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

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Abstract

Postoperative Cognitive Dysfunction (POCD) has been reported with widely varying frequency but appears to be strongly associated with aging. Outside of the surgical arena, chronic and acute cerebral hypoxia may exist as a result of respiratory, cardiovascular, or anemic conditions. Hypoxia has been extensively implicated in cognitive impairment, and disease states associated with hypoxia accompany and progress with aging. Perioperative cerebral hypoxia is likely underdiagnosed and its contribution to POCD underappreciated. Herein we discuss the various disease processes and forms in which hypoxia may contribute to POCD. Further, we outline hypoxia-related mechanisms, such as hypoxia inducible factor activation, cerebral ischemia, cerebrovascular reserve, excitotoxicity, and neuroinflammation, which may contribute to cognitive impairment and how these mechanisms interact with aging. Finally, we discuss opportunities to prevent and manage POCD related to hypoxia.

Introduction

Postoperative Cognitive Dysfunction (POCD) has been reported to occur with widely varying frequency, especially in older adults in the weeks to months following surgery[1]. Prospective studies with non-surgical control groups suggest the incidence of POCD is actually much lower than originally documented and that lingering effects are either minor or nonexistent[2–4]. In fact, in a cohort of over 10,000 patients followed over an average of 13 years, age-related cognitive decline following hospital admissions for either non-surgical

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reasons or stroke was greater than cognitive decline following major surgery[5]. Nevertheless, anesthetic exposure[6] and neuroinflammatory processes[7] continue to be frequently investigated as mechanisms for POCD. Several large scale prospective cohort[8], multi-center randomized studies[9], and meta-analyses[10] suggest that, at a minimum, anesthetic exposure by itself does not account for all, or even the majority, of POCD. Surgeries including cardiopulmonary bypass (CPB), associated with a profound inflammatory response, do not confer risk for worse cognitive outcomes than those without CPB[11]; and studies testing prevention of neuroinflammation using glucocorticoids have not demonstrated effect either[7].

While clarity continues to be sought on the role of anesthetics and neuroinflammation in the genesis of POCD, there is consensus that advanced age, especially with pre-existing cognitive impairment and other medical and neurologic comorbidities frequently associated with aging, increases the risk for POCD[12,13]. Risk factors which normally predispose an elderly individual to cognitive impairment, such as ApoE allelic expression, reduced cerebrovascular reserve, or increased vascular burden (i.e., presence of factors known to impair vascular structure and function, e.g., atherosclerosis, diabetes, hypertension, smoking, obesity, hypercholesterolemia, lack of physical activity, etc.; discussed below), may exacerbate the POCD risk. 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. We propose that cerebral hypoxia from any source should be considered as an important mechanism contributing to POCD.

Perioperative Hypoxia and POCD

Hypoxia has been classified into general categories arising from low oxygen uptake (hypoxic), ischemic, or anemic mechanisms. Each category has been independently linked to cognitive decline in diseases common in the elderly, with accumulating evidence that aging may exacerbate hypoxic stress. Further, major surgery, especially in older adults, involves procedures that decrease oxygen supply, including fluid overload, acute anemia, hypoperfusion, hypoventilation, and atelectasis. Postoperatively, sleep disordered breathing (present in patients with[14] and without[15] a history of obstructive sleep apnea [OSA]) and narcotics (commonly prescribed for postoperative pain control[16]) likely contribute to postoperative hypoxemia.

Intraoperative and postoperative hypoxemia occurs with a frequency previously unrecognized. Ehrenfeld et al.[17], found that 6.8% of patients experienced an intraoperative hypoxemic event, with a hypoxemic event lasting at least 2 minutes occurring in 3.5% of patients. More recently, Sun et al.[18] published the results of a prospective, blinded observational study in which pulse oximetry was recorded continuously in 1500 patients (mean age = 64 years) for 3 consecutive days postoperatively. Twenty-one percent (21%) experienced at least 10 minutes per hour (min/h) of hypoxemia, 8% experienced hypoxemia for at least 20 min/h, and 8% experienced severe hypoxemia (arterial hemoglobin oxygen saturation [SaO_2] < 85%). Prolonged hypoxemic episodes were also common, with 37% experiencing at least 1 episode lasting 1 hour minimum, 11% experienced at least 1 episode lasting 6 hours or more, and 3% experienced severe hypoxemia (SaO_2< 80%) lasting for 30 minutes or longer. Similar results have been reported by others[19].

