

Mild cognitive impairment is associated with subclinical diastolic dysfunction in patients with chronic heart disease

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Background

To examine mild cognitive impairment and its associations with subclinical cardiac dysfunction in patients with chronic heart disease yet to develop the clinical syndrome of chronic heart failure (CHF).

Methods and results

Patients from the Nurse-led Intervention for Less Chronic Heart Failure Study ($n = 373$ with chronic heart disease other than CHF; 64 ± 11 years, 69% men) were screened for mild cognitive impairment [Montreal cognitive assessment (MoCA) score <26] and underwent echocardiographic/clinical profiling. We investigated associations of mild cognitive impairment and MoCA cognitive domain subscores with global cardiac status ('normal' vs. 'diastolic dysfunction' vs. 'other cardiac abnormality') and individual echocardiographic parameters. Patients with mild cognitive impairment ($n = 161$; 43%) demonstrated a higher age-adjusted prevalence of diastolic dysfunction (37% vs. 24%; $P < 0.05$). Multivariate logistic regression (adjusted for age, sex, and other relevant clinical factors) indicated that the odds of mild cognitive impairment were two-times higher with diastolic dysfunction ($P = 0.030$) and 1.7-times higher with 'other cardiac abnormalities' ($P = 0.082$) vs. normal cardiac status. In turn, mild cognitive impairment was predicted by left-ventricular (LV) filling pressure (based on the ratio of early diastolic filling and annular velocities; adjusted odds ratio 1.07 per unit increase, $P = 0.022$), but not LV structural parameters. Specific deficits in the cognitive domains of executive functioning and visuo-constructional abilities were also independently predicted by diastolic dysfunction ($P < 0.05$).

Conclusion

Mild cognitive impairment is prevalent in patients with subclinical chronic heart disease at high-risk of CHF. Independent associations with LV diastolic dysfunction suggest a link between cardiac and cognitive functioning beyond shared risk factors.

Keywords

cognitive impairment • diastolic dysfunction • echocardiography • left ventricular function • left ventricular hypertrophy

Introduction

Advancements in cardiovascular prevention and management continue to improve survival and progressively shift the burden of disease toward comorbidities such as cognitive impairment. Even mild cognitive impairment (MCI)—defined by deficits in objectively assessed cognitive function but no apparent impact on activities of daily living—is associated with reduced quality of life and poor prognosis

(including dementia and death).^{1,2} Notwithstanding its clinical importance, MCI continues to be under-recognized and under-treated.

Chronic heart disease—particularly in an advanced form sufficient to cause the clinical syndrome of heart failure (CHF)—is now widely recognized as an antecedent of MCI.^{2,3} However, the disproportionately high prevalence of MCI with key CHF predecessors (e.g. coronary artery disease, atrial fibrillation, hypertension and type 2 diabetes)⁴ points to cognition also being affected during the *evolution*

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of CHF. In this context of subclinical (i.e. asymptomatic) disease, MCI may reflect the consequences of distinct cardiac structural and/or functional abnormalities readily detectable from echocardiography and/or other non-invasive imaging modalities.⁵ Several studies have indeed reported on the predictive capacity of broad-based haemodynamic factors (e.g. cardiac output) for cognitive function^{6,7}; however, compensatory mechanisms tend to maintain these parameters within a normal range until the onset of relatively advanced CHF. Thus, in the setting of subclinical disease, cardiac involvement in MCI is more likely to reflect early manifestations of left-ventricular (LV) impairment such as LV hypertrophy and/or diastolic dysfunction. However, these factors have only been investigated at the population level, with inconsistent results.^{8,9}

In the present study, we examined MCI in the Nurse-led Intervention for Less Chronic Heart Failure (NIL-CHF) Study—a trial directed at prevention of clinical CHF in high-risk individuals.¹⁰ Specifically, we sought the prevalence of MCI [measured via the Montreal Cognitive Assessment (MoCA) tool]¹¹ and its associations with echocardiographically determined cardiac structure and function (particularly LV geometry and diastolic function).

