Markers of Cardiac Dysfunction in Cognitive Impairment and Dementia

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Abstract: Markers of cardiac dysfunction such as amino terminal pro-brain natriuretic peptide (NTpro-BNP) and high sensitivity cardiac troponin T (hs-cTnT) may be associated with dementia. However, limited data exist on their association with either pre-dementia stages, that is, cognitive impairment no dementia (CIND), or the burden of cerebrovascular diseases (CeVD).

We therefore, examined the association of these biomarkers of cardiac dysfunction with CeVD in both CIND and dementia.

A case–control study, with cases recruited from memory clinics and controls from memory clinics and community. All subjects underwent collection of blood samples, neuropsychological assessment, and neuroimaging. Subjects were classified as CIND and dementia based on clinical criteria whilst significant CeVD was defined as the presence of cortical infarcts and/or more than 2 lacunes and/or confluent white matter lesions in two regions of brain on Age-Related White Matter Changes Scale.

We included a total of 35 controls (mean age: 65.9 years), 78 CIND (mean age: 70.2 years) and 80 cases with dementia (mean age: 75.6 years). Plasma concentrations of hs-cTnT were associated significantly with CeVD in both CIND (odds ratios [OR]: 9.05; 95% confidence interval [CI]: 1.64–49.79) and dementia (OR: 16.89; 95%CI: 2.02–142.67). In addition, NTpro-BNP was associated with dementia with CeVD (OR: 7.74; 95%CI: 1.23–48.58). These associations were independent of other vascular risk factors.

In this study, we showed that plasma NTproBNP and hs-cTnT are associated with dementia and CIND, only when accompanied by presence of CeVD.

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Abbreviations: AD = Alzheimer's disease, ARWMC = age related white matter changes, MMSE = mini-mental state examination, CeVD = cerebrovascular diseases, CIND = cognitive impairment no dementia, FLAIR = fluid attenuated inversion recovery, hs-cTnT = high sensitivity cardiac Troponin T, MoCA = montreal cognitive assessment, MPRAGE = magnetization prepared rapid gradient recalled echo, MRI = magnetic resonance imaging, NTpro-BNP = amino terminal pro-brain natriuretic peptide, VaD = vascular dementia, WML = white matter lesions.

INTRODUCTION

Vascular risk factors have been increasingly implicated as a cause and contributor to cognitive impairment and dementia.[1] With respect to vascular pathology in the brain, markers of cerebral small vessel disease such as lacunar infarcts and white matter lesions are not only related to vascular dementia (VaD), but also play an important role in the development of Alzheimer's disease (AD).[2,3] Besides systemic vascular diseases such as hypertension, the presence of cardiovascular diseases including ischemic heart disease, cardiac failure, and coronary artery disease have also been linked to impaired cognitive function.[4–7] As these cardiac diseases are late manifestations of vascular pathology, early biomarkers such as amino terminal pro-brain natriuretic peptide (NTpro-BNP) and high sensitivity cardiac troponin T (hs-cTnT) have been investigated. These biomarkers are not only raised during overt myocardial stress and injury, but may also be increased during the early phases of vascular pathology.[8–11]

Previous studies have shown that raised levels of plasma NTpro-BNP were associated with cognitive dysfunction.[8,9,12] However, the majority of these studies have not assessed pre-dementia stages, that is, cognitive impairment no dementia (CIND). Furthermore, data on association of these biomarkers with respect to burden of cerebrovascular diseases (CeVD) on brain magnetic resonance imaging (MRI) are lacking. Moreover, the association between other markers of cardiac dysfunction such as hs-cTnT and cognition has not been explored.

In the present study, we examined the association of plasma levels of NTpro-BNP and hs-cTnT in relation to CIND and dementia. Furthermore, we investigated their association with CeVD as determined by MRI.

