Relationship between Cognitive Impairment and Echocardiographic Parameters: A Review

Dimitri Arangalage, MD, Stéphane Ederhy, MD, Laurie Dufour, MD, Jérémie Joffre, MD, Clélie Van der Vynckt, MD, Sylvie Lang, PhD, Christophe Tzourio, MD, PhD, and Ariel Cohen, MD, PhD, *Paris and Bordeaux, France*

With >24 million people affected worldwide, dementia is one of the main public health challenges modern medicine has to face. The path leading to dementia is often long, with a wide spectrum of clinical presentations, and preceded by a long preclinical phase. Previous studies have demonstrated that clinical strokes and covert vascular lesions of the brain contribute to the risk for developing dementia. Although it is not yet known whether preventing such lesions reduces the risk for dementia, it is likely that starting preventive measures early in the course of the disease may be beneficial. Echocardiography is a widely available, relatively inexpensive, noninvasive imaging modality whereby morphologically or hemodynamically derived parameters may be integrated easily into a risk assessment model for dementia. The aim of this review is to analyze the information that has accumulated over the past two decades on the prognostic value of echocardiographic factors in cognitive impairment. The associations between cognitive impairment and echocardiographic parameters, including left ventricular systolic and diastolic indices, left atrial morphologic parameters, cardiac output, left ventricular mass, and aortic root diameter, have previously been reported. In the light of these studies, it appears that echocardiography may help further improve currently used risk assessment models by allowing detection of subclinical cardiac abnormalities associated with future cognitive impairment. However, many limitations, including methodologic heterogeneity and the observational designs of these studies, restrict the scope of these results. Further prospective studies are required before integrating echocardiography into a preventive strategy. (J Am Soc Echocardiogr 2014;■:■-■.)

Keywords: Echocardiography, Mild cognitive impairment, Dementia, Prevention

Since the early 1990s, many cross-sectional and longitudinal epidemiologic studies have revealed an association between vascular factors, including clinical, biologic, and echocardiographic parameters, and risk for cardiovascular events. The results of these studies have allowed the stratification of patients according to their individual risk, the aim being to develop treatments and preventive measures for use at an early stage of the disease.

With >24 million people affected worldwide and considering the increasing life expectancy of the population, dementia is becoming one of the main public health challenges modern medicine has to face.[1] It is one of the primary causes of loss of autonomy and institutionalization of elderly patients in many countries.[1] The path leading to dementia is often long, with a wide spectrum of initial clinical presentations. Moreover, an extended period exists during which subjects do not exhibit clinically noticeable symptoms despite the presence of neurodegenerative lesions.[2] Identifying early determinants of this process may lead to the initiation of specific treatments to slow the progress of the disease.[3] More particularly, clinical strokes and covert vascular lesions of the brain contribute to the risk for developing all types of dementia.[4-6] Although it is not yet known whether preventing such lesions reduces the risk for dementia, it is very likely that starting preventive measures early in the course of the disease may be beneficial. Prevention has had a significant role in the decline of many cardiovascular diseases, and the application of such measures to cognitive impairment could have major medical and economic impacts.[7,8]

An increasing volume of information has accumulated over the past two decades on the prognostic value of echocardiographic factors in cognitive impairment. In this article, we seek to provide an up-to-date review on the link between the two.

From the Service de Cardiologie, Hôpital Saint Antoine, Assistance Publique – Hôpitaux de Paris, Paris, France (D.A., S.E., L.D., J.J., C.V.d.V., S.L., A.C.); University Paris 6, Faculté de Médecine Pierre et Marie Curie, Paris, France (D.A., L.D., C.V.d.V., A.C.); and INSERM Research Center for Epidemiology and Biostatistics (U897), Team Neuroepidemiology, and University of Bordeaux, Bordeaux, France (C.T.).

Dr Tzourio has received fees from Fondation de Recherche sur l'Hypertension Artérielle for participating in a scientific committee. Dr Cohen has received a research grant from RESICARD (research nurses) and consulting and lecturing fees from AstraZeneca, Bayer Pharma, Boehringer Ingelheim, Daiichi-Sankyo, GlaxoSmithKline, and Sanofi. All other authors report no conflicts of interest.

Reprint requests: Ariel Cohen, MD, PhD, Department of Cardiology, Saint Antoine University and Medical School, Université Pierre et Marie Curie, 184 rue du Faubourg Saint-Antoine, 75571 Paris Cedex 12, France (E-mail: *ariel.cohen@sat.aphp.fr*).

0894-7317/$36.00

http://dx.doi.org/10.1016/j.echo.2014.11.009

CLINICAL DETERMINANTS OF COGNITIVE IMPAIRMENT

The main clinical factors associated with cognitive impairment are advanced age, hypertension, diabetes mellitus, high plasma cholesterol levels, obesity, tobacco smoking, and the presence of atherosclerotic vascular disease.[9-14] In addition to these risk factors,