Methods

Study cohort

Detailed methods for the NIL-CHF Study (Australian New Zealand Clinical Trials Registry No. 1260800022369) have been described previously.^{10,12} The trial was designed to evaluate an intervention to prevent clinical CHF in high-risk individuals during 3–5 years follow-up. Briefly, cardiac inpatients at an Australian tertiary referral hospital were eligible for enrolment if they were aged ≥ 45 years and were hospitalized with chronic heart disease but without evidence of clinical CHF. Congenital conditions, significant valve disease, terminal malignancy, or subsequent acute cardiac events within 30 days of hospital discharge (including acute heart failure), mandated exclusion from the study. Of 611 patients comprising the NIL-CHF Study intention-to-treat population, 454 (all English-speaking and without clinical CHF or asymptomatic systolic dysfunction at the time of examination) completed the MoCA, underwent echocardiographic examination for cardiac function, and were clinically profiled. Exclusion of patients with cerebrovascular disease ($n = 81$) left a final study cohort of $n = 373$. Data for 298 of these patients were taken from the baseline assessment performed one-month post-hospital discharge, with the remaining 75 patients' data collected at 36-month follow-up. The study was approved by the Alfred Hospital Human Research Ethics Committee and all patients provided written informed consent.

Clinical profiling

Standard demographic and clinical data were recorded at study entry (including age, sex, education level, medical history, and current medication regimen). The comprehensive cardiovascular assessment included body mass index (BMI), blood pressure (BP), blood biochemistry (by standard hospital pathology protocols) and lifestyle factors (i.e. smoking history and alcohol intake frequency—categorized as low [$< \text{once-weekly}$], moderate [$1\text{--}4 \text{ days/week}$] or high [$\geq 5 \text{ times/week}$]). Hypertension was defined as BP $\geq 140/90$ mmHg and/or use of antihypertensive medication. The International Physical Activity Questionnaire¹³ was administered to quantify physical activity (low being < 600 metabolic equivalent (MET)-minutes/week; moderate 600–1499 MET-min/week; high ≥ 1500 MET-min/week). Saturated fat intake was assessed using a validated dietary survey, with 'poor

dietary habits' reflecting non-compliance with a National Cholesterol Education Program Adult Treatment Panel III-recommended Therapeutic Lifestyle Changes diet.¹⁴ Presence of depressive symptoms was determined from the Centre for Epidemiologic Studies Depression scale¹⁵ subsequent to a positive response to Arroll's depression screening questions.¹⁶

Echocardiography

Standard 2D resting echocardiography was performed in the lateral decubitus position using a GE Vivid i ultrasound system (GE Healthcare, Chicago, USA) equipped with a 3.5 MHz (35-RS) transducer. All volume-based measurements were indexed to body surface area. Stroke volume and cardiac output were derived from pulsed-wave Doppler of the LV outflow tract. LV ejection fraction was calculated from LV end-diastolic and end-systolic volumes (modified Simpson's method [91%], or—in case of inadequate image quality—M-mode [cubed method; 5%], or visual/'eyeball' assessment [4%]). Left-atrial (LA) end-diastolic volume was calculated using the area-length method (subgroup of 315 patients only [84%]). LV mass index was calculated from the LV internal dimension and wall thicknesses according to the formula recommended by the European Association of Echocardiography/American Society of Echocardiography.¹⁷ Mitral inflow was characterized using pulsed-wave Doppler, from which the early diastolic filling (E) and septal annular (e') velocities were derived. The ratio of E/e' was calculated as a surrogate of LV filling pressure. Finally, scans of the right and left common carotid arteries (patient positioned supine; using a 12L-RS broadband linear array transducer [5–13 MHz]) enabled measurement of the mean intima-media thickness (IMT)—an indicator of atherosclerotic burden and potentially important covariate⁴—in a subgroup of 349 patients (94%).