Regardless of anesthetic approach (general vs regional) and surgical approach (off-CPB vs on-CPB), patients are subject to the same milieu of factors contributing to postoperative hypoxemia or hypoxia which may precede cerebral hypoxia. In fact, cerebral hypoxia has been associated with POCD following hip arthroplasty[20], abdominal surgery[21] and cardiac surgery[15,22].

Hypoxemic Hypoxia

Hypoxemic-hypoxia (HH), due to low oxygen uptake by the pulmonary circulation, is often present prior to surgery due to pathophysiological conditions. Clinically, HH is observed during respiratory failure, as experienced in chronic obstructive pulmonary disease (COPD), interstitial lung disease, OSA, and increased interstitial fluid, or pulmonary edema secondary to heart failure (HF), and pulmonary embolism.

The severity of respiratory disease, such as COPD or OSA, consistently correlates with poor performance on assessments of executive function, processing speed, and attention[23]. In a multi-center study of individuals over the age of 65 suffering from COPD, cognitive and motor impairment were inversely correlated to resting SaO_2[24]. Hypoxemia during sleep also plays a major role in cognition[25]. Treatment of hypoxemia suggests at least some cognitive function is recoverable[25] as observed in children[26] and adults with OSA.

Heart failure, in addition to hypoperfusion, may also cause HH secondary to an increased arteriolar-alveolar oxygen gradient with pulmonary edema and is associated with higher risk for cognitive decline[27]. The Cardiovascular Health Study found that global cognition declined more rapidly following incident HF than in age matched controls without HF[28]. The REGARDS study, a longitudinal study of racial and geographic disparities in incident HF, also reported that the rate of cognitive failure accelerated following incident HF. Acute decompensated HF, often accompanied by both pulmonary edema and hypoperfusion is associated with acute decline in cognitive performance compared to those with stable HF[29]. Rarely does HF exist in individuals without attendant atherosclerotic disease, therefore both ischemia and HH likely contribute to cognitive decline.

Ischemic Hypoxia

Ischemic-hypoxia, or ischemia, refers to low tissue oxygenation as a result of reduced blood flow and is the category most well recognized as being associated with cognitive failure. In the surgical arena, ischemia occurs secondary to acute and chronic embolic events or hypoperfusion. Embolic, ischemic, and hemorrhagic strokes have been widely recognized as important contributors to cognitive decline and dementia[30]. Resulting cognitive and behavioral impairments may be circumscribed or diffuse, as even focal brain damage may disrupt widespread functional networks. The most frequently impaired cognitive domains (and their associated brain regions) following a stroke include executive functions (prefrontal cortex, parietal cortex and underlying white matter), episodic memory (medial temporal lobe and subcortical structures), language/aphasia (dominant [usually left] cerebral hemisphere), attention/hemispatial neglect (brain stem, midbrain, prefrontal cortex, parietal cortex and underlying white matter), and visuospatial/visuo-constructional abilities (parietal cortex, nondominant [usually right] cerebral hemisphere)[31,32]. Risk factors for cognitive

impairment after stroke include older age, prior ischemic lesions, stroke severity (i.e., volume of tissue damaged), location of the stroke, and pre-stroke cognitive impairment[31–34].Gradual improvement occurs over time and is most notable in younger patients and within the first six months post-stroke, although many continue to demonstrate residual cognitive impairment years after stroke[32].

Patients who suffer from a transient ischemic attack (TIA) also demonstrate a range of cognitive deficits that are observed for months and years beyond the resolution of their focal TIA symptoms[35]. Individuals with a history of stroke and/or TIAs are at increased risk for future progressive cognitive decline[35]. Approximately 10% of stroke patients develop some form of dementia in the first year after stroke; which increases to over 30% with recurrent stroke[36]. Multiple strokes may lead to multi-infarct dementia, characterized by progressive, stepwise decline in cognitive function.

