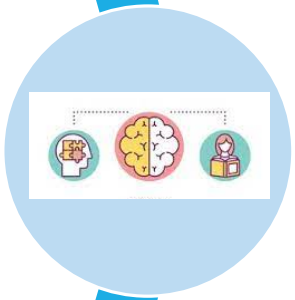
Neuroinflammation is often proposed as a central culprit in the onset of POCD. These overlaps provide further evidence that cerebral hypoxia may be at the epicenter of mechanisms of POCD.

Neuroinflammation arising from hypoxia is initiated by HIF-α, may be of neuronal or glial origin, and is correlated with cognitive impairment

INTERACTION BETWEEN AGING AND HYPOXIA



Aging Impairs Oxygenation



Aging Impairs the Hypoxic Response

Aging Induces Inflammation and Impairs Neurotransmission

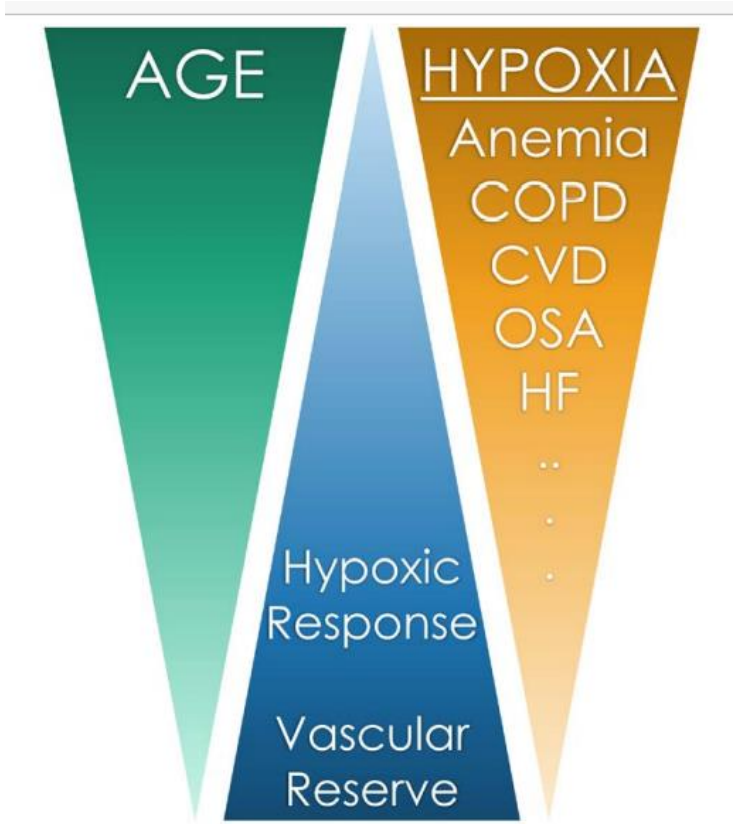


Figure 2. Interaction between age, hypoxia, and protective responses. Studies have demonstrated age-related impairments in molecular responses to hypoxia and vascular reserve at the same time of onset of diseases that cause hypoxia increase. This interaction may predispose aged adults to cognitive impairment when exposed to hypoxic insults. COPD indicates chronic obstructive pulmonary disease; CVD, cerebrovascular disease; HF, heart failure; OSA, obstructive sleep apnea.

INTERACTION BETWEEN AGING AND HYPOXIA
:AGING IMPAIRS OXYGENATION

Deficient response to vasopressin or nitric oxide

Loss of myogenic tone

Hypertension

Accumulated plaque deposition

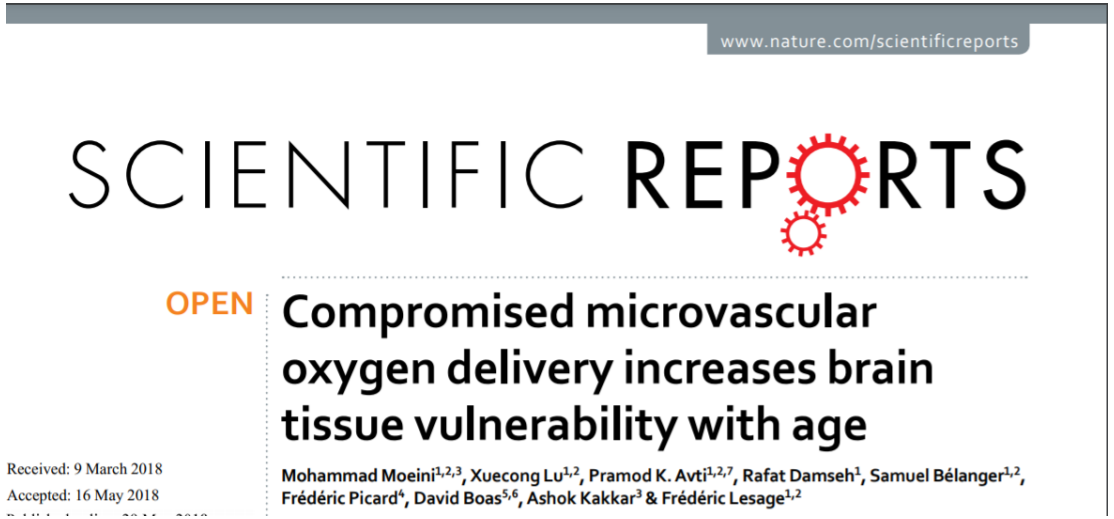
Reduced cerebrovascular reactivity and reserve