Characterization of cardiac structure/function

Global cardiac status was categorized as follows¹⁰:

- i. No evidence of a cardiac abnormality ('Normal')
- ii. 'Diastolic dysfunction' based on mitral inflow consistent with a pseudo-normalization pattern, or mild diastolic dysfunction with $E/e' \geq 15$ (adjudicated per guidelines¹⁸; excluding indeterminate cases)
- iii. any 'other cardiac abnormality', including: (a) LV hypertrophy based on LV mass; (b) septal or posterior wall thickening (> 1.1 cm); (c) mild-moderate valvular dysfunction; and (d) possible (but indeterminate) diastolic dysfunction

In addition to the global cardiac status categories, the following individual structural and functional parameters were analysed: (i) LV hypertrophy (LV mass index $\geq 102 \text{ g/m}^2$ [men] and $\geq 88 \text{ g/m}^2$ [women])¹⁷; (ii) LA enlargement (i.e. LA volume index $\geq 34 \text{ mL/m}^2$); (iii) LV filling pressure estimated by E/e' (where $\leq 8 = \text{normal}$, $8\text{--}15 = \text{indeterminate}$, $\geq 15 = \text{elevated}$)¹⁸; and (iv) elevated LV filling pressure estimated from both E/e' and LA volume index (i.e. E/e' ratio ≥ 15 or > 8 with concurrent LA enlargement). Analyses involving variables derived from LA volume were restricted to the 315 patients (84%) with available data.

Assessment of cognitive function

The MoCA is a validated one-page screening tool for MCI that was completed in-person by trained personnel.¹¹ It assesses a number of cognitive domains: short-term and working memory, visuoconstructional abilities, executive functioning, sustained attention and concentration, language abilities, and orientation. The total score out of 30—to which one point is added for ≤ 12 years formal education—reflects global cognition. MCI was indicated by a score < 26 .¹¹ Deficits in each of the six constituent

cognitive domains were defined by the relevant MoCA subscore being <100%.

Statistical analyses

Analyses were undertaken using IBM SPSS Statistics version 22.0 (IBM Corp, Armonk, NY, USA). Unless otherwise specified, missing data for all variables was <5% and $P < 0.05$ defined statistical significance. Continuous variables were expressed as mean \pm standard deviation (SD) or median with interquartile range, depending on normality of distribution (Kolmogorov–Smirnov test). Categorical data were expressed as percentages. Group comparisons of continuous and categorical variables were performed using unpaired t - and χ^2 -tests, respectively. Where adjustment for covariate(s) was required, analysis of covariance (ANCOVA; continuous variables) or binary/multinomial logistic regression (categorical variables) were applied.

Multivariate logistic regression (enter method) was used to examine independent associations of cardiac structure/function with MCI. An initial model featuring global cardiac status (i.e. 'diastolic dysfunction' and 'other cardiac abnormality' categories vs. 'normal') was considered the primary analysis. This was based on: (i) enabling of a direct comparison of the adjusted odds of MCI in the presence of functional, as opposed to structural abnormalities; and (ii) global cardiac status being considered the most robust indicator of subclinical cardiac disease given its integration of multiple echocardiographic parameters. Secondary analyses sought associations between MCI and individual echocardiographic parameters (separate models for each to avoid collinearity).

Results

MCI was identified in 161 patients (43% of the cohort) and subclinical cardiac disease in 260 patients (70% of the cohort; 109 [29%] with diastolic dysfunction and 151 [41%] an 'other cardiac abnormality'). Clinical characteristics according to MCI status are displayed in *Table 1*. Since those with MCI were older, comparisons of other variables were made with and without age-adjustment. The presence of MCI was characterized by more prevalent depressive symptoms, smoking, and poor dietary habits, less frequent alcohol consumption, and higher carotid IMT (where each of these group differences remained at least borderline significant after age-adjustment). The higher rate of atrial fibrillation in patients with MCI, along with their lower BMI and diastolic BP (and corresponding higher pulse pressure) became non-significant after age-adjustment.

MCI and global cardiac status (primary analysis)

In the primary multiple logistic regression model, the following covariates were entered alongside global cardiac status: age, sex, and education, variables found to be associated with MCI independent of age (i.e. depressive symptoms, smoking, poor dietary habits, and alcohol consumption—per *Table 1*) and other factors with recognized relationships to cognitive function (i.e. diabetes,¹⁹ atrial fibrillation²⁰ and associated therapy,²¹ physical activity,²² and pulse pressure²³). With respect to atrial fibrillation therapy, we favoured model adjustment for anticoagulation since it predicted MCI and resulted in a better model fit compared with adjustment for antiplatelet or antithrombotic (i.e. composite of antiplatelet and/or anticoagulation) therapy. In addition, we collapsed the physical activity categories of 'moderate' and 'high' into a binary variable since this also improved model fit.