All surgeries involve some risk of cerebral ischemia (i.e., “silent” stroke; not accompanied by any observable stroke symptoms and detected only on postoperative diffusion-weighted magnetic resonance imaging [MRI] imaging [DWI]) or clinical stroke (i.e., acute brain lesion with clinical manifestation lasting >24 h)[37]. Generally, silent strokes are more common than clinical strokes[38]; and risk is higher in cardiac surgery and in aged individuals. Stroke in nonsurgical populations and perioperative stroke share common patterns of resulting cognitive dysfunction, yet cerebral ischemia is not generally considered in the conceptualization of POCD[39]. This is particularly surprising, because postoperative MRI studies have demonstrated incidence rates of new ischemic lesions after both cardiac and noncardiac surgery ranging from <1% to 17%[37,40,41]. A slight increase in perioperative stroke has been reported from 2003 to 2014[42], which may be partially due to more careful perioperative surveillance. While stroke or TIA was diagnosed after surgical aortic valve replacement in only 7% of patients by the routine clinical care team, 19% were diagnosed when a formal stroke assessment protocol was in place[40].

In most studies of POCD, DWI scans are obtained several days after surgery, increasing the likelihood that “acute” lesions reflect irreversibly damaged tissue[43]. In large prospective studies, perioperative silent stroke on DWI was observed in 7 – 10% following non-cardiac, non-carotid artery surgery[38]. Silent ischemic lesions are even more common following cardiac surgery and procedures that involve instrumentation of the cerebral vessels or aorta[44]. After surgical aortic valve replacement, 61% exhibited silent infarcts on postoperative DWI[40]. Patients experiencing clinically “silent” ischemic events may be at greater risk for future cognitive decline. Cognitive decline one year after surgery was identified in 42% of surgical patients with perioperative silent stroke vs. 29% without[38].

Because silent lesions are not accompanied by overt stroke symptoms, the extent to which they contribute to POCD is debatable[40]. Studies showing no relation between new ischemic lesions and POCD typically include relatively small samples and report relatively small total lesion volumes (e.g., <1,000mm^3)[45,46]. However, a larger study showed that those with POCD had more and larger acute ischemic lesions on DWI five days after surgery, suggesting a threshold effect with poor cognitive outcomes observed only after the burden of multiple infarcts and/or a single large infarct reaches a tipping point[2].

Anemic Hypoxia

Anemic-hypoxia results from reduced oxygen carrying capacity of red blood cells. Inadequate oxygen transport may result from low hematocrit, low hemoglobin concentration, or reduced ability of hemoglobin to bind oxygen (sickle cell anemia, carbon monoxide poisoning). Acute anemia elicits cognitive impairment even in healthy individuals[47]. Anemia that accompanies HF[48], COPD[49] and lung cancer[50] has been associated with cognitive impairment, although the rate of anemia in chronic kidney disease may not contribute to cognitive decline[51]. Chronic anemia has been associated with impaired cognitive performance, even in otherwise healthy adolescents[52] and adults[53]. Further, worsening white matter lesions[54] during chronic anemia are associated with an increased incidence of cognitive impairment in older adults[55,56]. Finally, anemia prolongs cognitive recovery after stroke[57] and erythropoietin (EPO) therapy may improve cognitive performance[58].

Surgical candidates frequently present with anemia associated with chronic diseases, and major surgery in all arenas often results in acute and severe anemia. Several studies have demonstrated correlations between lower preoperative hemoglobin levels and adverse postoperative cerebral outcomes[59]. Mathew et al.[60] found that aged subjects randomized to a transfusion hematocrit threshold of 18% experienced a greater degree of cognitive impairment that those randomized to 27%. Finally, the time course of recovery from perioperative anemia[61] mimics recovery from POCD.

Finally, hypoxic challenges do not end in the operating room; they do not necessarily end in the recovery room, and they may often extend well beyond hospital discharge. Hypoxia is at the epicenter of the dysfunction of every organ in the perioperative period[62] and with aging[63], and thus cerebral hypoxia may indeed contribute to POCD.

Mechanisms of Cognitive Decline associated with Chronic & Acute Hypoxia or Hypoxemia

Outside of the surgical arena, diseases associated with acute and chronic cerebral or systemic hypoxia, such as stroke, TIA, cerebrovascular disease, COPD, OSA, lung cancer, congestive heart failure, renal failure, and lack of aerobic fitness are all associated with cognitive impairment[63,64]. Acute cognitive dysfunction also occurs in patients in the intensive care setting who have not undergone surgery or anesthesia[5].

