

Human Cognitive and Neuro-Psychiatric Bio-Markers in the Cardiac Peri-Operative Patient

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Abstract: Some of the complexities of surgical interventions include neurological and psychiatric disturbances. Prompt identification and early treatment of these complications are pivotal in achieving excellent clinical results. Recognizing major adverse events such as stroke, seizure or delirium is usually straight-forward, however the discovery of less frequent or more subtle post-operative changes such as cognitive dysfunction might be delayed due to lack of appropriate diagnostic tools. This review summarizes biological markers that can be utilized as surrogates in evaluating surgery-related neuro-psychiatric disorders.

Keywords: Bio-marker, complication, peri-operative period, post-operative cognitive decline, surgery.

BACKGROUND

Impaired central nervous system (CNS) functioning is among the many complications of surgical procedures. Their temporal characteristics including onset and duration are extremely diverse, and present with sundry severity: from resolving spontaneously to needing routine treatment, they can also lead to life-threatening conditions that require emergency intervention. The clinical presentations vary along a spectrum from neurological abnormalities to psychiatric manifestations such as stroke, seizure, delirium, affective disorders and cognitive dysfunction.

From a holistic point of view, a surgical patient is an individual and not a "pack of organs", therefore post-procedural brain lesions should not be addressed separately from the intervention. Patients undergoing operations, however, are hospitalized surgically and cared for by physicians trained mainly in surgery with some qualification in internal medicine but usually limited substantial knowledge and skill in neurology or psychiatry. Conversely, brain specialists may not necessarily be surgical experts. Therefore, in contrast to the most robust and relatively common complications that are well-known to any doctor, the less conspicuous or infrequent ones are not easily and immediately recognized in the peri-operative phase, and even if identified they might pose a diagnostic and treatment challenge even with the close team-work of inter-disciplinary specialists. In such cases an extensive medical evaluation is classically undertaken, including physical examination with neuro-psychiatric

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assessment, routine laboratory studies, toxicology screen and para-neoplastic panel, brain and body imaging, and sometimes even supplemented by EEG and lumbar puncture. Despite massive medical assessment, however, many relatively rare complications go unrecognized or are mis-diagnosed.

Even though most of the post-procedural neuro-psychiatric dysfunctions are well characterized, the patho-physiology of a handful of less well-known adverse events such as post-operative cognitive decline (POCD) is poorly understood despite an increasing effort to pin-point risk factors or biological markers that could be linked to them. This paper dissects the clinically relevant bio-markers with respect to such surgical complications.

RISK FACTORS

The development of surgery-related adverse events might depend on pre-existing pathological conditions, medications used, tissue damage induced by the procedure *per se*, and post-operative care of the patients. For example diabetes, atrial fibrillation (with or without thrombus in the heart) and carotid artery stenosis are risk factors of major neurological events such as stroke [1]. In addition, high creatinine-levels, hypertension, smoking and previous stroke all increase the incidence of post-surgical delirium [2]. Deep hypothermic circulatory arrest, aortic calcification or atheroma, and critical pre-operative state are independent risk factors for seizures after cardiac surgery [3].

A more subtle neuro-psychiatric complication following operations is POCD. Cognitive dysfunction has recently been recognized to be a common problem observed after various surgical interventions: it has a high incidence, especially following coronary artery bypass grafting (CABG) where it occurs in half of the patients at discharge, and approximately 36% at 6 weeks, 24% at 6 months, and 42% at 5 years [4] after surgical revascularization of the coronaries. Clinically relevant, persistent and slowly progressive changes in the mental processes also exist after heart operations. Lately, the term post-operative Alzheimer's disease (POAD) has also been coined and described [5]. Pre-operative parameters, such as advanced age, diabetes, renal failure and low education, as well as intra-operative hypo-tension, hypoxia, certain medications and even infections are all associated with POCD [6-8].

BIO-MARKER SOURCES

The probable diagnosis of cognitive disorders is made through clinical manifestations using neuro-psychiatric tests, and is only confirmed after a *post-mortem* examination of the brain as part of an autopsy. Bio-markers, therefore, are invaluable tools in identifying such maladies, and they also serve as surrogates in monitoring disease progression, response to treatment or even to predict the development of certain pathologies. The current state-

of-the-art strongly suggests that no single bio-indicator yet considered can be used reliably for the diagnosis of POCD. It is widely acknowledged that the best possible marker or set of markers is likely to come from the integration of parameters derived from different types of biomedical data and clinical information. No such bio-markers exist at present and the goal is to develop such a marker or a small set of biological markers for the assessment and care for cognitive impairment on an individual basis and for the prediction of cognitive decline in surgical subjects.