Cerebral metabolic rate of O2 (CMRO2) remains constant over the lifespan

INTERACTION BETWEEN AGING AND HYPOXIA
:AGING IMPAIRS OXYGENATION

Loss of cerebrovascular reserve in the elderly may thus impair their ability to recover from perioperative hypoxic stresses.

In addition to hypoperfusion, aging is associated with more frequent abouts of anemia as nutritional intake declines, gastrointestinal tract disorders and pharmaceutical intake increase, and hormone levels change.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SCIENTIFIC REPORTS

OPEN

Compromised microvascular oxygen delivery increases brain tissue vulnerability with age

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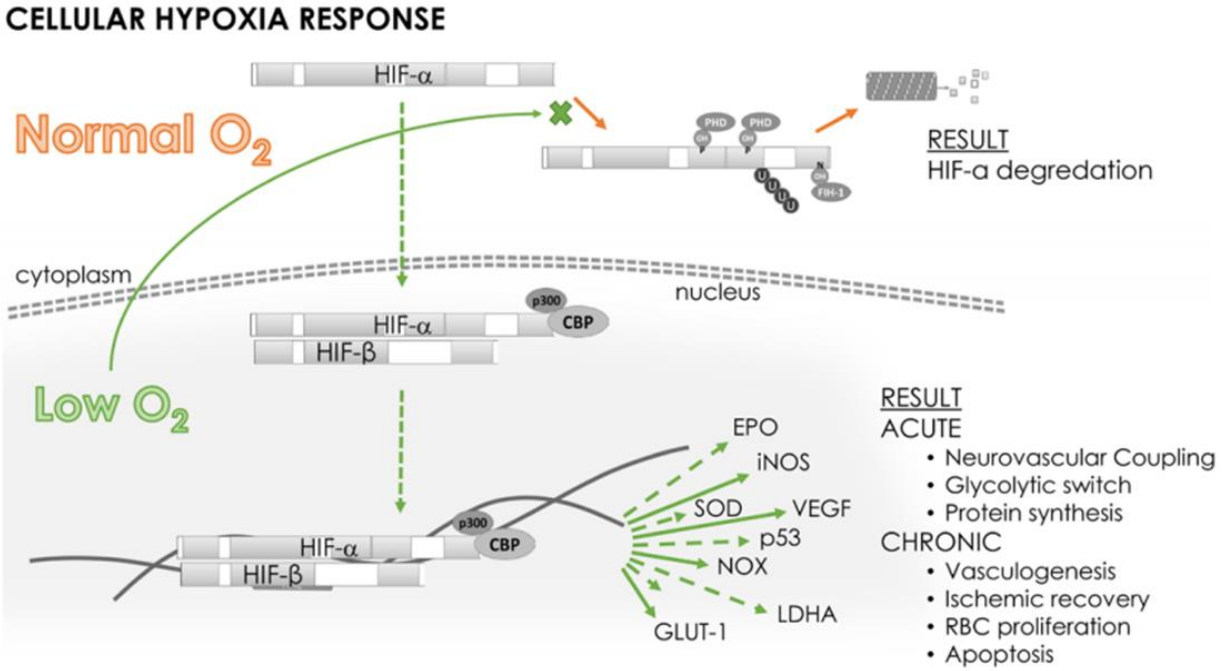
Accepted: 16 May 2018

Mohammad Moeini[1,2,3], Xuecong Lu[1,2], Pramod K. Avti[1,2,7], Rafat Damseh[1], Samuel Bélanger[1,2], Frédéric Picard[4], David Boas[5,6], Ashok Kakkar[3] & Frédéric Lesage[1,2]

INTERACTION BETWEEN AGING AND HYPOXIA
:AGING IMPAIRS THE HYPOXIC RESPONSE

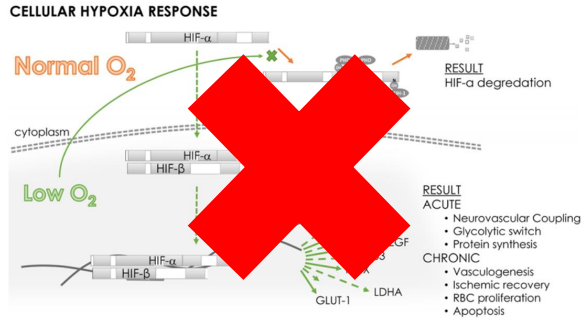
The normal cortical response to hypoxia stabilizes HIF-α leading to increased capillary density, blood flow, and glycolysis.



