

I have forgotten ever having undergone heart surgery...

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Sad though it is, despite stroke and other major complications, mild neuropsychiatric disturbances frequently occur after surgical interventions. Post-operative cognitive decline (POCD) is considered a transient condition, and it may be associated with technically any type of operation, regardless of its duration, 'severity' or any other surgical variables.¹ POCD, therefore, is just as common after routine appendectomy as it is with major operations, such as esophagectomy or heart surgery.

In contrast with non-cardiac interventions, however, a higher incidence rate of more permanent post-operative cognitive disturbances is characteristic for heart operations.² This may in a small portion of cases be attributable to developing vascular dementia. Indeed, patients with coronary artery disease have atherosclerotic plaques not only in their hearts, but also ubiquitously in their bodies, including the brain. Just as these pathologic deposits in the arterial intima lead to myocardial infarction, they may also produce scattered microscopic brain lesions, causing vascular dementia (VD). Micro-embolisms during coronary artery bypass grafting (CABG) may further the pre-existing ischemic brain damage to yield multiple 'micro-strokes' resulting in post-operative VD.

More interestingly, however, the incidence of Alzheimer's disease (AD) is also strikingly increased after CABG.^{3,4} Recent findings correlate changes in biochemical and inflammatory markers after CABG with cognitive decline, suggesting a pathologic link between AD and post-CABG encephalopathy.^{5,6} However, none of the previous long-term outcome studies included a control group, and it is therefore not possible to determine whether these late cognitive changes were due to delayed effects of the use of cardio-pulmonary bypass (CPB), non-specific effects of major surgery with general anesthesia, interim central nervous system events, normal aging or some overlapping pathology.

AD is a primary neurodegenerative disorder, characterized by the deposition of β -amyloid peptide (β AP) into fibrillar, protease-resistant polymers in the brain. Constitutively secreted monomeric β AP is a non-toxic physiological protein, produced by technically all living cells. Neurons and glia secrete β AP to the neuropil and cerebrospinal fluid, whereas circulating β AP is derived from peripheral tissues, such as platelets, lymphocytes and fibroblasts. These cells release β AP upon activation by cytokines, proteoglycans etc. factors that are known to be involved in the activation of endothelial cells, arterial smooth muscle cells, lymphocytes and other cells during atherosclerosis.

Platelet dysfunction and deficiency of the microvasculature occur early during the course of AD. These disturbed elements may result in altered β AP homeostasis in the periphery. Involvement of immune cells in this process may cause communication with and stimulation of their counterparts in the brain, leading to local cerebral inflammation, characteristic of AD, and disrupted β AP metabolism. On the other hand, β AP on the periphery may induce macrophage activation and smooth muscle cells to induce atherosclerotic lesions and plaques. This inter-relation of β AP-atherosclerosis gives a positive correlation between the two disorders.

These biochemical and other epidemiological data suggest a link between both multifactorial disorders: atherosclerosis and AD.⁷ As such, it has been hypothesized that any risk factors for atherosclerosis increase the risk of developing AD and VD. But what does CABG have to do with AD?

Any stress, be it hypoxic or surgical, activates β AP-producing cells and systems and triggers a controlled inflammatory response. Stress, however, is also present in major non-cardiac operations in a degree compatible with that seen in heart surgeries. But even so, non-cardiac interventions are not associated with a higher propensity of developing AD. Non-pulsatile flow during CPB should not be specifically blamed for producing AD, since off-pump CABG (i.e., CABG with normal pulsatile perfusion without CPB) is also associated with increased AD incidence. Drugs used in the peri-operative period, including anesthetics, have also been confirmed to be irrelevant in this regard.^{8,9}

Interestingly, stress not only induces β AP secretion, but also disturbs cholesterol metabolism. Cholesterol is accused in atherosclerosis and heart disease, but has been largely understudied in relation to brain function and neural structural and functional (i.e., activity dependent) plasticity. Cholesterol is implicated in basic

synaptic function, particularly in trafficking and recycling of synaptic vesicles, receptor function, activity of accessory synaptic proteins and modulation of membrane biophysical properties.¹⁰