The cerebro-spinal fluid (CSF) is considered to be a "window to the brain", and although it is an important seedbed of bio-markers, lumbar puncture involves invasiveness and an element of risk. Various alternative sources include blood (both cellular blood, such as lymphocytes, and the non-cellular part, *i.e.* serum), fibroblasts (usually skin biopsies or even hair follicles), urine, saliva, tear, *etc.* Although these are more easily accessible than CSF, however they may not genuinely reflect cerebral changes as the blood-brain barrier (BBB) serves as a border between the CNS and the rest of the body. Even if some metabolites (*e.g.* protein or lipid markers) cross or are transferred through the BBB, they may rapidly degrade or be excreted, making them improbable bio-identifiers. Nevertheless, the importance of evaluating non-CNS bio-marker sources is based on the emerging hypothesis that psychiatric disorders are actually systemic diseases with molecular alterations found in both central and peripheral tissues with the most prominent pathology in the brain functions [9-13].

BIO-MARKERS IN POCD AND POAD

β -Amyloid Peptide (β AP) and *tau*

β AP-induced neuro-toxicity is a pathognomonic factor in Alzheimer's dementia (AD). According to the amyloid-theory, this physiological peptide is deposited in the brain of affected individuals to form senile plaques and disrupt technically every cellular function. As a result of various perturbed signaling mechanisms, pathologically hyper-phosphorylated microtubule-associated protein *tau* is also accumulated into intraneuronal neuro-fibrillary tangles (NFTs). Cross-sectional AD studies typically demonstrate elevated levels of different epitopes of phospho-*tau* (*p-tau*) and a decreased concentration of the 42 amino-acid variant of β AP (β AP₁₋₄₂) in the CSF as a result of the ongoing patho-physiological processes in the brain. Combining these markers for AD diagnosis is at present the only bio-marker that meets the consensus diagnostic criteria [14-18]: the ratio of β AP₁₋₄₂/*p-tau* (Qa/t) confirms AD [19]. Although this is only diagnostic when measured from CSF, however low plasma β AP levels or β AP₁₋₄₂/ β AP₁₋₄₀ ratio may also be markers of cognitive decline [20].

Given the comparability of various cognitive disorders, several studies have investigated the role of β AP in POCD. Old mice submitted to abdominal (liver) surgery developed short-term (<5 days) POCD and

their brains showed gliosis, enhanced production of β AP, and hyper-phosphorylation of *tau* in the hippocampus [21], the mark of AD-like changes after major non-cardiac procedures. Significantly lower pre-CABG levels of plasma β AP₁₋₄₀ and β AP₁₋₄₂ have been reported in patients who developed POCD 3 months after surgery [22]. Serum *tau* was also higher in individuals with neuro-cognitive deficits following cardio-pulmonary bypass (CPB) in comparison with those who did not develop this condition [23]. The CSF profile of β AP and *tau* 6-months after off-pump CABG (OP-CABG) is resembled to that seen in AD [24].

The use of heart-lung machine or the type of surgery, therefore, might not be a key factor in these altered cognitive bio-markers. However, very nearly half of healthy patients aged 55 and older experience new onset, chronic (*i.e.* lasting at least a few months) deficits in memory and problem solving after anesthesia and non-cardiac surgery [25]. Recently, data has emerged that anesthetics interact with β AP and promote aggregation as one of the main molecular mechanism behind cognitive dysfunction following surgery: the smaller the drug, the easier for it to enter the cavity of the micro-aggregated β AP to advance oligomerization. This interaction is size-limited: larger anesthetics have no such effect as they do not fit in the pocket-like folded structure of β AP [26]. Tiny particles such as volatile narcotics are known to cause more pronounced cognitive disturbances than bulkier iv-anesthetics. Halothan, therefore, is the most potent pro-POCD drug, whereas fluranes (iso-, sevo-, des-flurane) and propofol are much safer in this respect, although they are all known to enhance β AP-oligomerization [27]. Moreover, isoflurane increased β AP production and reduces cell viability [28]. In contrast, relatively huge molecules such as thiopental are not known to cause any cognitive dysfunction. In addition, it has been reported that anesthesia could induce hyper-phosphorylation of *tau*, which largely depends on hypothermia: normal body-temperature resulted in *tau*-dephosphorylation [29].