MATERIALS AND METHODS

Study Population

For the present study, we employed a case–control design. Cases (CIND and dementia) with subjective complaints of memory loss and cognitive impairment on neuropsychological assessment were recruited from two study sites in Singapore (ie, memory clinics from National University Hospital and Saint Luke's Hospital). Controls were recruited from both memory

clinics and the community (Epidemiology of Dementia in Singapore study,[13] with a similar catchment area as cases). Controls (from memory clinic and community) were defined as those with subjective complaints of memory impairment but who were cognitively normal on objective neuropsychological assessment. All subjects underwent physical, clinical, and neuropsychological assessments and neuroimaging at the National University of Singapore (NUS) from 12 August 2010 till 25 July 2013. Ethics approval for this study was obtained from National Healthcare Group Domain-Specific Review Board (DSRB). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained, in the preferred language of the participants, by bilingual study coordinators prior to their recruitment into the study.

Examination Procedures

All the subjects underwent the following examinations.

Questionnaire

A detailed questionnaire was administered to collect relevant demographic and medical information. Data collected included age, gender, education, marital status, occupation, ability to live independently, handedness, previous head trauma, smoking, alcohol consumption, and family history of dementia. Previous medical history included stroke, cardiovascular diseases, hypertension, hyperlipidemia, diabetes mellitus, vitamin B 12 deficiency, thyroid disease, urinary and bowel incontinence, Parkinson's disease, depressive symptoms, and psychiatric illnesses were noted, and subsequently verified by review of the medical records. Barthel activities of daily living indices were assessed for functional status.

Physical Examination and Clinical Assessment

Clinical assessment included physical examination (blood pressure, pulse rate), clinical history, and the Clinical Dementia Rating Scale evaluations were performed by study clinicians.

Blood Tests

NTpro-BNP and hs-cTnT concentrations were measured by electrochemiluminescence immunoassay using the NTpro-BNP and hs-cTnT assay, respectively, on an automated Cobas e411 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). Quality controls in both assays were below 2 standard deviations, with the range of concentration values detected in the samples from 5 to 20,627 pg/mL for NTpro-BNP and 3 to 201.50 pg/mL for hs-cTnT.

Neuroimaging

Magnetic resonance imaging (MRI) scans were performed on a 3T Siemens Magnetom Trio Tim scanner, using a 32-channel head coil, at the Clinical Imaging Research Centre, NUS. A number of standardized and advanced MRI brain sequences were performed to allow morphologic, microstructure and functional assessments. The sequences included T1-weighted Magnetization Prepared Rapid Gradient Recalled Echo (MPRAGE), Fluid Attenuated Inversion Recovery (FLAIR), T2-weighted and Susceptibility Weighted Imaging sequences. Scanning time was approximately 60 minutes.

MRI markers of cerebrovascular diseases were graded using the following criteria:

- Cortical infarcts were defined as focal lesions with involvement of cortical gray matter, signal following CSF intensity, hyperintense rim on FLAIR images, and tissue loss of variable magnitude, with prominent adjacent sulci and ipsilateral ventricular enlargement.[14]
- Lacunes were defined as lesions, 3–15 mm in diameter, with low signal on T1 weighted image and FLAIR; a high signal on T2 weighted image, and a hyperintense rim with center following the cerebrospinal fluid intensity.[14] Lacunes were distinguished from perivascular spaces by the absence of hyperintense rim and fluid filled lesions that follow the typical course of the vessel.[13]
- White matter lesions (WML) were graded using the Age Related White Matter Changes (ARWMC) scale.[15]
- Significant cerebrovascular disease (CeVD) was defined as the presence of cortical infarcts and/or ≥2 lacunes and/or confluent white matter lesions in two regions of the brain (ARWMC score ≥8).

Cognitive Impairment and Dementia Assessment

Neuropsychological Test Battery

Trained research psychologists administered brief cognitive tests; the Mini-]Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) and a formal detailed neuropsychological test battery which has been locally validated in Singapore.[16] This battery assesses seven domains, five of which are non-memory domains.