INTERACTION BETWEEN AGING AND HYPOXIA
:AGING IMPAIRS THE HYPOXIC RESPONSE

Nonexistent response to hypoxia mediated by HIF-α is observed in the aged brain.

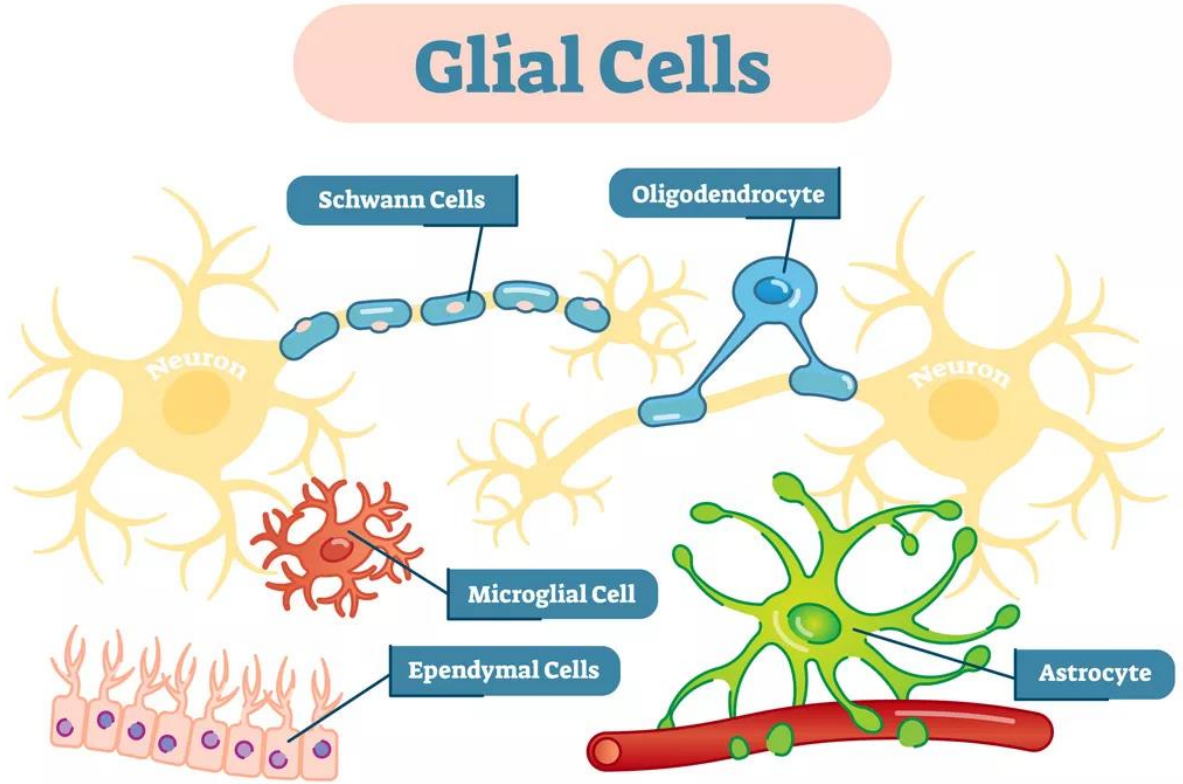
In combination with fewer and smaller mitochondria in carotid bodies. Furthermore, prolyl hydroxylases that regulate HIF-α expression also lose responsivity during aging.



