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Objective cardiac markers in dementia: Results from the Kerala-Einstein study

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Alzheimer's disease (AD) and vascular dementia (VaD), the most common causes of dementia worldwide, share many vascular risk factors. Atrial fibrillation and myocardial infarction on electrocardiogram (ECG) has been associated with AD and VaD [1, 2]. Left ventricular hypertrophy (LVH) on echocardiogram was linked to cognitive dysfunction [3, 4]. Echocardiographic LVH and aortic valve (AV) regurgitation are related to AD [5]. However, previous studies are limited by small samples [5, 6], restriction to single diseases [3, 6], not examined both ECG and echocardiogram abnormalities [1–6], or focused on single ECG abnormalities [1, 2]. Importantly, almost no research on cardiac markers in dementia has been conducted in developing countries.

Hence, we studied association of ECG and echocardiogram abnormalities with dementia in older adults participating at the Kozhikode site of the Kerala Einstein Study (KES) in the southern Indian state of Kerala. Participants with dementia were identified from neurology clinics. A control sample of cognitively normal adults was recruited from relatives of patients and patients with non-cognitive complaints. Inclusion criterion was age 55 and older. Exclusion criteria included severe audiovisual loss or presence of active medical or

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These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Conflicts of interest: None

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psychiatric illnesses. Informed consent was obtained from all participants and study protocols were approved by the local institutional review board.

Standard 12-lead ECG was analyzed following the Minnesota code classification by a study clinician, blinded to dementia status. The following abnormalities were reported: rhythm abnormalities, LVH, significant ST and T wave changes, Q waves, heart block, and bundle branch block. Major ECG abnormalities was defined as presence of any one of the following: Q-QS wave abnormalities, LVH, Wolff-Parkinson-White syndrome, complete bundle branch block or intraventricular block, atrial fibrillation or atrial flutter, or major ST-T changes. Agreement with original classification in a random sample of 5% of baseline ECG read by an independent cardiologist was good to excellent (Intra Class Correlations 0.45 to 0.93).

Transthoracic 2D echocardiograms were done by two cardiologists, who were not part of the KES team, and blinded to cognitive status. We examined LVH, valvular lesions and reduced left ventricular ejection fraction.

Descriptive statistics were used to compare dependent variables by dementia status and subtypes. Logistic regression analysis was used to report odds ratios (OR) with 95% confidence intervals (CI) for the association of ECG and echocardiographic abnormalities with dementia, adjusted for age, gender, and years of education.

Of the 360 participants enrolled in KES, 305 received ECG and 302 echocardiograms. Of the 305 subjects, 161 were men (52.8%), mean age was 68.4 years, and mean education 8 years. Sixty-six participants were diagnosed with dementia at consensus case conferences: 34 AD, 29 VaD, and three unclassified.

Baseline characteristics are presented in Table 1. Participants with dementia, AD, and VaD were older, less educated, and had worse cognitive scores than controls. The AD group had more women. There was a higher prevalence of hypertension and cerebrovascular disease in VaD. AD patients had lower prevalence of ischemic heart disease than controls.

Common ECG abnormalities in dementia subjects were ST/T wave changes (16.7% vs. 7.1% controls), LVH (13.6% vs. 3.8%), Q waves (3.0% vs. 3.3%), and bundle branch block (3.0% vs. 3.8%). There was no heart block. Only one control had atrial fibrillation. Prevalence of major ECG abnormalities was 28.8% in dementia and 15.9% in controls ($p = 0.037$).

Table 2 shows that LVH was associated with dementia (OR 4.53, 95% CI 1.52–13.51). LVH (OR 11.74, 85% CI 3.15–43.71) and ST/T abnormalities (OR 3.06, 95% CI 1.06–8.85) were associated with VaD. Major ECG abnormalities were associated with VaD (OR 4.25, 95% CI 1.79–10.11). The results were not materially different after excluding controls with mild cognitive impairment syndrome.

Common echocardiographic findings in dementia were LVH (43.8% vs. 35.3% controls), AV sclerosis (32.8% vs. 16.5%), AV regurgitation (21.9% vs. 9.7%), and reduced ejection fraction (10.9% vs. 8.8%). VaD was associated with LVH (OR 4.33, 95% CI 1.79–10.45). Valvular abnormalities and reduced ejection fraction were not associated with dementia status.

In this clinic-based sample of Indian seniors cardiac markers were associated with dementia, especially VaD. Previous cardiac marker studies have focused on AD [1, 2, 5] or do not distinguish dementia subtypes [4, 6]. ECG and echocardiogram showed different strengths of association, even for the same marker. For instance, LVH on ECG (OR 11.74) was more

strongly associated with VaD than echocardiographic LVH (OR 4.33). While echocardiogram and ECG complement each other, some degree of divergence is to be expected since they measure different aspects of cardiac function. Our findings showed that major ECG abnormalities are associated with VaD. This variable may prove useful in identifying dementia as well as cardiac risk [7].