Apo-Lipoprotein E (apoE)

The apoE is a multi-functional protein that plays a key role in the metabolism of cholesterol and triglyceride. The three main apoE isoforms (E2, E3, and E4) are coded by 3 common alleles of apoE (ϵ 2, ϵ 3 and ϵ 4), resulting in 6 main genotypes (ϵ 2/ ϵ 2, ϵ 2/ ϵ 3, ϵ 2/ ϵ 4, ϵ 3/ ϵ 3, ϵ 3/ ϵ 4, and ϵ 4/ ϵ 4) [30]. Genetic variation/polymorphism of the apoE gene has been associated with variations of lipid plasma levels (dyslipidemia), relative risk of atherosclerosis, coronary artery/heart disease (CAD/CHD) and AD [31-39].

The premature presence of Alzheimer's hallmark lesions (*i.e.* cortical senile plaques and NFTs) in the brains of non-demented patients with ischemic heart disease (IHD) suggests a neuro-pathologic link between CAD and AD [40]. Aortic atherosclerosis correlates positively with cerebral β -amyloidosis as well. This is also confirmed by the finding that anti-atherogenic therapies, including dietary regimens, may

be effective in prevention and treatment of AD [41]. This is in part because of the underlying atherosclerotic lesions throughout the body, including the heart and brain: it is known that atherosclerosis is one of the (major) risk factors for AD [41]. Previous myocardial infarction (MI) or CAD also often occur in and may increase the risk of AD. Expression of apoE4 likely contribute to the development of CAD by elevating blood cholesterol and the risk of AD *via* proposed interactions with β AP and/or free radicals [42, 43]. As such, synergistic mechanisms may be involved in the pathogenesis of atherosclerosis and primary degenerative dementia of the Alzheimer-type [24].

This stunningly unique inter-relationship is also signified during cardiac interventions. Patients undergoing (OP-) CABG are not rarely affected by poly-distrectual atherosclerotic disease, hypertension and diabetes: all factors related to the risk of progressive cognitive impairment. Not surprisingly, the apoE genotype is linked with a decline in cognitive performance 6 weeks after heart procedures involving CPB [44], but no association has been demonstrated among apoE genotype, various blood-based bio-markers, and cognitive decline [45, 46] or post-operative delirium [47, 48] following major non-cardiac surgery. The use of apoE as a cognitive bio-marker for POCD, however, is yet to be confirmed in large scale studies.

Inflammatory Markers

Escalating evidence indicates that immune mechanisms play a crucial role in POCD. Minor abdominal surgery induces glial activation and inflammatory response in the hippocampus that can be related to cognitive changes [49, 50]. Cytokines, especially inter-leukin (IL)-1 β , are associated with memory impairment in an animal model of tibia surgery [51]. Plasma IL-6 and IL-8 is increased in elderly patients with delirium [52], and their concentration is also elevated following reconstruction of hip fracture [53]. However, pre-operative levels of IL-6, C-reactive protein (CRP) and insulin-like growth-factor-1 (IGF-1) do not correlate with delirium after hip-surgery [54]. On the other hand, serum cytokine levels are markedly increased within a few hours after heart procedures in patients who develop delirium, but not in those without any post-surgical psychological pathology [55]. Moreover, elevated IL-6 and CRP are associated with the POCD following CABG [56].

Post-operatively deranged cytokine levels are seen not only in the serum, but also in the CSF of cardiac patients: acute over-production of the pro-inflammatory IL-6 normalizes within 6 months after the intervention along with a gradually increased suppressor IL-4 levels in the CSF, suggesting a regulated intra-theal immune response. The delayed compensatory processes are intended to reduce cerebral inflammation and prevent the development of dementia after heart surgery [57]. The CABG-induced cytokine changes differ from those seen after major non-cardiac surgeries (*e.g.* hemicolectomy, esophagectomy), and correlate with

the pronounced incidence of cognitive impairment seen mainly after heart operations [58].