Cellular Hypoxic Response

Protective responses to hypoxia are controlled at the cellular level by hypoxia-inducible factors (HIF)[65] (figure 1). Hypoxia immediately stabilizes the various isoforms of HIF-alpha (HIF-1α, HIF-2α, HIF-3α) to regulate acute and chronic responses to hypoxia. HIF-α controls expression of over 600 genes[66] including EPO and vascular endothelial growth factor (VEGF), metabolic switching proteins like glucose transporter-1 and lactate dehydrogenase-A, vasoactive nitric oxide, and reactive oxygen species (ROS) generating nicotinamide adenine dinucleotide phosphate oxidase (NOX).

Although their roles overlap to some degree, the expression ratio of the isoforms modulates acute or chronic hypoxic outcomes to match oxygen supply with metabolic needs. For example, elevated HIF-1α:HIF-2α expression within carotid bodies is an integral component of the hypertensive response to chronic intermittent hypoxia, causing elevated sympathetic excitatory transmission[67], whereas HIF-2α is the primary modulator of EPO within astrocytes and is integral to maintaining memory[68]. Mitochondrial function under hypoxia is mediated by the various HIF-α isoforms, and dysfunction (i.e. impaired membrane potential, lower number, aberrant morphology) is implicated in a number of diseases and cognitive failure[69]. Cognitive failure associated with hypoxia may be overcome by mimicking the effects of HIF-α, such as by administration of EPO[58]

Effect of Cerebrovascular Impairment

The cerebrovascular response to hypoxemia is vasodilation to increase cerebral blood flow and oxygen delivery[70]. In the case of anemia, the marked increase in cerebral blood flow (CBF) is driven primarily by cerebral oxygen demand[71]. This global response appears to be largely intact with aging[72–74]. Evidence abounds that limitations in regional cerebrovascular reserve[75] could potentially contribute to cerebral hypoxia and/or ischemia under multiple scenarios, to include severe anemia[76,77], hypotension, low cardiac output, and intra- and extracranial cerebrovascular occlusive disease[78]. Conversely, intentional isovolemic hemodilution in the management of acute ischemic stroke does not appear to worsen or improve outcomes[79].

Progressive cognitive decline is observed as a consequence of chronic cerebral hypoperfusion, even in the absence of acute stroke/TIA[30,31]. The effect of chronic diseases of the vasculature (e.g., small vessel disease, carotid disease, atherosclerosis, endothelial dysfunction, deficient cerebral autoregulation,[80] amyloidosis[81], integrity of the blood brain barrier [BBB][82]) on the brain are observed in reliable neuroimaging (MRI) markers, including small punctate lesions, microbleeds, and white matter hyperintensities (WMH, also called leukoarioisis, and lacunes)[82]. Zhong et al. found that increased severity of carotid disease was associated with higher risk of cognitive impairment during a 10-year follow up[83]. WMH and lacunes (small subcortical cavities arising from arterial disease) have been associated with general cognitive impairment and decline in information processing speed and executive function[82,84] and WMH with increased risk for mild cognitive impairment and dementia[82,85].

Similarly, deficient hemoglobin saturation or diminished release of oxygen at tissue sites due to anemia contributes to poor cognitive outcomes[47]. In fact, multiple hypoxic sources can coexist as evidenced by an elevated risk of developing WMH due to anemia[55,86], which is exacerbated by coexistent hypertension[77,86]. Further, the age dependent elevation of cortical HIF (in spite of preserved tissue oxygenation) in a chronically hypertensive rat model of acute isovolemic hemodilution, suggests hypertension and anemia interact to cause a failure of oxygen delivery equated with cellular hypoxic states[77].

The terms vascular cognitive impairment, vascular dementia, and Binswanger’s disease are all used to denote progressive decline in cognition from chronic vascular disease[87,88]. These disorders are similar to Alzheimer’s disease (AD) in that cognitive impairment progresses

slowly over time. However, these disorders differ from AD in that the cognitive impairment profile is notable for deficits in processing speed and executive function, as opposed to episodic memory impairment and the loss of recognition memory observed in AD.

More recent conceptualizations of dementia recognize the complexity of neurodegenerative neuropathology and include a prominent role for vascular pathology/cerebral ischemia[89]. Current research suggests that cerebrovascular pathology has a dose-dependent effect on cognition[82,84,90,91], independent of other pathologies[92]. These observations have led to 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,[30,31,36] as well as vascular reactivity[93] on the degree of cognitive impairment and age-related brain atrophy[84,94]. Consequently, investigators have focused on understanding the role of cerebrovascular pathologies in AD and have discovered that cerebrovascular disease reduces the threshold of AD-specific pathologic burden of cortical pathology (e.g., cortical amyloid plaques, cortical atrophy) needed to produce cognitive impairment[84,95].