The non-memory domains tested were:

- Executive Function: Frontal Assessment Battery[17] and Maze Task,[18]
- Attention: Digit Span, Visual Memory Span[19] and Auditory Detection,[20]
- Language: Boston Naming Test[21] and Verbal Fluency,[22]
- Visuomotor speed: Symbol Digit Modality Test,[23] Digit Cancellation,[24]
- Visuoconstruction: Weschler Memory Scale—Revised (WMS-R) Visual Reproduction Copy task,[19] Clock Drawing,[25] and Weschler Adult Intelligence Scale—Revised (WAIS-R)subtest of Block Design.[26]

The memory domains tested are:

- Verbal Memory: Word List Recall[27] and Story Recall,
- Visual Memory: Picture Recall and WMS-R Visual Reproduction.[19]

The assessment was administered in the subject's habitual language and was completed in approximately an hour.

Diagnosis of Cognitive Impairment and Dementia

Diagnosis of cognitive impairment and dementia were made at weekly consensus meetings attended by study clinicians and neuropsychologists. The clinical features, blood investigations, psychometrics, and neuro-images were reviewed. Cognitive impairment without dementia (CIND) was defined as impairment in at least one domain of the neuropsychological test battery using education-adjusted cut-offs of 1.5 standard deviations below established normal means on individual tests. Failure in at least half of the tests in a domain constituted failure in that domain. The etiological diagnoses of

AD was made using the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) and the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l' Enseignement en Neurosciences (NINDS-AIREN) criteria for VaD and mixed dementia.[28,29]

Covariates

Risk factors such as hypertension and cardiovascular diseases were collected from physical and clinical interview and medical records and classified as present or absent. Hypertension was defined as systolic blood pressure $\geq$140 mm Hg and/or diastolic blood pressure $\geq$90 mm Hg or use of antihypertensive medications. Cardiovascular diseases were classified as a previous history of atrial fibrillation, congestive heart failure and myocardial infarction. Education was categorized as low education (years of education $\leq$6) and higher education (years of education >6).

Statistical Analysis

Statistical analysis was performed using standard statistical software (Statistical Package for Social Science, SPSS V21, SPSS, Inc., USA). Analyses of covariance or Chi-square test were used to compare the characteristics of the cases and controls groups. The levels of biomarkers of cardiac dysfunction were included as a determinant in the logistic models and were categorized into tertiles in order to secure enough numbers in each category. Dementia and its preclinical stages were taken as outcome. Multiple logistic regression analysis with odds ratios (OR) and 95% confidence interval (CI) were computed initially for CIND and dementia. Further regression analysis was then constructed for both CIND and dementia stratified by CeVD on MRI. The models were initially adjusted for age, gender, education, and additionally for hypertension and cardiovascular diseases. *P* value <0.05 was considered significant.

RESULTS

A total of 259 subjects (49 controls, 98 CIND, and 112 dementia) were recruited into this study, of whom sufficient blood samples were available in 193. Table 1 shows the baseline characteristics of the controls (n = 35) and subjects with CIND (n = 78) or dementia (n = 80). Compared to controls, subjects with CIND or dementia were older, had lower education, and had higher prevalence of hypertension and diabetes. Among the 78 subjects with CIND, 37 were classified as having significant CeVD on MRI. For the 80 cases with dementia, there were 46 subjects with significant CeVD, that is, 31 AD and 15 VaD. Plasma levels of these markers of cardiac dysfunction were raised in individuals with atrial fibrillation, myocardial infarction and congestive heart failure.

Table 2 shows the association between markers of cardiac dysfunction and cognitive impairment. A trend of association was observed from CIND to dementia with higher tertiles of NTpro-BNP and hs-cTnT after adjustment for age, gender, education, hypertension, and cardiovascular diseases. However, these associations remained non-significant for both the markers of cardiac dysfunction with cognition.

Table 3 shows the relationship of markers of cardiac dysfunction with CIND and dementia stratified by presence and absence of CeVD. Higher tertiles of hs-cTnT was associated with both cognitive impairment and dementia in patients with significant CeVD whereas the higher tertiles of NTpro-BNP was only associated with dementia with significant CeVD. These associations remain unaltered after correcting for all the covariates. Further adjustment with age^2 yielded similar association.