Physiological β AP is thought to be a functional player in the activity-dependent cholesterol neurochemical pathways and in synaptic structure-functional plasticity. The change in β AP biochemistry in AD and related disorders might be a functional, but not pathologic compensatory phenomenon aiming to counterbalance impaired cholesterol dynamics and associated neurotransmission and synaptic plasticity.¹⁰ Moreover, cholesterol has been shown to play a role in the amyloidogenic processing of the amyloid precursor protein (APP), yielding excessive β AP. Furthermore, as β AP is, in part, removed from the brain by high density lipoprotein, dyslipidemia might alter β AP clearance. This might explain why ApoE ϵ 4 is a risk factor for AD, and also why it plays an important role in atherosclerosis. Indeed, non-demented patients with atherosclerosis or coronary heart disease have more cortical AD plaques than subjects without these conditions.¹¹

Dyslipidemia, a major risk factor for atherosclerosis, therefore may play a role in this scenario during CABG. Taken together, it is reasonable to hypothesize that cardiac surgery is not a unique intervention of all types of surgeries with respect to developing AD. What makes CABG special is the underlying atherosclerotic plaque ubiquitously present in the body. A pre-existing lesion, which already is a major risk factor for AD, boosted by a major surgical stress undoubtedly precipitates AD. This is confirmed by the knowledge that pathological lesions precede by decades the clinical onset of AD. Patients with coronary artery disease (or generalized atherosclerosis) may have mild cognitive impairment even in the absence of cardiac surgery, and persons with hypertension, diabetes or other risk factors for cerebrovascular disease may show some cognitive decline over time. As such, patients who develop AD post CABG

are probably the ones who would show AD pathology later anyway, without surgery. CABG, therefore, 'only' speeds up the process of patients with preclinical AD. In these subsets of patients AD is most likely caused by a combination of normal aging and a progression of underlying cerebrovascular disease. This also confirms the cholesterol hypothesis in AD.

The present hypothesis might clarify why biomarker patterns become similar to that seen in AD within as little as 6 months after coronary heart surgery,⁵ whereas AD is a slowly progressive disorder. Furthermore, it may also confirm why not a single variable has been shown to be blamed for neuro-psychiatric changes post CABG, including anesthesia.^{8,9} The role of CABG as only an 'accelerator' in developing AD in a group of patients vulnerable to cognitive impairment with known high incidence of cerebrovascular disease also explains the insignificant differences between biomarker profiles after heart and major non-cardiac operations.¹² It is reasonable to hypothesize, therefore, that any patient in this high-risk patient group who undergoes a major non-cardiac surgery will also develop similar AD-specific changes post-operatively, and inversely, individuals without particular AD risk factors such as generalized atherosclerosis would not show AD-like pathology after heart operations. This latter cohort would include patients undergoing non-CABG interventions, for example, valve surgeries. As such, it is the underlying generalized atherosclerosis that fills the gap between surgery and POCD/AD.

Having said this, we should not sit on our laurels and 'forget' about this story. Contrary, further studies on the association among atherosclerosis, CABG and AD are necessary. It will be also of utmost importance to evaluate the aforementioned cohorts in this regard, including patients with generalized atherosclerosis undergoing major non-cardiac surgeries: on the basis of this atherosclerotic (dyslipidemia)-based theory, this group of subjects would also develop AD at a higher rate. A comparison of patients who

underwent (OP-)CABG with a demographically similar non-surgical control group with documented coronary artery disease (or generalized atherosclerosis) or an evaluation of non-coronary heart interventions, etc., would also be desirable.

And who knows, these studies may confirm in a few years' time that CABG has something specific in it to trigger AD not only in AD-prone patients.

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Duality of interest

The author declares that he has no conflict of interest.

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