Impaired Connectivity

Even in the surgical arena, recent studies underscore the relevance of vascular burden for understanding POCD. Accumulating evidence shows that presurgical neuroimaging markers of general vascular health[96], cerebral ischemia[97], and presurgical cognitive status are all strong predictors of POCD[97,98]. A recent systematic review of 15 neuroimaging (MRI) studies[44] reported that POCD was more frequently associated with presurgical imaging markers of cerebrovascular ischemia (WMH) than neuroimaging markers of neurodegenerative changes (i.e., global and regional brain volumes). Therefore, mechanisms which hinder cerebral vascularization may be of particular interest in future investigations of POCD.

Cerebral white matter is critical for rapid signaling among both close and distant neuronal circuits. Disturbances indicated by WMH disrupt neuronal transmission and functional network connectivity, leading to widespread cerebral dysfunction and cognitive impairment[99]. For instance, in patients with chronic ischemia due to carotid artery stenosis but without overt indicators of clinical stroke, MRI network analyses show imaging patterns associated with cognitive impairment in the form of impaired cerebral connectivity[100] and altered resting state blood oxygen level dependent (BOLD) signal[101].

Neurons have a high metabolic rate, resulting in a need for rapid and precise regulation of CBF[102] and making them particularly vulnerable to damage from both acute and chronic hypoxia. Oligodendrocytes, glial cells that compose the cerebral white matter, may be even more sensitive than neurons[103]. Acute and complete oxygen deprivation to cerebral tissue downstream of an ischemic insult, such as a major clinical stroke, can result in relatively focal cell death (infarct) within minutes, leading to disruption of focal and widespread cognitive and sensorimotor functions, dependant upon the infarct size and location[102]. 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[102,104].

Regional responses to cerebral hypoxia often differ. The severity of OSA has been correlated with *hypo*perfusion of lateral cortical regions in elderly patients, but *hyper*perfusion of medial and subcortical regions[105] which may be a contributing factor in the loss of cortical and hippocampal gray matter associated with cognitive dysfunction in OSA[106]. Additionally, sleep disordered breathing damages cerebellar and hypothalamic control of sympathetic tone[107] and is associated with diminished working memory[108]. In HF, low CBF is observed in the posterior hippocampal regions[109], resulting in depressed mood and impairment of delayed and immediate recall[109,110].

Excitotoxicity

Elevated ROS from hypoxia induces cytokine transcription and elevates intracellular calcium[69,111,112]. These molecules modulate the composition and number of postsynaptic excitatory and inhibitory receptors[107], leading to more frequent excitatory postsynaptic potentials and altered synaptic connectivity. Excitotoxicity induces the neuronal loss associated with cognitive dysfunction observed in hypoxia[108,112]. Excitotoxicity is reported in the brainstem, cerebellar Purkinje neurons, and memory centers of the central nervous system (CNS) during hypoxia[107]. Cholinergic neurons (integral to many cognitive pathways) appear to be particularly vulnerable to excitotoxicity as fewer are evident in the forebrain of young adult male rats following as little as fourteen days of chronic intermittent hypoxia and their loss contributes to impairments in spatial working memory[113].

Neuroinflammation

Many studies demonstrate that hypoxia induces inflammation both systemically and centrally[114,115]. Neuroinflammation arising from hypoxia is initiated by HIF-α[116], may be of neuronal or glial origin and is correlated with cognitive impairment[111,117]. Cognitive effects are attenuated by administrated by EPO[118]. Neuroinflammation is often proposed as a central culprit in the onset of POCD[7]. These overlaps provide further evidence cerebral hypoxia may be at the epicenter of mechanisms of POCD.

Interaction between Aging and Hypoxia

Older adults are particularly vulnerable to perioperative hypoxia as aging is the leading risk factor for POCD[13] and older adults are at highest risk of needing surgical intervention. Dysregulation is observed in cerebrovascular reactivity[119], oxygen delivery[120–122], neural connectivity[82], neuroinflammation[123], and responsiveness to hypoxia[124] during aging (figure 2). Current literature suggests that protective molecular processes fail to respond to hypoxic conditions during aging and may exacerbate negative cognitive outcomes.

