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Original Research Article

Cardioprotection and Anticholinesterases in Patients with Alzheimer's Disease: Time for Reappraisal

Fiammetta Monacelli^a Patrizio Odetti^a Marina Sartini^c
Antonello Parodi^b Claudio Brunelli^b Gianmarco Rosa^b

Sections of ^aGeriatrics and ^bCardiology, Department of Internal Medicine and Medical Specialties (DiMI), and ^cDepartment of Health Sciences (DISSAL), University of Genoa, Genoa, Italy

Key Words

Vortex formation index · Diastolic dysfunction · Alzheimer's disease · Anticholinesterase therapy · Cardiovascular protection

Abstract

Background/Aim: Traditional risk factors, like impaired transmitral flow in diastolic filling [vortex formation time (VFT) as echocardiographic parameter], contribute to Alzheimer's disease (AD). Moreover, we observed that acetylcholinesterase inhibitors provide a significant cardioprotection. We assessed the pathogenetic role of VFT as early cardiovascular risk factor in 23 AD patients and 24 controls. **Results:** The results showed no statistical difference between the two groups, but the VFT values were significantly lower in nontreated AD patients, and higher value were observed in AD patients treated with anticholinesterases. **Conclusions:** The results support the beneficial effects of anticholinesterases on the cardiovascular system of AD patients. Thus, the transition to evidence-based medicine and an in vivo model of cardiomyocytes might strengthen these results.

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Introduction

In the Western world, Alzheimer's disease (AD) is growing exponentially due to the aging population [1], and the prevalent sporadic form is the result of an entangling genetic and epigenetic pathway to which several cardiovascular risk factors significantly contribute [2].

Fiammetta Monacelli, MD, PhD
Department of Internal Medicine and Medical Specialties (DiMI)
Viale Benedetto XV, 6
IT-16132 Genoa (Italy)
E-Mail Fiammetta.Monacelli@unige.it

Literature data have clearly shown a pathogenetic association between AD and traditional cardiovascular risk factors such as hypertension, diabetes, atherosclerosis, dyslipidemias and stroke [3, 4], enlarging the diagnostic overlap between AD, vascular dementia, and mixed dementia [5]. A common susceptibility gene to shared risk factors may account for a higher coincidence of AD and vascular dementia [6, 7]. In addition, atrial fibrillation [8] and subclinical heart disease [9] have been regarded as important cardiovascular contributors to AD.

Recently, de La Torre [10] showed that carotid ultrasound and echocardiography are effective screening tools to detect carotid artery narrowing and persistent low heart-to-brain blood flow (low cardiac output or low ejection fraction), known to promote cognitive impairment and AD, anticipating the possible diagnosis before the clinical onset of the disease.

Impaired diastolic filling has also been regarded as a specific risk factor for AD. Specifically, a study by Belohlavek et al. [11] reported an impaired transmitral flow efficiency of diastolic filling, measured by an echocardiographic parameter such as the vortex formation time (VFT), as a distinguished hemodynamic parameter to assess the cardiovascular risk in AD patients. Altered diastolic relaxation, which displayed an age-related decline [12], may result in a significant hampering of diastolic filling, heralding a diastolic failure in AD patients [11].

Acetylcholinesterase inhibitors have been reported to have harmful effects on the heart [13], but to also own significant protective effects [14]. According to these premises, we conducted a clinical study on a sample of patients affected by mild-to-moderate dementia of the Alzheimer type, based on NINCDS-ADRDA criteria [15], in order to assess the pathogenetic role of the echocardiographic VFT parameter of altered diastolic function as early and specific cardiovascular risk factor in AD.