INTERACTION BETWEEN AGING AND HYPOXIA
:AGING INDUCES INFLAMMATION AND IMPAIRS NEUROTRANSMISSION

Glial cells are particularly vulnerable to aging and hypoxia

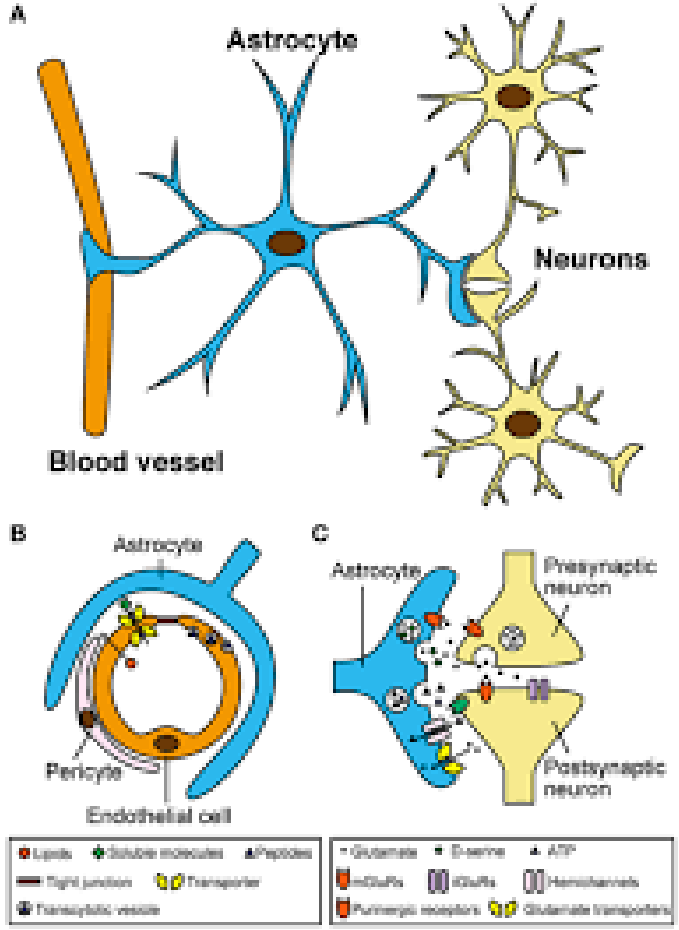
Typical neuroprotective glial activities are diminished while reactive and senescent phenotypes flourish in aged brains.



INTERACTION BETWEEN AGING AND HYPOXIA
:AGING INDUCES INFLAMMATION AND IMPAIRS NEUROTRANSMISSION

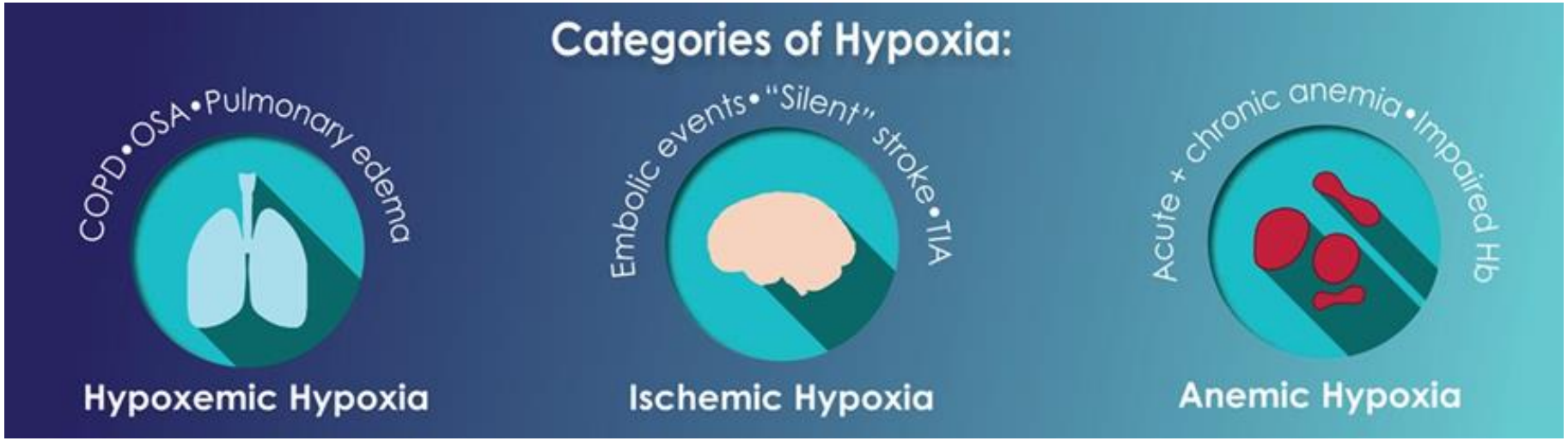
Damage to oligodendrocytes and astrocytes affects both dendritic spine stability and diffuse connectivity.

Impaired astrocytic support combined with reduced cardiovascular reserve, vascularization, and hypoxic responsiveness renders aged neurons more vulnerable to hypoxic insults than young neurons, as evidenced by diminished excitatory output, smaller postsynaptic density, and lower tissue volume in aged hippocampi.



PERIOPERATIVE HYPOXIA AND POCD

- Hypoxemic Hypoxia
- Ischemic Hypoxia
- Anemic Hypoxia



PERIOPERATIVE HYPOXIA AND POCD
:HYPOXEMIC HYPOXIA

- Low oxygen uptake in the blood.