Aging Impairs Oxygenation

Of primary concern is the contribution of hypertension, loss of myogenic tone, accumulated plaque deposition, and deficient response to vasopressin or nitric oxide to reduced cerebrovascular reactivity and reserve[119] during aging, in spite of the fact that cerebral metabolic rate of oxygen ($CMRO_2$) remains constant over the lifespan[125]. Low cerebral oxygenation and worsening cerebral hypoxia is evident even in older adults without diagnosed hypoxia and is associated with memory impairment[126]. Further, unlike young

adults, lower CBF is associated with inattention in older individuals[120]. Indeed, low resting CBF in older adults is associated with higher WMH volume[127] and is a strong predictor of the number of newly developed cortical WMH observed 18 months later[128]. The loss of cerebrovascular reserve in the elderly may thus impair their ability to recover from perioperative hypoxic stresses.

Preclinical studies indicate the oxygen pressure within cerebral tissue declines in middle age and continues into old age[129]. The oxygen pressure setpoint in the CNS has a narrow range and extremes lead to vascular dysregulation. Temporary fluctuations in tissue oxygenation early in adulthood have been linked to rapid subsequent vascular dysregulation (e.g., hypertension) and working memory impairment that is not evident until later in life[130,131].

In addition to hypoperfusion, aging is associated with more frequent bouts of anemia as nutritional intake declines, gastrointestinal tract disorders and pharmaceutical intake increase, and hormone levels change[122]. Although Price et al.[121] found no difference in circulating EPO in non-anemic individuals of any age, EPO concentration was lower in elderly, but not young, anemic patients. Other studies suggest EPO production slows with age and coincides with lower cerebral metabolism[122]. Additionally, aged spontaneously hypertensive rats experienced greater memory impairment and evidence of cellular hypoxia (elevated HIF expression) after anemia caused by isovolemic hemodilution which is not evident in their younger adult counterparts[77].

Aging Impairs the Hypoxic Response

Elegant studies performed by the LaManna lab demonstrate the normal cortical response to hypoxia stabilizes HIF-α leading to increased capillary density, blood flow, and glycolysis (figure 1)[132]. Unfortunately, a blunted or, in some cases, nonexistent response to hypoxia mediated by HIF-α is observed in the aged brain[66,124,133]. Aged rats exhibit low VEGF in carotid bodies under normal oxygen conditions and an attenuated response to 12 hours of 12% oxygen for 12 days than young rats do[133]. Cortical vascularization and expression of HIF-controlled proteins (e.g. EPO, inducible nitric oxide synthase, and heme oxygenase-1) following hypoxia are lacking in aged models[66,133] in combination with fewer and smaller mitochondria in carotid bodies[133]. Further, prolyl hydroxylases which regulate HIF-α expression also lose responsivity during aging[134]. Therefore, the primary adaptive hypoxia pathway may be particularly susceptible to acute and chronic hypoxic insults during aging. Investigations using aged pre-clinical models to investigate HIF-α mechanisms in specific brain regions and cell types are scarce and represent an area of active inquiry.

Aging Induces Inflammation and Impairs Neurotransmission

Aged rodent and postmortem human brain samples exhibit low grade inflammation and aberrant glial morphology[123,135]..Recent studies suggest glial cells are particularly vulnerable to aging and hypoxia[104] and typical neuroprotective glial activities[136] are diminished while reactive and senescent phenotypes flourish in aged brains[137,138]. 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 post-synaptic density, and lower tissue volume in aged hippocampi[137,139].

Management of Hypoxia related POCD

Thankfully, long term cognitive impairment after surgery appears to be a very infrequent phenomenon, with most resolving within weeks to months. Ischemic-hypoxic events may pose the greatest risk for long term effects, while lingering anemia and cardiorespiratory failure in recovery may also contribute. Management of hypoxia-related POCD starts with recognition of the contribution of hypoxia to cognitive performance and identification of those at risk. While aging has been recognized as a major risk factor, older patients with superimposed cerebrovascular disease, chronic anemia, and those with pre-existing cardio-respiratory failure identify subgroups at the highest levels of risk. Those at the highest levels of risk may be further stratified by preoperative cognitive evaluation, as preoperative cognitive status in and of itself appears to be a risk factor for further decline[140].