Post-procedural infection is also a key instigator of POCD. Endo-toxins, lipo-poly-saccharide (LPS) components of the cell wall of Gram-negative bacteria, are potent activators of macrophages and dendritic cells. Decreased endo-toxin immunity contributes to elevated endo-toxin levels and the associated inflammatory reaction during contamination: the resulting intense signaling cascade and the secreted cytokines may set off cognitive changes. Indeed, low pre-operative anti-endo-toxin core IgM antibody levels have also been linked with increased risk of POCD following CABG [59, 60]. Anti-biotic cover in the peri-operative period therefore prevents not only infections, but indirectly may also preclude cognitive changes.

Cortisol

Serum cortisol is known to rise following any stressful situation. Apart from its many beneficial functions, gluco-corticoid treatment may induce acute psychosis and delirium [61-63]. Hippocampal atrophy is also seen in conditions with chronically elevated circulating cortico-steroid concentrations, such as in Cushing's disease [64], and cognitive impairment might also ensue [65].

As a fundamental cortisol-response to stressors, increased gluco-corticoid levels are also present following operative procedures [66]. Surgical stress-induced higher cortisol has been associated with confusion and delirium after abdominal interventions [67, 68], and the same has been observed in cardiac or orthopedic surgery as well [69, 70].

Serum Anti-Cholinergic Activity (SAA)

The relationship of the cholinergic system to memory and cognitive functions is well established. However, many commonly prescribed drugs have anti-cholinergic effects such as anti-emetics, anti-spasmodics, broncho-dilators, anti-arrhythmic drugs, anti-histamines, analgesics, anti-hypertensives, anti-parkinsonian agents, cortico-steroids, skeletal muscle relaxants, anti-ulcer drugs, sedative and psycho-tropic drugs. Additive long lasting anti-cholinergic side effects, therefore, are one of the main reasons for cognitive decline and delirium in the elderly [71]. The cumulative anti-cholinergic toxicity can be identified in the peripheral blood utilizing a muscarinic anti-cholinergic radio-receptor assay in comparison to atropine [72]. Because this serum assay is known to reflect CNS anti-cholinergic status, SAA is described as a marker of cognitive dysfunction [73]. Indeed, higher SAA has been correlated with cognitive impairment or lower cognitive test scores (e.g. mini-mental state examination, MMSE) especially in dementia [74-76].

Medications with anti-cholinergic properties (e.g. sedatives, narcotics, and antibiotics) are regularly applied in peri-operative conditions, and surgical patients are pre-medicated with central anti-cholinergics such as scopolamine or midazolam,

leading to an increased anti-cholinergic burden around the procedure. These drugs are likely to have a more toxic effect during surgery or in an ageing brain because of increased permeability of the BBB, slower metabolism and drug elimination, and poly-pharmacy [71]. Consequently, association between SAA and delirium has been reported in various clinical settings, including surgical patients [74, 77].

S100 β and Neuron-Specific Enolase (NSE)

The brain-derived S100 β protein and NSE have recently emerged as potential serum and CSF markers for ischemic cerebral injury. Their levels are also elevated after both adult and pediatric cardiac procedures [24, 78, 79], and this increase is even more prolonged (>30 hr) after heart surgery with CPB [23, 80]. Serum NSE is presumed to be an important bio-marker for early cognitive dysfunction 36 hr post-CABG [81] where coronary atherosclerosis is a key role-player, but not in other type of heart operation [82, 83]. S100 β might also be a good predictor of neurological outcome after cardiac surgery, and its level 24 hr after surgery possesses around 90% sensitivity and specificity for cerebral lesions. However, ischemic heart can also release S100 β , suggesting that the source of this bio-marker can be the cardiac injury and may not always genuinely reflect intra-thecal damage [84]. Nonetheless, significantly increased S100 β level is also present in delirium in major non-cardiac (e.g. orthopedic) surgical elderly patients [70].

Table 1. Summary of bio-markers.

Bio-Marker	Relevance in Cognitive Impairment Associated with
β AP	AD, CABG
<i>tau</i>	CPB
<i>p-tau</i>	AD
apoE	CPB
IL-1 β	animal model of tibia surgery
IL-6	hip fracture, CABG
IL-8	hip fracture
cortisol	abdominal interventions, cardiac and/or orthopedic surgery
SAA	dementia
S100 β	(pediatric) cardiac procedures, major non-cardiac (e.g. orthopedic) surgical elderly patients
NSE	(pediatric) cardiac procedures, CABG

Imaging

Radiological Markers

Computerized tomographic (CT) and structural magnetic resonance imaging (sMRI) of AD brains show thin cortical gyri of the postero-temporal and postero-parietal lobes, enlarged (lateral) ventricles, and atrophy of the hippocampus. These findings, however, are not

specific. Apart from measuring cortex volumes, task-activated functional MRI (fMRI) studies have found decreased cortical activity in the hippocampal and para-hippocampal regions and in the medial temporal lobe. Because these changes can also predict memory decline [85, 86], radiological approaches may be important to investigate cognitive deficit after surgery as well.