As shown in *Figure 1*, both diastolic dysfunction and other cardiac abnormalities (vs. normal) were independently associated with MCI—the latter being borderline significant.

Concurrent predictors of MCI were older age, atrial fibrillation, smoking, poor dietary habit (all $P < 0.05$) and depressive symptoms (trend only; $P = 0.073$). Anticoagulant therapy and moderate alcohol intake demonstrated borderline significant reduced odds of MCI. In subsequent sensitivity analyses, additional adjustment for coronary artery disease, BMI, MAP, and carotid IMT did not substantively impact results (data not shown).

MCI and specific cardiac structural/functional markers

Echocardiographic parameters according to MCI status are displayed in *Table 2* (with and without age-adjustment). The predictive capacity of these parameters for MCI (with and without adjustment for the same covariates outlined in the primary analysis) is reported in *Table 3*.

Cardiac structure

Consistent with the higher prevalence of 'other cardiac abnormalities' relative to 'Normal', patients with MCI demonstrated significantly greater relative wall thickness and a trend toward higher LV mass index; however, on an age-adjusted basis, none of these group differences were significant (*Table 2*). In the fully-adjusted prediction models (*Table 3*), no associations were apparent between MCI and LV hypertrophy; nor LV mass index and relative wall thickness expressed as continuous variables.

Cardiac diastolic function

Poorer values for all individual diastolic functional markers (i.e. e' , E/e' , LA volume index, and derived markers of LV filling pressure) were observed in the group with MCI (*Table 2*). With the exception of E/e' (when expressed categorically) and e' itself, these differences appeared largely independent of age (i.e. at least borderline significant post-adjustment). With full adjustment (*Table 3*), E/e' expressed as a continuous variable independently predicted MCI. When analysed as a categorical variable, elevated E/e' (≥ 15) vs. normal E/e' (≤ 8) was a borderline significant predictor. In contrast, the univariate association of MCI with e' was attenuated and became non-significant following covariate adjustment; likewise LA volume index and derived markers of LV filling pressure.

Associations of cardiac structure/function with deficits in specific cognitive domains

The proportions of patients with deficits in specific cognitive domains are displayed in *Figure 2*. Short-term/working memory was affected in the majority of the cohort (regardless of MCI). The next most commonly observed impairments were in executive functioning and visuoconstructional abilities (>70% of patients with MCI vs. <50% without MCI). Conversely, orientation domain scores indicated largely preserved function (deficit rate <20% in each group).

Of the six MoCA domains, global cardiac status was related to deficits in executive functioning (χ^2 , $P = 0.002$) and visuoconstructional abilities (χ^2 , $P = 0.009$), but not to language ability, short-term/working memory, sustained attention/concentration, or orientation.

Table 1 Clinical characteristics of the study cohort by MCI status

	MCI (n = 161)	No MCI (n = 212)	P	P (age-adjusted)		
Age (years)	67 ± 12	62 ± 9	<0.001			
Male (%)	71	68	0.55			
Education ≤12 years (%)	47	42	0.27			
Living alone (%)	41	39	0.72			
Clinical profile (%)	Coronary artery disease	73	68	0.30	0.24	
	Peripheral artery disease	14	11	0.32	0.998	
	Diabetes	25	24	0.86	0.84	
	Hypertension	91	93	0.56	0.38	
	Atrial fibrillation	19	10	0.015	0.17	
	Chronic kidney disease	17	11	0.075	0.997	
	Cancer	16	10	0.14	0.60	
	Depressive symptoms	29	18	0.010	0.001	
	Lifestyle risk factors (%)	Smoking	26	15	0.012	<0.001
Physical activity	Low	56	49	0.37	0.63	
	Moderate	21	23			
	High	24	28			
	Poor dietary habit	39	24	0.002	<0.001	
	Alcohol intake frequency	Low	57	43	0.033	0.060
		Moderate	24	33		
High		19	24			
Clinical measures	Body mass index (kg/m ²)	27.7 (24.5–31.1)	27.9 (25.3–32.4)	0.042 ^a	0.21 ^a	
	Systolic BP (mmHg)	134 ± 19	133 ± 17	0.59	0.91	
	Diastolic BP (mmHg)	74 ± 12	76 ± 12	0.040	0.50	
	Pulse pressure (mmHg)	59 (50–71)	56 (48–66)	0.035 ^a	0.89 ^a	
	MAP (mmHg)	94 ± 12	95 ± 12	0.29	0.64	
	Total cholesterol (mmol/L)	3.9 (3.2–4.8)	3.9 (3.2–4.7)	0.81 ^a	0.69 ^a	
Medical therapy (%)	Antithrombotic	76	80	0.36	0.26	
	Antiplatelet	69	71	0.63	0.74	
	Anticoagulant	12	14	0.72	0.18	
	Statin	68	73	0.36	0.42	
	ACE or ARB	70	72	0.75	0.48	
	β-Blocker	47	51	0.53	0.56	
	Calcium channel blocker	24	22	0.64	0.97	
	Diuretic	15	9	0.075	0.38	
	Digoxin	7	3	0.066	0.35	
Carotid intima-media thickness (mm)	0.73 (0.63–0.86)	0.67 (0.58–0.76)	<0.001 ^a	0.029 ^a		