Management of patients at risk for hypoxia-related POCD should start with prevention via optimization of pre-existing disease that carries the hypoxic burden. The strong relationship between cognitive performance, cardiovascular fitness[141] and cardiovascular disease in the general population[142] clearly demonstrates their interdependence. Prerehabilitation programs have shown benefit in reducing overall and pulmonary morbidity and may therefore impact hypoxia-related cognitive performance after surgery[143]. Patients at risk with pre-existing anemia may benefit from preoperative supplementation and possibly EPO[58,144].

Intraoperative efforts should obviously focus on prevention of hypoxemia and heightened attention to the predisposition of certain high-risk groups such as those with morbid obesity and those undergoing lung transplantation. Intraoperative use of cerebral oximetry has yet to clearly demonstrate benefit in prevention of POCD[145]. We remain without high quality guidance as to a patient-specific transfusion trigger to guide us either intraoperatively or postoperatively for organ protection, brain or otherwise. Advances in the approach to the heavily calcified aorta[146] and use of intra-arterial emboli trapping devices to date have not been as effective as originally hoped in altering the frequency of perioperative stroke and POCD[147], likely due to the fact that stroke risk continues beyond the critical period of aortic manipulation.

Postoperatively, it can be assumed that physicians already attempt to optimize cardiopulmonary function and carefully balance the risks and benefits of transfusion in their patients. In the management of anemia, perhaps more aggressive approaches to iron replacement and the use of EPO should be considered to speed the recovery of erythrocyte volume. Enhanced attention to the impact of narcotic use on pulmonary function in those with respiratory compromise from multiple etiologies may include more aggressive and prolonged respiratory monitoring, administration of supplemental oxygen, and advancement of lower or nonnarcotic approaches to pain control[148]. Earlier and more accurate diagnosis of perioperative stroke may be enhanced by anesthetic techniques which allow for immediate postoperative assessment[149], implementation of more frequent and rigorous

stroke assessment protocols[40], and judicious application of advances in interventional strategies[150]

Conclusion

There is voluminous evidence that short to intermediate term age-related changes in cognition occur in the perioperative arena. However, the evidence connecting those changes to modern anesthetic use is tenuous. Aging is accompanied by hypoxic conditions which have been firmly established as risk factors for cognitive dysfunction outside the surgical arena. Surgery, as well as critical illness, may elevate hypoxic exposure through hypoperfusion, hypoventilation, pulmonary edema, and blood loss. Given these parallels, it is therefore conceivable that hypoxia, in its many forms, contributes importantly to POCD and may share similar mechanisms with hypoxia-related cognitive failure in the general population. Future studies fully elucidating the role of hypoxia in age-related memory loss in chronic and acute settings may also clarify the role of hypoxia in POCD.

Glossary of Terms:

AD	Alzheimer's Disease
BBB	blood brain barrier
BOLD	blood oxygenation level dependent imaging
CBF	cerebral blood flow
$CMRO_2$	cerebral metabolic rate of oxygen
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CPB	cardiopulmonary bypass
DWI	diffusion weighted imaging
EPO	erythropoietin
HH	hypoxemic hypoxia
HIF	hypoxic inducible factor
HF	heart failure
MRI	magnetic resonance imaging
NOX	nicotinamide adenine dinucleotide phosphate oxidase
OSA	obstructive sleep apnea
POCD	Postoperative Cognitive Dysfunction
ROS	reactive oxygen species

SaO_2	arterial hemoglobin oxygen saturation
TIA	transient ischemic attack
VEGF	vascular endothelial growth factor
WMH	white matter hyperintensities

