The heart of the matter: a link between troponin and dementia?

Christian H. Nolte and Matthias Endres

This editorial refers to ‘High-sensitivity cardiac troponin T and cognitive function and dementia risk: the atherosclerosis risk in communities study’, by A.L.C. Schneider et al., on page 1817.

The term ‘cardiogenic dementia’ was first introduced in the Lancet some 25 years ago and was used to describe reduced cognitive function in the presence of cardiac failure. Schneider and colleagues now present novel data on the association of cardiac troponin T (cTnT) and cognitive function. High-sensitivity cTnT (hs-cTnT) assays were used to detect even minor elevations indicating subclinical myocardial damage. The authors evaluated serum samples available from 9472 individuals (mean age 63 years) of the ‘Atherosclerosis Risk in Communities (ARIC)’ population cohort without coronary heart disease, myocardial infarction, heart failure, or stroke at baseline. Strikingly, as many as two-thirds of all participants had hs-cTnT levels above the lower limit of detection (≥3 ng/L) while only 7% reached the higher pre-defined concentration (≥14 ng/L). The study combines two separate designs (i.e. cross-sectional and prospective) with the following two major findings: (i) elevations in hs-cTnT were associated with lower scores in memory and executive function tests independent of traditional risk factors; (ii) elevated hs-cTnT was also predictive for incident hospitalization with an ICDS (International Classification of Diseases 9th revision) code for dementia during a median of 13 years of follow-up. These findings were robust through several elaborate sensitivity analyses and adjustments for several potential confounders.

The authors have to be commended for their work. They present data on a large patient sample, used specific and highly sensitive assays, state-of-the-art statistical evaluation, and comprehensive measurement of confounders, and, most of all, they provide new arguments for a heart and brain interaction. Until now, the relationship of cardiac biomarkers such as hs-cTnT and dementia has received relatively little interest. Of course, cTnT is the preferred biomarker to diagnose myocardial infarction. We have to be reminded, however, that troponin release is non-specific with respect to the aetiology of cardiomyocyte injury. The advent of high-sensitivity assays and lower diagnostic cut-offs has allowed the detection of myocardial injury in several conditions unrelated to coronary ischaemia. Whatever the underlying disorder, elevated hs-cTnT has emerged as a highly relevant prognosis marker: it predicts cardiovascular risk and death in the general population, chronic coronary disease, acute or chronic cardiac disease, cerebrovascular disease, and non-cardiac disease. Schneider and colleagues now add cognitive function and the prediction of dementia to that list.

The weaknesses of the study are mostly discussed by the authors and include the fact that hospitalizations were evaluated as endpoints (instead of incident dementia) and the diagnosis of dementia was not necessarily the reason for hospitalization nor was the diagnosis validated. The primary diagnosis for hospitalization would have been of interest as many physical conditions (stroke, infection, new-onset heart failure in the absence or presence of atrial fibrillation, or renal failure) can lead to impairment of cognition. Cross-sectional analyses focused on the cognitive domains of memory and executive function, while more global scores were not included. The study used a single measurement of hs-cTnT, but measurements may vary and dynamic changes over time may help to increase the prognostic value. Lastly, there is no information on brain imaging.

Dementia has a heterogeneous aetiology in many patients, and brain imaging belongs to the diagnostic work-up. The two main dementia entities are Alzheimer’s and vascular dementia. Both conditions are preceded by a stage of cognitive impairment. Both have been linked to cardiovascular disease, and classical vascular risk factors are associated not only with vascular but also with neurodegenerative dementia. Remarkably, Schneider et al. performed analyses with subcategories of dementia within an exploratory analysis and showed that hs-cTnT is particularly associated with vascular dementia. The causative link remains open.

Several possible mechanisms may explain the link between hs-cTnT and cognitive dysfunction (Figure 1). A direct mechanism
by which troponin itself mediates cognitive decline is highly unlikely as troponin is not known to be neurotoxic. As pointed out by the authors, it is likely that shared risk factors for both myocardial and brain injury play an important role. Hs-cTnT may be a marker of atrial fibrillation, and atrial fibrillation is associated with cardio-embolic strokes. While we doubt that reductions in absolute cerebral blood flow may explain cognitive dysfunction (as clinically manifest heart failure had been excluded at baseline and left ventricular hypertrophy was adjusted for in subgroup analysis), impaired endothelial function may play a role. Endothelial function within both the heart and brain may be affected by common shared risk factors such as diabetes, hypertension, and autonomic nervous imbalance (stress). Individual susceptibility may then lead to subclinical cardiac and brain damage, leading to subtle cognitive impairment through cumulative risk factor burden. Cerebral blood vessels of the white matter play a crucial role in brain health, not only for the delivery of oxygen and nutrients, but also for trophic signalling that inextricably links the well-being of neurons and glia within the neurovascular unit. In fact, hs-cTnT is independently associated with silent brain infarcts, and both overt and covert (silent) strokes contribute to dementia. Silent strokes appear more often in patients with atherosclerotic disease. Future studies on cardiac biomarkers and cognitive dysfunction should include brain imaging to assess (silent) strokes and white matter disease.

Schneider and colleagues performed careful and thorough adjustments for known risk factors of vascular and cognitive disease including age, sex, education level, income, body mass index, physical activity, alcohol consumption, cholesterol, diabetes, systolic and diastolic blood pressure, and blood pressure-lowering medication. Additional analyses were performed to account for stroke, atrial fibrillation, left ventricular hypertrophy, and subclinical atherosclerosis (assessed by carotid intima-media thickness). Adjustment for chronic kidney disease is not reported. Renal dysfunction may explain cTnT elevations without any evidence of cardiac injury and is also associated with dementia and cerebrovascular disease. Taken together, (subclinical) kidney disease emerges as another possible link between troponin and cognitive decline.

In addition, inflammation may play an important role. Elevated levels of troponin have been found in sepsis and myocarditis. It is of note that an association of inflammation markers with
unfavourable long-term functional outcome is very likely for stroke. Inflammation induced by pathogens or of autoimmune origin is particularly harmful to terminally differentiated organs with poor regenerative capacity, such as the heart and brain. Chronic inflammation is thought to impair heart failure, neurodegenerative diseases, and metabolic syndrome.

Interestingly, increased resting heart rate has been linked to cognitive decline after ischaemic stroke. This observation is supported by animal experiments demonstrating deleterious effects of chronic stress on ischaemic brain injury mediated by increased heart rate. Interestingly, damage to the cerebral insular lobe (or ‘insula’) following stroke or subarachnoid haemorrhage causes autonomic dysfunction and sympathetic overactivation (stress), and may lead to neurocardiogenic damage and troponin elevation. Therefore, not only may subclinical myocardial injury (as reflected by elevated cTnT) lead to cognitive dysfunction, vice versa it is also possible that brain injury (associated with cognitive dysfunction) causes cardiac damage.

Finally, we think that an important contribution has been made to the heart and brain interaction. The roles of shared common harmful mechanisms (e.g. autonomic nervous imbalance, inflammation), subclinical (silent) stroke, and white matter disease need to be investigated to uncover the heart of the matter.

Conflicts of interest: none declared.

References