Data are mean ± standard deviation, median (interquartile range), or % (unadjusted). *P*-values reflect *t*-test or χ^2 . Age-adjusted *P*-values are based on analysis of covariance (continuous variables) or binary/multinomial logistic regression (categorical variables).

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BP, blood pressure; MAP, mean arterial pressure; MCI, mild cognitive impairment.

^aIndicates log-transformed data used for *t*-test/analysis of covariance (due to skewed distribution).

Detailed data are shown in Supplementary data online, (Table S1). Diastolic dysfunction was a predictor of deficits in both executive functioning and visuoconstructional abilities (i.e. unadjusted, as well as in multivariate analyses featuring the same covariates described for aforementioned MCI prediction models; Figure 1). In contrast, classification in the 'other cardiac abnormality' category predicted a visuoconstructional ability deficit, but was unrelated to executive functioning. *E/e'* expressed as a continuous variable was an

independent predictor of executive functioning, but not visuoconstructional ability.

Discussion

To our knowledge, this is the first report linking diastolic dysfunction with MCI in patients with subclinical chronic heart disease at high-risk of developing the clinical CHF syndrome. We found that the

prevalence of MCI was relatively high (43%) in this setting. In turn, those with evidence of LV diastolic dysfunction based on sensitive echocardiographic markers demonstrated odds of concurrent MCI that were approximately two-times higher than for individuals with

normal cardiac function, even after adjustment for age, sex, and other relevant clinical covariates. Collectively, these findings suggest links between cardiac and cognitive function not only with advanced disease associated with impairment of cardiac haemodynamics, but also at earlier, subclinical stages within the evolution of CHF.

Cognitive impairment in cardiac disease

Cognitive screening with the MoCA tool indicated MCI in almost half of the current cohort. This should be generalizable to the broader subclinical CHF population given our study's relatively unrestrictive eligibility criteria. Indeed, reported prevalence is likely to be conservative given that patients with cerebrovascular disease and systolic dysfunction were excluded. That MCI is a more frequent finding in those at risk of clinical CHF compared with the general older population (where prevalence estimates span 10–20% in those >65 years),¹ is not unexpected given previous reports of poorer cognitive function in association with individual CHF antecedents on which enrolment in the NIL-CHF study was based (i.e. coronary artery disease,³ hypertension,⁴ type 2 diabetes,¹⁹ and atrial fibrillation²⁰). Comparison of the clinical profiles of patients with and without MCI demonstrated similar burdens of these comorbidities except for atrial fibrillation, which was more common in patients with MCI. Notably, lifestyle-related risk factors (i.e. smoking, diet, and alcohol intake) were more disparate between groups.