- Often present before surgery due to pathophysiological conditions.
  - COPD, interstitial lung disease, OSA, increased interstitial fluid, pulmonary edema secondary to HF, pulmonary embolism

PERIOPERATIVE HYPOXIA AND POCD
:HYPOXEMIC HYPOXIA

Cognitive impairment in obstructive sleep apnea

K Gagnon [1], A-A Baril [2], J-F Gagnon [1], M Fortin [3], A Décary [4], C Lafond [5], A Desautels [2], J Montplaisir [2], N Gosselin [6]

Affiliations + expand

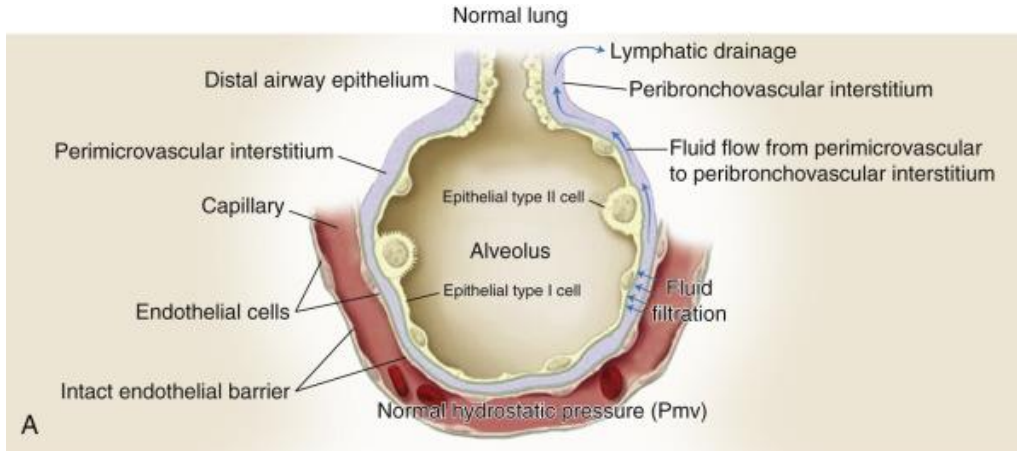
PMID: 25070768 DOI: 10.1016/j.patbio.2014.05.015

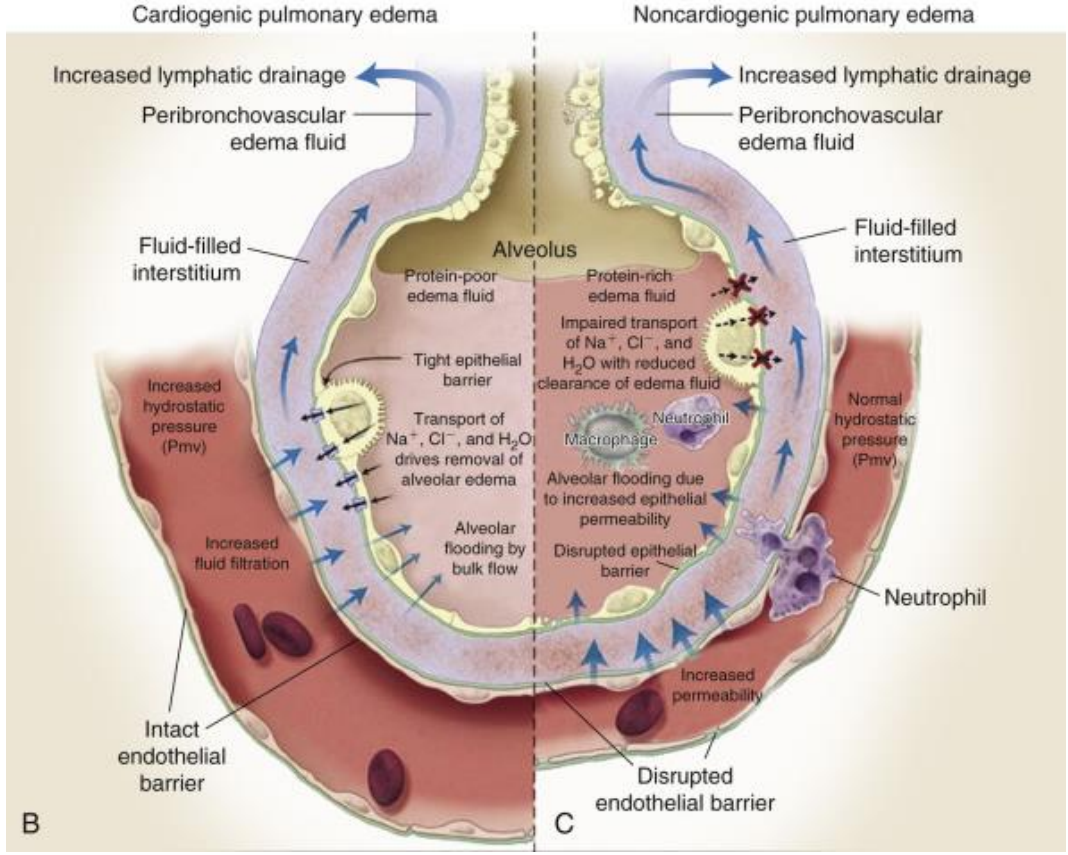
Studies have shown that OSA is associated with daytime sleepiness and cognitive dysfunctions, characterized by impairments of attention, episodic memory, working memory, and executive functions.