Abbreviations

AF = Atrial fibrillation

CO = Cardiac output

GLS = Global longitudinal strain

LA = Left atrial

LV = Left ventricular

LVEF = Left ventricular ejection fraction

MRI = Magnetic resonance imaging

hyperhomocysteinemia, diets comprising high levels of saturated fats, excessive alcohol consumption, and physical inactivity increase the risk for developing Alzheimer's disease.[15] These risk factors are also associated with an increase in the incidence of cerebrovascular diseases.[15] Although the exact mechanisms are still unknown, heart failure[16,17] and the occurrence of acute coronary syndromes[18] are also associated with risk for cognitive impairment, probably because of the increased risk for vascular disease in this category of patients.[19] The occurrence of cardioembolic strokes and reduced cardiac output (CO) leading to decreased cerebral perfusion may also explain the increased risk for cognitive impairment in patients with heart failure.[16,17] Atrial fibrillation (AF) is also independently associated with the onset of cognitive impairment and Alzheimer's disease, although the exact mechanism explaining this link remains unclear.[20,21] With an annual incidence of 4.5%, AF is the primary cause of ischemic stroke, causing up to 15% of reported events.[22] The development of brain imaging techniques including magnetic resonance imaging (MRI) has revealed the occurrence of silent brain infarctions in patients with AF, causing damage to the brain parenchyma, leading to further cognitive impairment.[21] Moreover, patients with mild cognitive impairment face an increased risk for conversion to dementia if they have associated diagnoses of AF.[23] Another important determinant of cognitive impairment is the presence of cerebral white matter lesions detected on brain MRI. These lesions are associated with reduced performance of many cognitive functions, such as executive functions, processing speed, and immediate and delayed memory.[24,25]

COGNITIVE IMPAIRMENT RISK EVALUATION MODELS

It is now accepted that a preclinical phase exists in dementia, hence the early identification of patients at risk for developing the disease is likely to be a key step.[2] In 2006, Kivipelto *et al.*[26] proposed a cognitive impairment risk evaluation model, the Cardiovascular Risk Factors, Aging and Dementia risk score, to predict the 20-year risk for dementia in middle-aged people. This model stratifies patients by age, sex, education, hypertension, body weight, physical activity, hyperlipidemia, and apolipoprotein E genotype.[27] Since then, several studies have assessed the usefulness of different risk scores to predict the onset of cognitive impairment and dementia.[28-34] It is worthy of note that most of the risk factors associated with dementia used in these algorithms, such as diabetes mellitus, hypertension, hypercholesterolemia, and obesity, are modifiable and are shared with cardiovascular diseases, illustrating the close link between the brain and the heart.[13,35-41] This link was further strengthened when the Framingham general cardiovascular disease risk score and the Framingham stroke risk score were compared with the Cardiovascular Risk Factors, Aging and Dementia risk score.[27] Following the examples of risk scores used in AF, acute coronary syndromes, or cardiac surgical risk evaluation algorithms, creating a multimodal risk evaluation model on the basis of various parameters including ultrasound-based measures is an appealing idea that may help further enhance our capacity to predict cognitive impairment. However, the usefulness of integrating echocardiographic parameters in a cognitive impairment risk evaluation model has never been assessed.

CONVENTIONAL ECHOCARDIOGRAPHIC PARAMETERS OF THE LEFT VENTRICLE AND COGNITIVE IMPAIRMENT

The presence of a heart disease may alter left ventricular (LV) function, leading to a reduction in cerebrovascular blood flow causing subclinical brain injury and cognitive impairment.[42-45] It was described previously that patients with severe chronic heart failure may have reduced cerebral blood flow, by approximately 30%, despite the activation of physiologic neurohormonal counterregulatory mechanisms such as the renin-angiotensin system and the sympathetic nervous system.[46]

LV Systolic Function

LV systolic dysfunction, measured by the LV ejection fraction (LVEF), appears to be particularly correlated with cognitive impairment (Table 1, Figure 1).[47-53] Jerskey *et al.*[49] found that reduced sustained attention and vigilance is correlated with an LVEF ≤ 55%. In the Framingham Heart Study cohort, comprising participants free of stroke or dementia, a nonlinear association between LVEF and measures of cognitive impairment was suggested.[48] In that study, LVEF was not linearly associated with white matter lesions on brain MRI or with any neuropsychological variables, although patients in the lowest and highest LVEF quintiles had abnormal cognitive changes.[48] Interestingly, patients belonging to the highest LVEF quintile also had a significant association with reduced cognitive functions in verbal and visuospatial memory, executive functioning, and visuoperceptual abilities. This association persisted despite adjustment for many confounding factors and after the inclusion of multiple covariates. The exact mechanism explaining this phenomenon is unknown.[48] Furthermore, an increased risk for future cognitive impairment and stroke is associated with white matter lesions and silent brain infarcts.[5,54-57] It is worth mentioning that in several studies, an association between white matter lesions on brain MRI and LV systolic dysfunction has been demonstrated.[42,58,59]

Recently, Russo *et al.*[60] published the first article studying the association between LV global longitudinal strain (GLS) and subclinical brain disease in a community-based cohort (Table 1). The definition of an abnormal LV GLS value was based on a measure lower outside the 95th percentile of the LV GLS distribution in a subgroup of healthy participants and corresponded to LV GLS ≥ −14%. This article highlighted an association between lower LV GLS and the existence of subclinical cerebral white matter lesions on brain MRI in subjects without dementia symptoms and without overt cardiac disease independently of LVEF. Moreover, significantly lower LV GLS values were observed in participants with silent brain infarcts despite having similar LVEF values.[60]

LV Diastolic Function

LV diastolic dysfunction appears particularly associated with lower cognitive function in patients with heart diseases (Table 1).[47,61] Van den Hurk *et al.*[47] showed, in a cohort of healthy people, that LV diastolic dysfunction assessed by E/e′ ratio[62-64] at baseline was associated with lower scores on attention and executive functioning at follow-up. Similarly, in a population of patients with cardiovascular