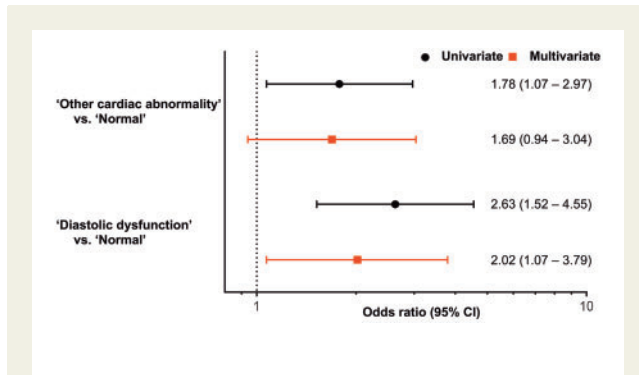


Figure 1 Prediction of MCI by global cardiac status (primary analysis). The multivariate logistic regression model (enter method) was adjusted for age, sex, education ≤ 12 years, atrial fibrillation, anticoagulant therapy, diabetes, depressive symptoms, smoking, poor dietary habit, physical activity, alcohol intake, and pulse pressure. CI, confidence interval.

Table 2 Cardiac structure/function in patients with and without MCI

	MCI (n = 161)	No MCI (n = 212)	P	P (age-adjusted)
Global cardiac status (%)			0.002	0.047
Normal	22	37		
Other cardiac abnormality	42	40	0.028	0.10
Diastolic dysfunction	37	24	0.001	0.015
Stroke volume index (mL/m ²)	40 (35–45)	38 (33–45)	0.30 ^a	0.66 ^a
Cardiac index (L/min/m ²)	2.4 (2.1–2.9)	2.4 (2.0–2.8)	0.10 ^a	0.23 ^a
Ejection fraction (%)	63 ± 7	64 ± 7	0.16	0.24
Fractional shortening (%)	35 (33–38)	36 (32–39)	0.40 ^a	0.71 ^a
Cardiac structure				
LV mass index (g/m ²)	92 ± 18	89 ± 18	0.096	0.32
LV hypertrophy (%)	38	27	0.032	0.26
Relative wall thickness	0.46 ± 0.09	0.44 ± 0.08	0.049	0.45
Cardiac (diastolic) function				
e' (cm/s)	6.5 ± 1.9	7.1 ± 2.0	0.008	0.82
E/e'	11.3 (8.8–15.4)	10.1 (8.1–12.9)	<0.001 ^a	0.069 ^a
E/e' category (%)			0.005	0.27
≤8	14	23		
8–15	59	62	0.14	0.41
≥15	27	15	0.002	0.11
LA volume index (mL/m ²) ^b	37 (31–41)	33 (29–39)	0.001 ^a	0.027 ^a
LA volume index ≥34 mL/m ² (%) ^b	63	44	0.002	0.044
Elevated LV filling pressure (%) ^b	60	39	<0.001	0.051

Data are mean ± standard deviation, median (interquartile range), or % (unadjusted). P-values reflect t-test or χ^2 . Age-adjusted P-values are based on analysis of covariance (continuous variables) or binary/multinomial logistic regression (categorical variables).

e', early diastolic septal annular velocity; E/e', ratio of early diastolic filling and septal annular velocities; LA, left-atrial; LV, left-ventricular; MCI, mild cognitive impairment.

^aIndicates log-transformed data used for t-test/analysis of covariance (due to skewed distribution).

^bLA volume measurements available in a subgroup only (n = 315; 84%).

Table 3 Independent prediction of MCI by specific cardiac markers

	Univariate			Multivariate*		
	n	OR (95% CI)	P	n	OR (95% CI)	P
Cardiac structure						
LV mass index, per 10 g/m ²	365	1.10 (0.98–1.24)	0.096	363	1.02 (0.88–1.18)	0.80
Relative wall thickness, per 0.1 units	371	1.28 (1.00–1.64)	0.050	369	1.10 (0.83–1.46)	0.52
LV hypertrophy	365	1.62 (1.04–2.53)	0.033	363	1.31 (0.79–2.18)	0.30
Cardiac diastolic function						
<i>E/e'</i> (per unit)	373	1.08 (1.04–1.13)	<0.001	371	1.07 (1.01–1.13)	0.022
<i>E/e'</i> category						
8–15 vs. ≤8	373	1.53 (0.88–2.69)	0.14	371	1.42 (0.74–2.70)	0.29
≥15 vs. ≤8	373	2.96 (1.50–5.82)	0.002	371	2.13 (0.92–4.96)	0.079
<i>e'</i> (per 1 cm/s)	371	0.87 (0.78–0.97)	0.009	369	0.95 (0.83–1.10)	0.50
LA volume index (per 1 mL/m ²)	315	1.04 (1.02–1.06)	0.001	314	1.02 (0.99–1.05)	0.14
LA volume index ≥34 mL/m ²	315	2.09 (1.32–3.31)	0.002	314	1.41 (0.82–2.43)	0.22
Elevated LV filling pressure	315	2.41 (1.52–3.82)	<0.001	314	1.51 (0.85–2.69)	0.17

*Multivariate logistic regression models (enter method) were adjusted for age, sex, education ≤12 years, atrial fibrillation, anticoagulant therapy, diabetes, depressive symptoms, smoking, poor dietary habit, physical activity, alcohol intake, and pulse pressure (i.e. as per Figure 1).