Hypoxemia during sleep also plays a major role in cognition. Treatment of hypoxemia suggests that at least some cognitive function is recoverable, as observed in children and adults with OSA.

Heart failure

- Hypoperfusion
- Pulmonary edema
  - Increased arteriolar-alveolar oxygen gradient





European Journal of Heart Failure (2012) **14**, 404–413
doi:10.1093/eurjhf/hfs015

Cognitive function in patients with decompensated heart failure: the Cognitive Impairment in Heart Failure (CogImpair-HF) study

Ingrid Kindermann[1]*†‡, Denise Fischer[1]*†‡, Julia Karbach[2], Andreas Link[1], Katrin Walenta[1], Christine Barth[1], Christian Ukena[1], Felix Mahfoud[1], Volker Köllner[3], Michael Kindermann[4]‡, and Michael Böhm[1]‡

Global cognition declined more rapidly following:

- HF than in age-matched controls without HF.
- Acute decompensated HF than those with stable HF.

Conclusion Decompensated heart failure patients are highly impaired in cognitive functioning, which improves but does not normalize after compensation. Neuropsychological diagnostics delivers important details for daily life activities and might identify individuals deserving special care.

PERIOPERATIVE HYPOXIA AND POCD

:ISCHEMIC HYPOXIA

- Low tissue oxygenation as a result of reduced blood flow.

- Embolic, ischemic, and hemorrhagic strokes have been widely recognized as important contributors to cognitive decline and dementia.

- Risk factors for cognitive impairment after stroke include older age, prior ischemic lesions, stroke severity (ie, volume of tissue damaged), location of the stroke, and prestroke cognitive impairment.

PERIOPERATIVE HYPOXIA AND POCD

:ISCHEMIC HYPOXIA

In the surgical arena, ischemia occurs secondary to acute and chronic embolic events or hypoperfusion.

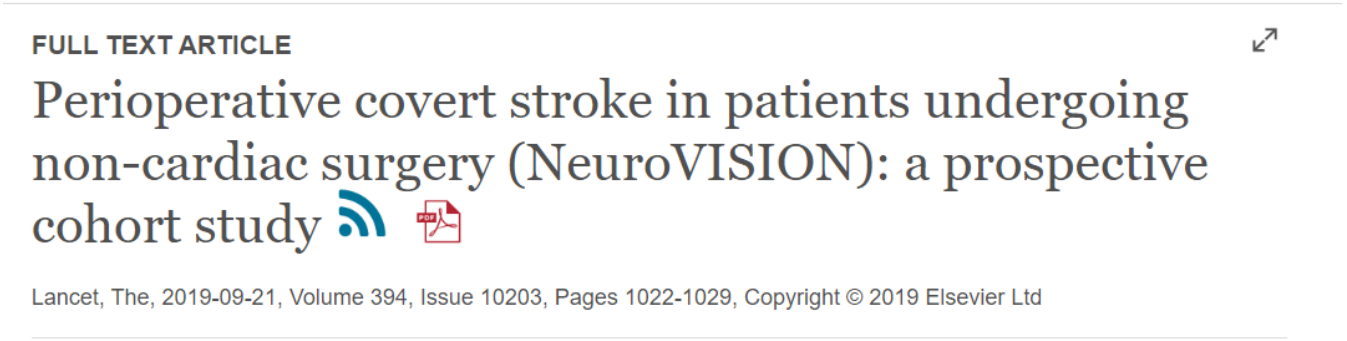
- All surgeries involve some risk of cerebral ischemia

  (ie, “silent” stroke; not accompanied by any observable stroke symptoms and detected only on postoperative diffusion-weighted imaging [DWI] and magnetic resonance imaging [MRI]).

- Risk is higher in cardiac surgery and procedures that involve instrumentation of the cerebral vessels or aorta.