Materials and Methods

During a 6-month period (January to June 2013), 23 patients affected by mild-to-moderate AD dementia and followed by dementia clinics of the IRCCS University Hospital S. Martino, Genoa, Italy, and 24 age-matched and healthy, nondemented (ND) controls were enrolled. The study was approved by the Institute's Committee on Human Research, and ethical safeguards and protocols were followed. Written informed consent was obtained prior to the start of the study. Clinical characteristics of the patients, including major cardiovascular ailments, are summarized in table 1. AD patients were further divided in patients receiving a symptomatic anticholinesterase therapy (n = 10, treated AD patients) and AD patients receiving no symptomatic therapy (n = 13, nontreated AD patients). Exclusion criteria were applied for brain-related neurological or psychiatric comorbidity, such as epilepsy, cerebral infarction or hemorrhage, brain tumors, or brain traumas, neurological degenerative disorders, major depression or psychotic disorders as well as clinical instability.

All patients underwent a standard transthoracic echocardiography with second-harmonic imaging. Recordings were made with the patient in the left lateral decubitus position during quiet respiration. The 2-dimensional and Doppler recordings were made in standard parasternal and apical views. Recording and measurements of the M-mode, 2-dimensional and diastolic-systolic function (thickness, diameters, volumes, ejection fraction, pulmonary systolic arterial pressure) were performed according to the recommendations of the American Society of Echocardiography [16].

VFT was defined based on the physics of fluid ejected from a piston/cylinder setup [17] as $VFT = U_t/D \times t$, where U_t is the time-averaged speed of the fluid flow in centimeters per second; t is the duration of fluid ejection, and D is the diameter of the mitral annulus in centimeters [18] obtained in our study as the mean of the largest diameters measured during early diastolic filling in the 2-, 3-, and 4-chamber views. Since the vortex ring of interest forms in the

Table 1. Clinical characteristics of the patients in the three examined groups

Clinical parameters	Treated AD patients (n = 10)	Nontreated AD patients (n = 13)	Age-matched controls (n = 24)	χ^2 * or KW value#, p value
Age, years	83.10±0.95	83.62±1.47	76.04±2.32	p = n.s.
Gender, M/F	4/6	5/8	6/18	
Polypathology (GIC score)	1.88±0.11	1.69±0.17	0.82±0.38	KW: 25.95, p < 0.0001
MMSE score	18.60±4.37	21.62±1.47	29.08±0.21	KW: 22.96, p < 0.0001
Hypercholesterolemia, %	0	0	10	n.s.
Hypertension, %	36	36	40	n.s.
Diabetes, %	18	18	1.2	n.s.
Ischemic cardiopathy, %	18	18	1.2	n.s.

Data are expressed as mean ± SEM. GIC = Geriatric Index of Comorbidity.

* χ^2 contingency analysis. # When comparing three parameters, the KW nonparametric analysis of variance was used. p < 0.05 was considered statistically significant.

Table 2. VFT parameter in the three examined patient groups

Parameter	Treated AD patients (n = 10)	Nontreated AD patients (n = 13)	Age-matched controls (n = 24)	KW value#, p value
VFT	4.33±0.31	2.95±0.42	3.28±0.39	KW 6.13, p < 0.04

KW nonparametric analysis of variance.

early phase of diastolic filling, the term $U_t \times t$ can be represented by the echocardiographically measured time velocity integral during the E-wave component (TVIE) of the left ventricular filling in centimeters [19], and the VFT then becomes an index defined as $VFT = TVIE/D$ [17].

All patients showed normal right and left ventricular dimensions and volumes as well as preserved systolic function (ejection fraction), respectively. No significant cardiac valvulopathy was detected (stenosis or valvular regurgitation). Neither pulmonary hypertension nor advanced diastolic dysfunction (pseudonormal restrictive diastolic pattern) was detected in all examined subjects (echocardiographic parameters are not shown). Thus, the patients did not display any cardiac interfering factor with VFT measurement, confirming an age-related impairment in diastolic relaxation.

VFT was calculated according to the formula derived by Gharib and colleagues [20, 21] and measured in treated AD patients, nontreated AD patients and ND age-matched controls, as shown in table 2.