DISCUSSION

In this study, we found that the biomarkers of cardiac disease such as NTpro-BNP and hs-cTnT were associated with cognitive impairment and dementia in patients with significant CeVD, independent of other vascular risk factors.

Coronary heart disease and congestive heart failure have been previously associated with impaired cognitive function.[30–32] However, by the time cognitive impairment becomes clinically apparent significant cerebral damage may have already occurred in the brain.[33,34] Hence, early markers of cardiac dysfunction such as NT-proBNP and hs-cTnT are of interest so that timely interventions may be employed. NT-proBNP is secreted from the cardiomyocytes primarily in response to cardiomyocyte stretch whereas hs-cTnT is a sensitive and specific marker for myocardial injury with established clinical application in the diagnosis of acute myocardial infarction. Several studies have shown that NT-proBNP is associated with cognitive decline and dementia.[9,35,36] These associations remain unaltered in individuals with[8] and without history of cardiovascular risk factors.[35] With respect to pre-dementia stages, there is some data to suggest that NT-proBNP was

TABLE 1. Baseline Characteristics of the Participants Based on Their Cognitive Categories (n = 193)

Characteristics	Controls (n = 35)	CIND (n = 78)	Dementia (n = 80)	*P* Value
Age, years, mean (SD)	65.9 (6.3)	70.2 (9.6)	75.6 (8.2)	**<0.001**
Female, no. (%)	15 (42.9)	34 (43.6)	46 (57.5)	0.15
Education, primary $\geq$6, no. (%)	13 (37.1)	36 (46.2)	59 (73.8)	**<0.001**
Hypertension, no. (%)	23 (65.7)	58 (74.4)	69 (86.3)	**0.03**
Hyperlipidemia, no. (%)	21 (60)	60 (76.9)	59 (73.8)	0.17
Diabetes, no. (%)	8 (22.9)	27 (34.6)	39 (48.8)	**0.02**
Smoking, no. (%)	10 (28.6)	29 (37.2)	22 (27.5)	0.39
Cardiovascular disease, no. (%)	3 (8.6)	16 (20.5)	19 (23.8)	0.17
Pro brain natriuretic peptide, mean (SD), pg/mL	101.6 (116.6)	242.8 (370.2)	450.8 (726.1)	**<0.001**
High sensitivity Troponin T, mean (SD), pg/mL	8.9 (6.5)	12.5 (9.4)	15.3 (9.9)	**<0.001**

CIND = cognitive impairment no dementia, SD = standard deviation, no. = number, pg/mL = picogram/milliliters.

TABLE 2. The Association Between Markers of Cardiac Dysfunction (Tertiles) and Cognitive Impairment Expressed as Odds Ratios With 95% Confidence Intervals

	CIND (n = 78) OR (95% CI)[*]	Dementia (n = 80) OR (95% CI)[*]
Pro brain natriuretic peptide		
1st tertile	1	1
2nd tertile	1.52 (0.57–4.04)	0.79 (0.23–2.69)
3rd tertile	3.12 (0.61–15.99)	5.44 (0.98–30.21)
High sensitivity Troponin T		
1st tertile	1	1
2nd tertile	1.64 (0.60–4.43)	1.04 (0.27–4.01)
3rd tertile	2.66 (0.69–10.29)	4.13 (0.83–20.51)

CI = confidence interval, CIND = cognitive impairment no dementia, OR = odds ratios.
[*] Adjusted for age, gender, education, hypertension, and cardiovascular diseases (atrial fibrillation, congestive heart failure, and myocardial infarction).

associated with progression from mild cognitive impairment to AD.[37] Moreover, for the subtypes of dementia, two studies showed a stronger association with VaD compared to AD.[9,12] Nevertheless, these studies were limited by either none or low resolution (1.5T) MRI neuroimaging to objectively supplement the diagnosis of dementia and a neglect of the pre-dementia stages of cognitive impairment. Furthermore, there are no previous reports on the association of hs-cTnT with cognitive impairment and dementia.