PERIOPERATIVE HYPOXIA AND POCD

:ISCHEMIC HYPOXIA



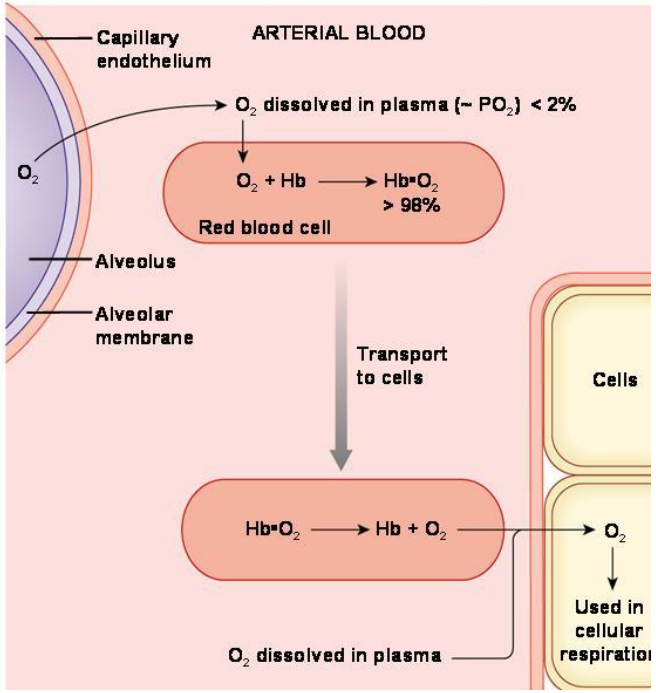
Perioperative silent stroke on DWI was observed in 7% following noncardiac, noncarotid artery surgery.

Patients experiencing clinically “silent” ischemic events may be at greater risk for future cognitive decline. Cognitive decline 1 year after surgery was identified in 42% of surgical patients with perioperative silent stroke versus 29% without.

PERIOPERATIVE HYPOXIA AND POCD

:ANEMIC HYPOXIA

reduced oxygen carrying capacity of red blood cells.



- Inadequate oxygen transport may result from
  - low hematocrit
  - low hemoglobin concentration
  - reduced ability of hemoglobin to bind oxygen (sickle cell anemia, carbon monoxide poisoning)

Oxygen Content (CaO_2)

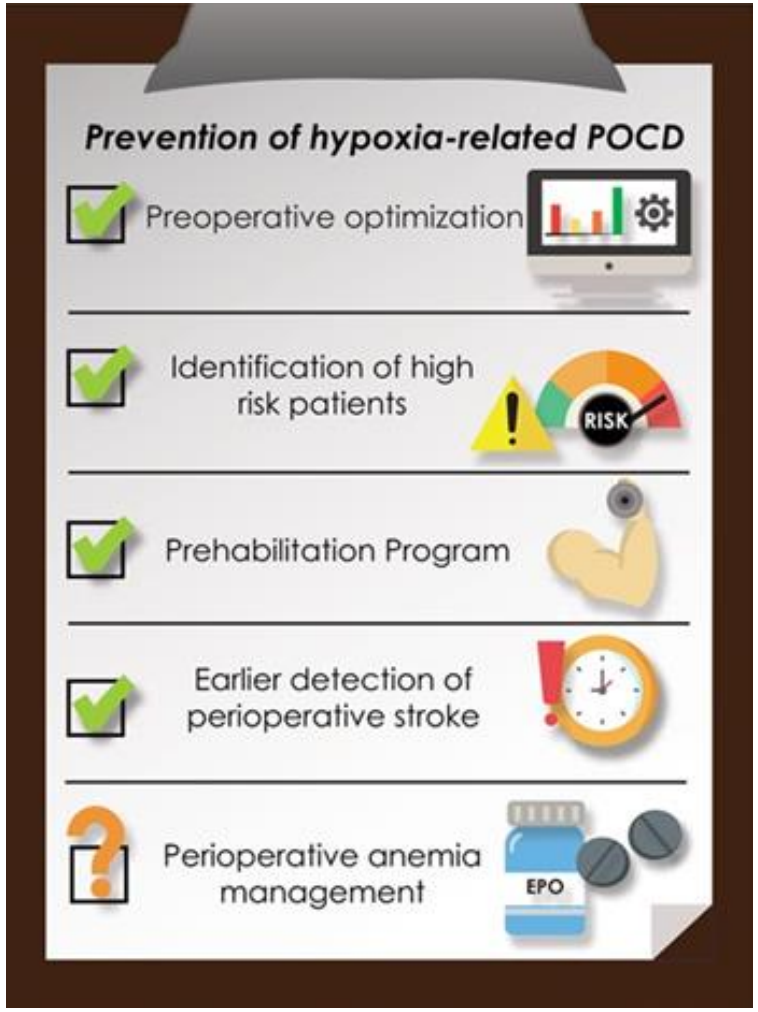
Quantity O2 bound to Hemoglobin

$CaO_2 = [(1.34 \times Hgb \times SaO_2) + (0.003 \times PaO_2)$

Quantity O2 dissolved in plasma

(units = ml O2/dl)

MANAGEMENT OF HYPOXIA-RELATED POCD



1. Identification of those at risk.
   - older patients with superimposed cerebrovascular disease, chronic anemia, and preexisting cardiorespiratory failure

2. Prevention via optimization of preexisting disease
   - Prerehabilitation programs
   - Preexisting anemia :Fe supplementation and possibly EPO.