Our results are supported by a study that showed ECG LVH predicted stroke, even after adjusting for echocardiographic LVH [8]. Cardiac markers were not related to AD in our study. A previous study in a smaller sample showed an association between AD and echocardiographic LVH and valvular abnormalities [5]. In a population based sample, unrecognized (Q-wave) myocardial infarction was associated with risk of AD and VaD in men but not women [2]. We did not differentiate between clinical and occult myocardial infarctions.

Strengths of our study include the large sample, dementia diagnosis blinded to cardiac findings, standardized assessments, and homogeneous population. The cross-sectional design limits causal inferences. Reverse causality needs to be considered; cardiac abnormalities can result from dementia pathology or strokes [9]. Longitudinal studies are needed to validate our findings.

Cardiac studies are not currently recommended in dementia work up. If our findings are validated, ECG could be included in dementia work up or used to stratify cognitive risk. Since our findings suggest that ECG may contain greater prognostic value than echocardiogram and is widely available, technically easy, and inexpensive, it may be a valuable asset to identify and predict dementia risk in resource poor settings.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [10].

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Table 1

Baseline characteristics of subjects by dementia status.

	Overall	Controls	Dementia	AD	VaD
N	N = 305	N = 239	N = 66	N = 34	N = 29
Gender, men (%)	52.8%	54.8%	45.5%	35.3% *	55.2%
Age (years)	68.4±6.4	67.3±5.7	72.4±7.3 *	71.0±7.8 *	73.1±6.2 *
Education (years)	8.0±3.8	8.4±3.8	6.5±3.4 *	5.8±3.6 *	7.0±3.1 *
Cognitive Tests					
MMSE	24.4±7.0	27.4±3.2	13.5±6.1 *	14.5±5.8 *	12.9±6.2 *
ACE	69.4±22.2	78.4±13.1	36.0±16.7 *	38.9±15.9 *	34.1±17.1 *
RAVLT	3.8±3.5	4.8±3.3	0.1±0.6 *	0.2±0.8 *	0.0±0.0 *
Digit span test	8.9±3.6	9.9±3.3	5.3±2.3 *	5.5±2.3 *	5.0±2.3 *
GDS	4.9±3.4	4.6±3.4	6.2±3.3 *	5.7±3.2	6.8±3.5 *
Clinical Diagnosis (%)					
Hypertension	31.6%	30.1%	36.9%	20.6%	58.6% *
Dyslipidemia	12.2%	12.6%	10.8%	8.8%	13.8%
Cerebrovascular disease	8.2%	5.0%	20.0% *	0.0%	44.8% *
Ischemic heart disease	11.8%	12.6%	9.2%	0.0% *	20.7%
Diabetes mellitus	21.1%	21.8%	18.5%	17.6%	20.7%

Values are mean ± standard deviation unless otherwise noted.

* = p-value < 0.05, computed using chi-square and t-tests

MMSE: Mini-mental State Examination; ACE: Addenbrooke Cognitive Examination; RAVLT: Rey auditory verbal learning test; GDS: Geriatric depression scale.

Table 2

Association of ECG and echocardiographic findings with dementia and subtypes.

	All Dementia	AD	VaD
ECG abnormalities			
N	66	34	29
Major ECG abnormalities	1.98 (0.98–4.00)	0.68 (0.21–2.17)	4.25 (1.79–10.11) *
LVH	4.53 (1.52–13.51) *	0.89 (0.10–8.25)	11.74 (3.15–43.71) *
ST and T abnormalities	2.03 (0.82–5.00)	1.00 (0.25–3.96)	3.06 (1.06–8.85) *
Q waves	0.57 (0.10–3.15)	†	1.24 (0.22–6.95)
Bundle branch block	1.14 (0.21–6.21)	1.26 (0.14–11.25)	0.98 (0.10–9.16)
Echocardiographic abnormalities			
N	64	32	29
Ejection Fraction < 55%	1.30 (0.48–3.53)	1.06 (0.28–4.07)	1.38 (0.39–4.85)
LVH	1.53 (0.82–2.83)	0.60 (0.24–1.51)	4.33 (1.79–10.45) *
Aortic Regurgitation	1.82 (0.80–4.10)	1.60 (0.54–4.77)	2.35 (0.87–6.35)
Aortic Sclerosis	1.67 (0.82–3.39)	1.64 (0.65–4.11)	1.87 (0.75–4.65)
Mitral Regurgitation	0.43 (0.12–1.60)	0.62 (0.13–2.92)	0.25 (0.03–2.01)
Mitral Calcification	0.83 (0.14–4.74)	†	1.02 (0.11–9.62)

Results are shown as OR (95% CI), adjusted for age, gender, and education.

* p-value < 0.05,

† insufficient data.

LVH: left ventricular hypertrophy