CI, confidence interval; *e'*, early diastolic septal annular velocity; *E/e'*, ratio of early diastolic filling and septal annular velocities; LA, left-atrial; LV, left-ventricular; OR, odds ratio.

Deficits in specific cognitive domains in the current cohort were most prevalent for short-term/working memory, followed by executive functioning and visuoconstructional abilities; however, relationships with cardiac function were detected only for the latter two. These findings are largely consistent with previous investigations of cognitive function in cardiometabolic disease, which point to executive functioning—a domain with major implications for disease management—being particularly vulnerable to deterioration.³

Cognitive impairment and LV dysfunction

Cognitive impairment is a widely recognized adjunct of clinical CHF and several lines of evidence suggest that this reflects the haemodynamic consequences of CHF, rather than shared risk profiles alone. To date, this evidence has overwhelmingly come from studies in pre-established clinical CHF associated with concurrent systolic dysfunction (i.e. reduced ejection fraction), which may coincide with cerebral hypoperfusion and correlate with the severity of cognitive decline.^{2,3,24} Perhaps for this reason, existing literature linking cognitive impairment with specific cardiac characteristics—not just in CHF, but also in population-based studies—has focused heavily on markers mainly reflective of LV systolic function.^{3,5} Although diastolic function and geometric factors were investigated in the Hoom⁹ and Southall and Brent Revisited (SABRE)⁸ cohorts, these were population-based and thus inclusive of individuals with reduced ejection fraction (both symptomatic and subclinical). To our knowledge, the current analysis is the first to address whether MCI is linked to diastolic dysfunction, hypertrophy, and/or other early markers of LV damage after removing the confounding haemodynamic consequences of systolic dysfunction. A key finding was the over-representation of diastolic dysfunction in the subgroup with MCI. This association was evident for diastolic dysfunction *per se* (i.e. primary analysis of global cardiac status), as well as markers of LV filling pressure.

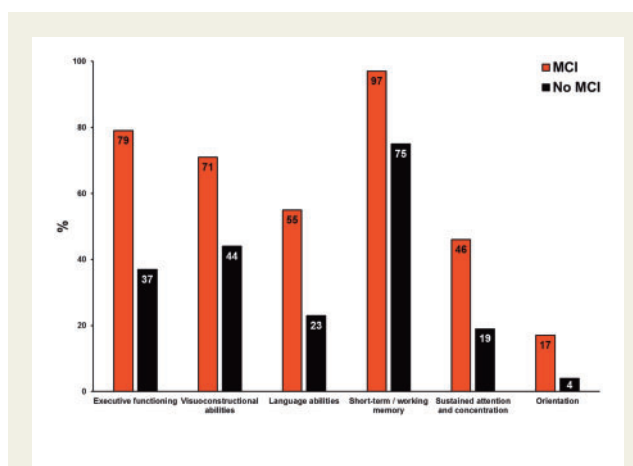


Figure 2 Proportion of patients with deficits in six cognitive domains, according to global MCI status. $P < 0.001$ for MCI vs. no MCI (for all). MCI, mild cognitive impairment.

Importantly, both diastolic dysfunction and *E/e'* predicted MCI independently of relevant clinical covariates. This finding is significant in its advocacy of diastolic dysfunction at least as a risk marker for MCI, but potentially also as a risk factor and therapeutic target.