MANAGEMENT OF HYPOXIA-RELATED POCD

3. Prevention of intraoperative hypoxemia

- High-risk groups such as those with morbid obesity and those undergoing lung transplantation
- High-risk operation such as approach to the heavily calcified aorta, aortic manipulation, intraarterial emboli trapping devices.

CEREBRAL OXIMETRY

Cerebral oximetry based on near-infrared spectroscopy (NIRS) is increasingly used during the perioperative period of cardiovascular operations.

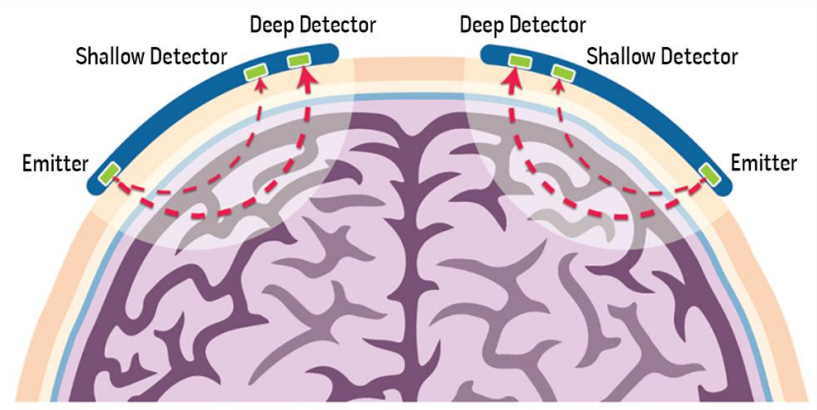
It is a noninvasive technology that can continuously monitor the regional oxygen saturation of the frontal cortex.

Normal rSO_2 values, prior to the induction of general anesthesia.

CEREBRAL OXIMETRY

The principal behind the determination of regional hemoglobin oxygen saturation is the change of optical properties of hemoglobin when binding to oxygen and the consequent change of absorption pattern for specific light wavelengths.

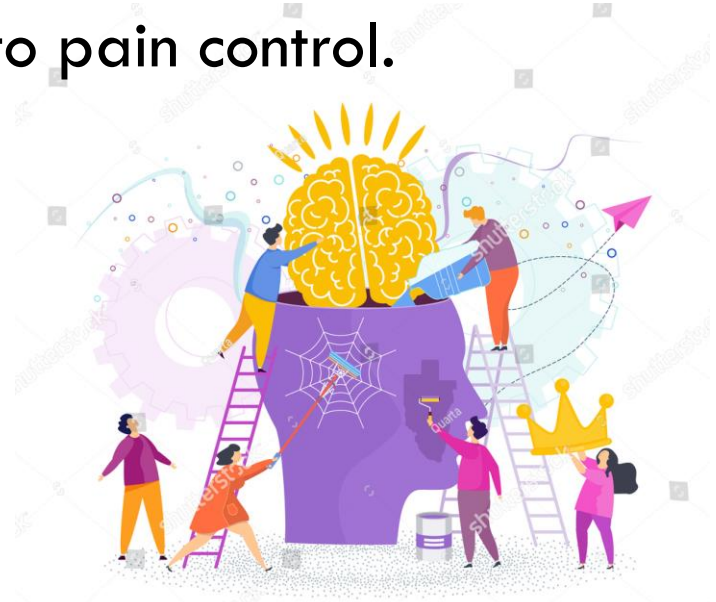
NIRS interrogates arterial, venous, and capillary blood within the field so rScO2 represents a weighted value from these 3 compartments.



MANAGEMENT OF HYPOXIA-RELATED POCD

4. Optimize postoperative cardiopulmonary function

- Balance the risks and benefits of transfusion in their patients.
- More aggressive approaches to iron replacement and the use of EPO.
- Advancement of lower or non-narcotic approaches to pain control.



TAKE HOME MESSAGE

POCD is a syndrome defined by worsening performance on neuropsychologic tests postoperatively compared to baseline, resolves within months ; however, individual patients may remaining up to 5 years or longer