Reduced activity in the pre-frontal region was detected after on-pump CABG using fMRI, and changes in the signal intensity correlated with the number of micro-emboli and cognitive impairment [87, 88]. Although peri-operative ischemic lesions underscore vascular dementia (VD), new such brain lesions do not explain POCD after CABG or valve procedures [89, 90]. This is also confirmed by the fact that despite trans-cranial ultra-sound (doppler)-recordings demonstrate rare gaseous and/or solid micro-emboli during OP-CABG when compared to procedures involving heart-lung machine, POCD and ischemic lesions found at sMRI are seen after non-CBP coronary surgeries at a rate similar to that reported for on-pump CABG [91-93]. Cognitive changes, however, have been more convincingly linked with asymmetrical cerebral blood flow following carotid endarterectomy, as demonstrated by magnetic resonance perfusion scans [94]. Apart from these functional alterations, no cortical volumetric MRI changes are known to exist after surgery that can relate to POCD.

Electro-Encephalo-Graphy (EEG)

EEG is a non-invasive tool for examining neuro-physiological temporal dynamics by monitoring the summation of electrical activity of multiple neuronal populations. AD is characterized by an increase of power in the lower frequencies (<4Hz δ , and 4-8Hz θ waves), reduced higher frequencies (8-13Hz α , and 13-30Hz β), and decreased synchronization of the very high frequency (30-100Hz γ -band activity) [95, 96]. These functional changes are attributable to the cholinergic cellular loss, and reflect the functional disconnection of neuro-cognitive networks leading to reduced information transmission among cortical areas.

Because impaired cognitive performance correlates with the shift of the power spectrum to lower frequencies, less complex activity, and reduced coherences among cortical regions / fast rhythms, alterations in the EEG pattern have also been used to investigate POCD. Slowed mean EEG frequency has been consistently reported following CABG, but not after major non-cardiac procedures, however its predictive value in evaluating post-surgical cerebral functional deficit is weak [97, 98].

Neuro-Psychiatric (Cognitive Function) Tests

MMSE is a widely accepted neuro-cognitive test frequently used to evaluate patients after surgical procedures as well. Scores less than 25 (out of 30) are indicative of impaired cognitive function. Although a general decline in MMSE after CABG or other types of surgery has been demonstrated in several reports, this

decrease is not clinically relevant [24] and usually lasts for a few days/weeks only, unless other neuro-psychiatric co-morbidity also develops.

Elderly patients submitted to CABG who suffered post-procedural multiple brain infarctions as identified by MRI had significantly reduced scores in the Hasegawa dementia score (HDS), a modification of MMSE, when compared to those with only small or no such lesions at all [99]. Ischemic brain lesions after valve replacement, however, produced no difference in the psychometric tests scores [90]. Considering that patients with CAD may have generalized arterial disease affecting the brain vessels as well, individuals with cerebral atherosclerosis – being a risk factor for AD and other cognitive disorders – presumably have a reduced *cognitive functional reserve capacity*, making these patients vulnerable to POCD [100]. Indeed, pre-existing cognitive impairment might influence the appearance of post-operative mental complications, and might be a significant predictor for a development of POCD following surgery [4, 101]. MMSE, therefore, could serve useful as a marker of POCD in IHD.

In addition to CABG, 54% of elderly patients with hip fracture submitted to surgery had MMSE<23 before the operation, and this figure increased to 66% the following day of the procedure, but normalized to 58% on day #5 after the intervention [102]. Moreover, a slight (*ie.* clinically not relevant) but significant reduction in MMSE was also observed in patients who underwent elective hip or knee surgery within a week [103, 104].

Interestingly, although most of the studies show a reduction in the neuro-cognitive scores after various types of surgery, carotid endarterectomy triggers a significant improvement in MMSE [105, 106] perhaps due to an increased cerebral blood-flow following the intervention.