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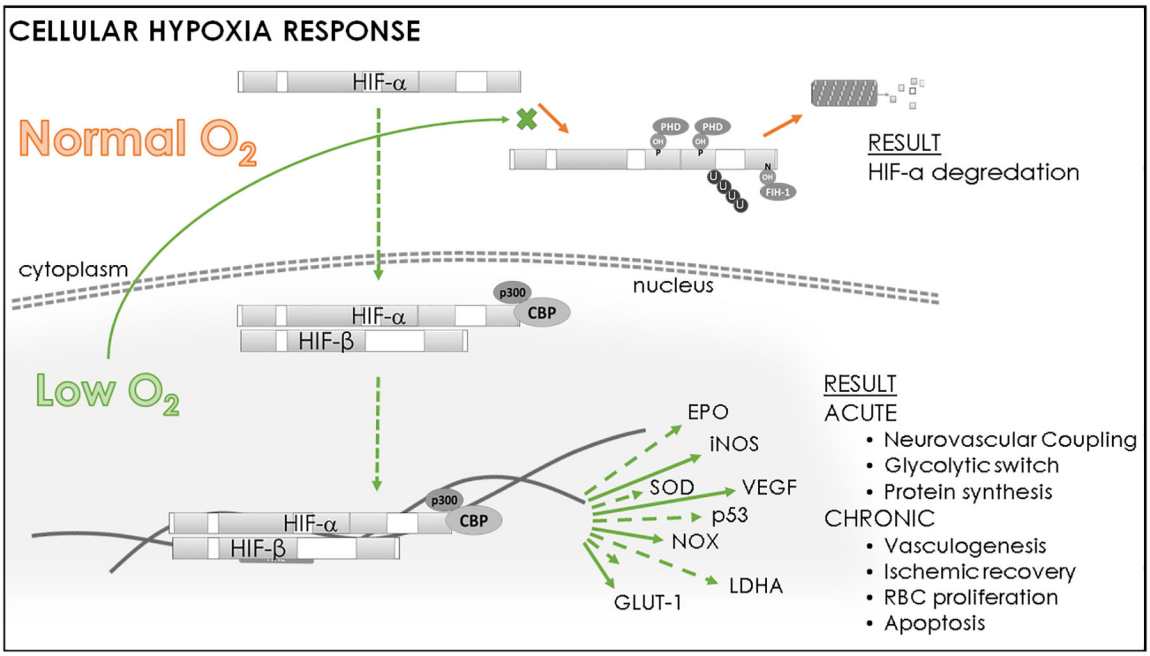

Figure 1: Cellular Hypoxic Response

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

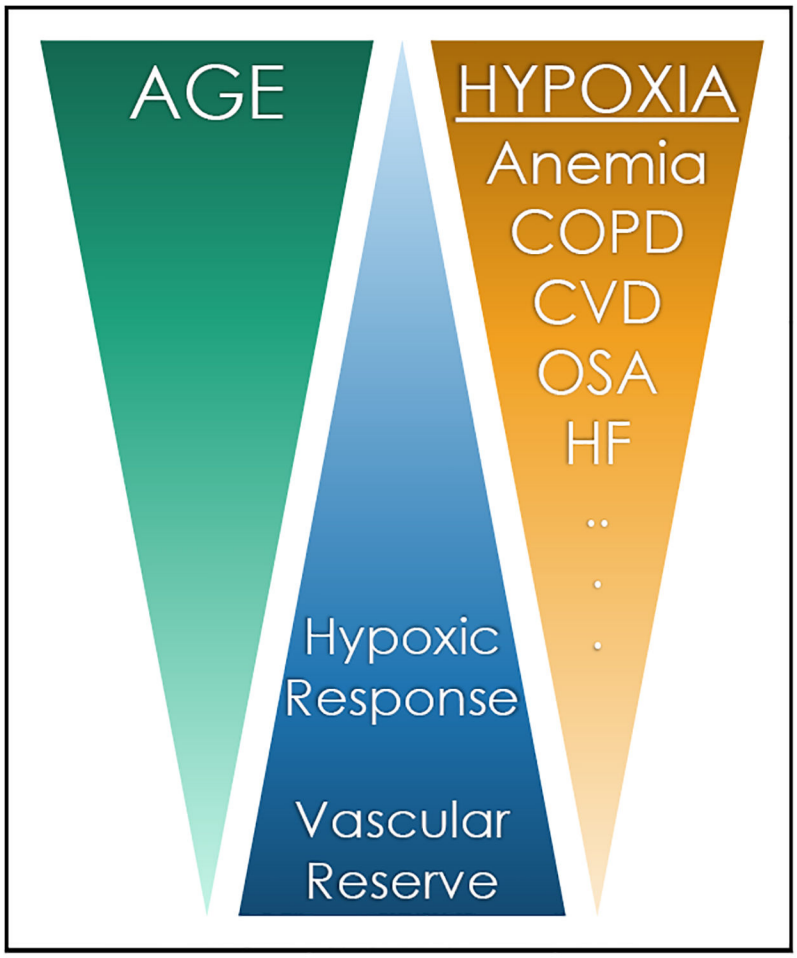

Figure 2: Interaction between age, hypoxia, and protective responses

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