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Commentary

A new approach to hypobaric hypoxia induced cognitive impairment

The reduction in barometric pressure and the consequent fall in the partial pressure of oxygen at high altitudes lead to hypobaric hypoxia (HH). It is now widely accepted that ascent to high altitude slows down performance, particularly on more complex tests of cognitive and motor function. Error rates also increase, a number of investigators have suggested that slowing might be a strategy designed to minimize mistakes[1]. However, it is not known whether general hypoxaemia or hypoxia specific to certain neural tissues impairs cognitive performance. Nelson[2] have reported that the critical altitude for changes in cognitive function appears to lie between 4000 and 5000 m, above sea level. An acclimatized lowlander can survive for some time on the summit of Everest without supplemental oxygen, but is so close to the limit that even a little excess exertion may impair brain function. Lionel Terray has described his experience at 7400 m on Annapurna in 1950 as: "At times I would force so much that a black veil began to form in front of my eyes and I fell to my knees, panting like an overdriven beast"[3].

The term cognition describes those mental processes that allow us to perform day-to-day functions, for example, the ability to pay attention, to remember and to solve problems are all parts of cognition. Mild cognitive impairment (MCI) has emerged as a classification for a prodromal phase of cognitive decline that may precede the emergence of dementia. The three most commonly described domains of cognition are attention, memory and executive function and recent research suggests that deficits in these domains appear much earlier and are more consistently associated with the later development of dementia.

The effects of HH on cognitive impairments in humans are well documented at different altitudes and duration. Among these, the hippocampal memory deficit is well known. As the altitude increases, maximum oxygen uptake (VO_2 max) decreases. At the summit of Mount Everest, it is no more than 25-30 per cent of the sea-level. A small additional diminution in supply or increase in need is sufficient to cause brain injury. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies have documented focal failure of neuronal function within the brain. Di Paola *et al* studied the effects of high altitude exposure on nine world-class mountain climbers using a quantitative MRI technique, voxel-based morphometry[4]. They have reported a region of reduced white matter density/volume in left pyramidal tract near the primary (BA_4) and supplementary (BA_6) motor cortex when mountain climbers at baseline were compared with controls. Further, when mountain climber's scans before and after the expedition were compared, a region of reduced grey matter density/volume was found in the left angular gyrus (BA_{39}). These findings suggest that extremely high altitude exposures may cause subtle white and grey matter changes that mainly affect brain regions involved in motor activity. HH induced brain injury has been attributed to several factors including increased oxidative stress, glutamate excitotoxicity, decreased growth factors, apoptosis, *etc*. However, the exact mechanism that underlie the cognitive impairments and whether these impairments persist even after acclimatization is poorly understood. Pagani *et al* have documented a marked cognitive decline on exposure to high altitude above 5350 m and then significant improvement over a 15 days period of acclimatization[5]. The improvements resulting from acclimatization were more evident in the organization of information than in information storage. Hornbein *et al*[6] carried out a study on the members of the American Medical Research Expedition (AMREE). They compared performance following hypoxic exposure with that prior to ascent and found decrements in short-term memory, aphasic deficits and decreased

finger tapping speed. A year later, memory and aphasia deficits were no longer apparent but in 13 of 16 participants, finger-tapping speed remained impaired. Regard *et al*[7] have also reported similar results in eight world-class mountaineers. It can be concluded from these observations that even if there is no loss of consciousness or overt evidence of impaired function while at high altitude, some individuals do suffer from brain injury which persists even after return to sea level. The vulnerability to such hypoxia induced brain injury varies from individual to individual. In a recent study, Janocha *et al* have reported that ascent to altitudes 5000m and above leads to increased levels of intracellular red-cell forms of nitric oxide, S-nitrosohaemoglobin and iron nitrosyl haemoglobin[8]. They concluded that nitric oxide-haemoglobin interactions that occur parallel to genetic hypoxia-inducible factor controlled protein responses contribute to acclimatization. Some researchers have suggested that hypoxia preconditioning produces tolerance against hypoxic brain injury[9]. Preconditioning is a process by which a tissue is rendered more tolerant to a subsequent lethal insult such as hypoxia. The best way to acclimatize the humans to high altitude hypoxia is to induce necessary physiological and genetic changes in the body of the humans before they are inducted to high altitude by hypoxia pre-conditioning. Acclimatization after sudden ascent does not completely reverse the hypoxic brain injury.

The commonly used cognitive tests for the screening of MCI measure performance only in a limited number of domains of cognition. Additional domains are assessed by adding different complexities to the tasks. For example, intact attention abilities are required to concentrate on and complete even the simplest task, while preserved memory is additionally needed to perform well on tasks of new learning. The mini mental state examination (MMSE), although widely used is not sensitive enough for the diagnosis of MCI especially if the subjects have high levels of education or high IQ. One study showed a 70 per cent sensitivity and specificity using a cut-off of 26 or less for cognitive impairment[10]. The Mini-Cog is a simple test for detecting MCI which uses a three-item recall test for memory and a simply scored Clock-drawing test (CDT). Though Mini-Cog is twice as fast as MMSE and is less affected by subject ethnicity, language and education, there are conflicting reports as to which one has higher sensitivity and specificity[11]. The combination of Mini-Cog with a Functional Activities Questionnaire (FAQ), administered to a family member or friend significantly improves its efficacy to identify individuals with MCI. The Montreal Cognitive Assessment (MoCA) was designed as a rapid screening instrument for MCI. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations and orientation. MoCA has more emphasis on tasks of frontal executive functioning and attention than the MMSE which makes it more sensitive than MMSE to identify early cognitive impairment[12]. A battery of neuropsychological instruments is more sensitive than a single test and provides a more complete profile of a person's current cognitive state. Therefore, an effective screening device for MCI would incorporate measures of multiple cognitive domains, measure changes over time and be cost efficient.

In a large number of previous studies cognitive functions have been evaluated in non-acclimatized subjects during short term exposure to HH by not so sensitive tests like MMSE, MoCA, Mini-Cog, computer administered neuropsychological score (CANS)-MCI and patient reported outcomes in cognitive impairment (PROCOG). The study by Hota *et al*[13] in this issue is unique because it assesses the prevalence of MCI in acclimatized lowlanders, staying at altitudes above 4267 m for more than 12 months with a newly designed test that evaluates cognitive performance domain-wise. This multi-domain cognitive screening test (MDCST) is easy to administer, evaluates a greater number of domains and is more sensitive than MMSE, MoCA and Mini-cog for the detection of early stages of MCI. The study has important clinical implications. Persistence of decline in immediate recall, procedural memory and mind body co-ordination even after one year of acclimatization emphasizes the need of hypoxia preconditioning.

It is premature to suggest that MDCST is the most sensitive and specific test for the screening of MCI because P300 is used clinically as the earliest marker of cognitive decline. The P300 event-related potential (ERP) reflects neuroelectric activity related to cognitive processes such as attention allocation and activation of immediate memory. The P300 latency time is generally accepted as a measure of speed of cognitive processing, and its amplitude to reflect the number of neurons allocated to the eliciting task. A comparative study between MDCST and P300 to evaluate whether MDCST is better than P300 in terms of earlier detection and quantifying the level of cognitive impairment is an

important direction for future research. At high altitudes it is desirable to have a psychometrically robust, user-friendly instrument for the screening of MCI rather than a cumbersome evoked potential machine. Further investigations on brain function and electrophysiology at high altitudes could provide valuable information in devising clinical management strategies for HH induced cognitive impairment.

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