Other Possible Markers

Neuro-Filament Heavy Chain (NfH)

Neuro-filament is a cyto-skeletal structural protein, whose heavy-chain isoform is a marker for axonal degeneration. Serum NfH is also elevated in hyper-acute brain damage, and although there is no evidence that it is a specific indicator of neuro-cognitive impairment, NfH is accumulated in different brain diseases including multiple sclerosis [107], amyotrophic lateral sclerosis (ALS) [108], vascular dementia and AD [109]. Even though it can be measured from blood and is associated with axonal and neuronal degeneration, there is yet no evidence that NfH could be used as a bio-marker for POCD. However, serum NfH is reported to be a sensitive bio-marker for diffuse ischemic brain damage following carotid endarterectomy [110].

Iso-Prostane (isoP)

β AP-induced neuro-toxicity involves uncontrolled oxidative stress that leads to excessive formation of free-radicals. Their target includes fatty acids to produce, among others, prostaglandin-like isoP. It is

not only an accurate indicator of lipid peroxidation, but also a bio-marker in AD. Although it is not specific for the disease, however isoP demonstrates the greatest increase of all CSF proteins over the course of dementia, suggesting that it is a good candidate to monitor disease progression [111].

Hypoxia

Acute anemia has been shown to result in impaired working memory and learning in older hypertensive rats [112], however this was matched by an age-dependent increase in molecular markers of cellular hypoxia, such as the hypoxia-inducible factor (*ie.* anemic hypoxia). Patients who developed cognitive deficit 4 days after laparoscopic cholecystectomy had more nitric oxide (NO) post-operatively when compared to those without POCD [113]. Over-expression of the vaso-dilator NO may alleviate cognitive disturbances caused by surgical vaso-constriction-related brain hypoxia. This is supported by the finding that polymorphism in the promoter region of inducible NO-synthase provides protection against moderate/severe cognitive dysfunction 1 month after carotid endarterectomy [114]. Decreased peri-operative regional cerebral oxygen-saturation has also been observed in post-surgical delirium [115]. These suggest that low cerebral perfusion and/or hypoxia might be an important marker for predicting post-operative delirium/POCD.

Future Markers

Several proteins have been identified as potential bio-markers in plasma and serum of AD patients reflecting a variety of patho-physiological processes. These include inflammation (cytokines, acute phase proteins, complement-factor-H), oxidative stress (isoP, homo-cystein), lipid metabolism (total cholesterol, apoE and other apo-lipo-proteins such as apoA₁, apoJ), enzymes and anti-proteases (α_1 -anti-chymotrypsin, α_2 -macroglobulin), *etc.* [20]. The majority of these constitute verified or candidate AD risk factors [116], whose potential to become clinically exploitable biological markers for cognitive dysfunction needs replication in POCD as well.

Discovery of such future bio-indicators, however, is marred by several factors. Traditional marker studies have analyzed one gene or protein at a time out of a possible ~40,000 genes or ~500,000 proteins based on a *priori* assumption on the pathogenesis of the disease. Previous reports, therefore, evaluated arbitrarily selected molecules only, and could have provided limited findings as they might have missed important ones that were not included in the study. In order to identify all possible markers, a global proteomics method has been used to assess CSF following CABG. Utilizing surface-enhanced laser desorption / ionization time-of-flight (SELDI-TOF) mass-spectrometry (MS), an analysis detected 16 proteins which were substantially altered after heart surgery. These molecules were recognized based on their mass/charge (*m/z*) ratio, and their identification is underway. Although naming of these peptides is un-resolved, the handful of these CSF markers discriminated a sub-group of individuals

from POCD, POAD or from any known cognitive disorders based on clinical characteristics and specific CSF protein profile. This new type of post-procedural neuro-psychiatric syndrome demonstrated complete separation of patients from other forms of post-surgical cognitive impairment, confirming the value of this new set of bio-markers [5]. Histo-pathological hallmarks, if any, are to be described once evaluation of brains of these patients will be available post-mortem.

CONCLUSION

Recognizing cognitive impairment is rather challenging, as their diagnosis is mainly based on subjective patient interviews and neuro-psychiatric tests. Many cases after CABG remain largely undetected or simply neglected because the underlying cardio-vascular disease or other major surgical complications appear to be more "important" or severe. The use of objective bio-markers may help prompt identification of POCD. However, although correlation between various markers and cognitive decline exists, current data are sometimes still controversial and therefore prospective confirmation of bio-indicators in controlled matched populations is warranted.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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