Our study adds further to the existing literature by showing significant association of markers of cardiac dysfunction with cognitive impairment only in the presence of CeVD. It has been suggested that the left ventricular dysfunction and ischemic heart disease not only releases these biomarkers but also activates several other inflammatory markers which leads to ischemic damage in regions selective to cognitive function.[38] NT-proBNP has been previously correlated with silent brain infarcts and white matter lesions in individuals with subclinical brain injury.[10] Moreover, higher level of NT-proBNP is also linked to atrial fibrillation[39] which in turn is associated with cardioembolic stroke[40] and reduced cognitive function.[41] Our findings thus are consistent with those reported previously

where NT-proBNP was significantly associated with VaD[9,12] and AD with CeVD indicating significant cerebrovascular damage to the brain. These associations remain significant after accounting for atrial fibrillation, ischemic heart disease, and congestive heart failure.

Our study has several limitations. First, as these data were examined cross-sectionally it is not possible to establish the temporal association between these markers of cardiac dysfunction and the development of cognitive impairment. Second, we were unable to examine the association with VaD separately due to small numbers. Third, cases and half of the controls were derived from 2 locations, memory clinic and community, although representative of the elderly population in Singapore. The control group was relatively younger and had less burden of CeVD compared to cognitively impaired individuals which could have resulted in selection bias and residual confounding. Also there is a higher burden of vascular risk factors (hypertension, hyperlipidemia, and diabetes) in our sample which limits generalizability of the results to the general population. Fourth, due to lack of power it is possible that we were unable to detect the associations of these markers of cardiac dysfunction with CIND and dementia without the presence of CeVD.

TABLE 3. The Association Between Markers of Cardiac Dysfunction (Tertiles) and Cognitive Impairment Stratified by Significant Cerebrovascular Diseases Expressed as Odds Ratios With 95% Confidence Intervals

	Presence of Significant Cerebrovascular Diseases			
	Absence		Presence	
	CIND (n = 37), OR (95% CI)[*]	Dementia (n = 34), OR (95% CI)[*]	CIND (n = 41), OR (95% CI)[*]	Dementia (n = 46), OR (95% CI)[*]
Pro brain natriuretic peptide				
1st tertile	1	1	1	1
2nd tertile	0.87 (0.28–2.77)	0.51 (0.11–2.39)	2.35 (0.72–7.66)	1.50 (0.38–5.99)
3rd tertile	2.52 (0.44–14.35)	4.77 (0.63–36.06)	4.59 (0.75–27.93)	7.74 (1.23–48.58)
High sensitivity Troponin T				
1st tertile	1	1	1	1
2nd tertile	0.96 (0.28–3.29)	0.61 (0.12–3.08)	4.36 (1.14–16.71)	3.62 (0.47–27.69)
3rd tertile	1.35 (0.28–6.47)	3.82 (0.55–26.38)	9.05 (1.64–49.79)	16.89 (2.02–142.67)

CI = confidence interval, CIND = cognitive impairment no dementia, OR = odds ratios.
[*] Adjusted for age, gender, education, hypertension, and cardiovascular diseases (atrial fibrillation, congestive heart failure, and myocardial infarction).

Strengths of the study include; extensive neuropsychological assessment to diagnose cognitive impairment and dementia, availability of 3T neuroimaging to grade and classify individuals with significant CeVD.

CONCLUSIONS

In conclusion, we showed that subjects with higher concentrations of NTpro-BNP and hs-cTnT were more likely to be cognitively impaired only in the presence of cerebrovascular disease independent of vascular risk factors. This suggests that raised markers of cardiac dysfunction may help identify patients at risk for developing cerebrovascular disease-associated cognitive decline and dementia. Our study provides further insights into the pathophysiology of cognitive impairment and dementia for which vascular pathology has long been implicated. Further prospective studies are needed to unravel the additional value of markers of cardiac dysfunction in predicting cognitive decline and if they may serve as surrogate outcomes in evaluating the effectiveness of novel cerebrovascular disease related dementia treatments.

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