Results

Our results showed no statistical significant difference of the mean VFT value between AD patients and age-matched controls (3.64 ± 0.27 vs. 3.57 ± 0.47 ; $U = 232.5$; p = n.s.). The data are in net contrast with the report of Belohlavek et al. [11], which addressed a more

pronounced diastolic impairment (altered filling and/or relaxation) in AD patients as a specific cardiovascular risk factor, speculating on a possible suboptimal intraventricular blood rheologic process responsible for ultimate brain dysfunction in this subset of patients.

According to our results, this information seems questionable, since all examined patients displayed similar diastolic patterns, whose slight alteration may be attributable to the age-related diastolic impairment.

However, when patients are divided according to the acetylcholinesterase inhibitors treatment, the results showed a significant difference of the mean VFT value among the treated AD patients (4.33 ± 0.31), nontreated AD patients (2.95 ± 0.42) and the age-matched controls (3.28 ± 0.39) [Kruskal-Wallis (KW) 6.13; $p < 0.04$].

The mean VFT values displayed a medium score in the ND control group, a lower value in nontreated AD patients and, intriguingly, a significant higher value in AD patients treated with anticholinesterases (a 9.5 mg/24 h rivastigmine patch for at least 6 months).

Discussion

Surprisingly, the present data allow some interesting speculations, when analyzed in detail. The VFT echocardiographic parameter is to be considered normal within a range of 3–5, according to a recent study by Kheradar et al. [22]; however, the lower the value, the higher is the risk of impaired diastolic filling and dysfunction. Thus, applying this paradigm and extrapolating our data, it seems that AD patients treated with anticholinesterases would display a better diastolic performance even compared to healthy ND controls. The data may turn to be innovative, since the patients are matched for age, comorbidity, and cardiovascular ailments but not for symptomatic therapy for AD. Thus, it may be inferred that anticholinesterases would confer a protection toward diastolic dysfunction and progression towards diastolic heart failure, at least in demented patients with a low-to-moderate grade of cardiovascular comorbidity.

This speculation receives scientific support in a recent study by Sato et al. [23], which showed, retrospectively, the protective role of donepezil treatment in moderate-to-severe AD on overall cardiovascular mortality. The physiopathology is still partially elucidated, pointing out some prevailing hypothesis. Thus, the enhanced heart acetylcholine availability might counterbalance the diminished cardiac vagal activity, associated with poorer cardiac outcome [24]; interestingly, recent studies have suggested that the antiarrhythmic effect of vagal stimulation was paralleled by the preservation of phosphorylated connexin 43 protein, responsible for the age-related heart calcium downregulation and known for hampering the heart sinus node and conduction system [25, 26]. Furthermore, increased acetylcholine may protect cardiomyocytes from acute hypoxia and ischemia [27] with endothelial dysfunction [28] even inducing a direct cardiac cell acetylcholine synthesis [29, 30].

Moreover, availability increased by acetylcholine has been shown to have a positive impact on heart rate variability, and cardiac autonomic balance [31, 32] as well as anticholinesterase therapy in AD have demonstrated to increase low frequency/high frequency, modulating the autonomic function [33, 34]. Then, it may be conceivable that the optimal trans-mitral flow preserves the cardiac electric conduction system and the diastolic filling while an impaired flux may account for altered blood vortex formation, altered diastolic relaxation, and increased thrombus formation representing an early and reliable cardiovascular risk factor.

In conclusion, the present study has limitations due to the small size of the study cohort and to the low number of patients with cardiac comorbidity. Nevertheless, the results support a growing body of evidence on the beneficial effects of anticholinesterases on cardiovascular

morbidity and mortality in patients with dementia. Thus, a further clinical and experimental insight in this field is plausible: the transition from observational to randomized controlled trial studies may provide higher levels of evidence, and the setup of an in vivo model of cardiomyocytes exposed to pharmacological doses of anticholinesterases may strengthen the data, overturning the role of anticholinesterases in dementia from 'prone to cardiac side effects to cardioprotective and highly recommended'.

Disclosure Statement

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