The predictive capacity of diastolic dysfunction for global MCI appeared to primarily reflect associations with executive functioning and visuoconstructional abilities (i.e. there was no relationship with the domains of memory, attention, language or orientation). This is largely concordant with the Hoom study, in which LV diastolic markers were related to executive functioning, but not memory.⁹ In the SABRE cohort, diastolic dysfunction (classified as per the current study) was unrelated to global and domain-specific indices of cognitive function, though markers of LV filling pressure (*E/e'* and LA

diameter) correlated with memory.⁸ Aside from methodological differences between studies (particularly with respect to cognitive assessment modality), we contend that these divergent findings probably reflect variation in the relative importance of diastolic function for cognition across different clinical contexts.

Despite LV hypertrophy frequently coexisting with diastolic dysfunction, it contrarily demonstrated no significant relationship with MCI. This result adds to a conflicting body of evidence pertaining to LV mass and its relationship with cognition,^{9,25,26} which may reflect between-study differences in patient population and extent of covariate adjustment. Our exclusivity to subclinical CHF probably limited our capacity to detect an association that may exist across a broader range of disease severity.

Possible mechanisms

Since this study did not attempt to interrogate causality or mechanisms, it must be acknowledged that—despite statistical adjustment for a number of potential covariates—diastolic and cognitive decline may simply represent parallel processes arising from a number of shared risk factors. However, plausible links between diastolic dysfunction and MCI for future investigation include coincident arterial stiffening and blunting of cardiac functional reserve, both of which predispose to cerebral circulatory dysfunction. Given we excluded stroke and adjusted for carotid IMT, a role for *macrovascular* disease is unlikely. *Microvascular* disease on the other hand may be relevant in the context of associations between LV dysfunction and white matter hyperintensity (WMH) volume²⁷; however, in the absence of WMH and other microvascular indices modifying associations between diastolic and cognitive function in the SABRE study,⁸ this would appear an incomplete explanation.

Study limitations

Methodological drawbacks include reliance on a single screening tool for MCI rather than comprehensive assessments of specific cognitive domains. Since the cross-sectional design precludes causal assumptions, longitudinal and/or prospective trial data will be necessary to determine the extent to which observed associations reflect mechanistic links and/or common risk pathways. Given sample size requirements for multivariate analyses, we did not investigate whether independent associations in the full cohort were consistent across relevant subgroups. This also precluded adjustment for other potential MCI antecedents. Finally, it is unclear whether our findings will be generalizable to non-ischaemic disease since coronary artery disease represented the predominant CHF antecedent.

Conclusions

The present study points to a high burden of MCI in patients with chronic heart disease at high-risk of CHF. This supports the contention that even subclinical cardiac disease has an adverse impact on cognitive function. Indeed, our data indicate that the odds of MCI are two times higher in patients with diastolic dysfunction compared to those with normal cardiac structure/function. Further work is warranted to determine the potential role of diastolic dysfunction in MCI risk prediction and its value as a therapeutic target.

Supplementary data

Supplementary data are available at *European Heart Journal—Cardiovascular Imaging* online.

Conflict of interest: None declared.

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References

- Langa KM, Levine DA. The diagnosis and management of mild cognitive impairment: a clinical review. *JAMA* 2014;**312**:2551–61.
- Abete P, Della-Morte D, Gargiulo G, Basile C, Langellotto A, Galizia G *et al*. Cognitive impairment and cardiovascular diseases in the elderly. A heart-brain continuum hypothesis. *Ageing Res Rev* 2014;**18**:41–52.
- Eggermont LH, de Boer K, Muller M, Jaszchke AC, Kamp O, Scherder EJ. Cardiac disease and cognitive impairment: a systematic review. *Heart* 2012;**98**:1334–40.
- Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C *et al*. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011;**42**:2672–713.
- Arangalage D, Ederhy S, Dufour L, Joffre J, Van der Vynckt C, Lang S *et al*. Relationship between cognitive impairment and echocardiographic parameters: a review. *J Am Soc Echocardiogr* 2015;**28**:264–74.
- Jefferson AL, Himaji JJ, Beiser AS, Au R, Massaro JM, Seshadri S *et al*. Cardiac index is associated with brain aging: the Framingham Heart Study. *Circulation* 2010;**122**:690–7.
- Sabayan B, van Buchem MA, Sigurdsson S, Zhang Q, Harris TB, Gudnason V *et al*. Cardiac hemodynamics are linked with structural and functional features of brain aging: the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study. *J Am Heart Assoc* 2015;**4**:e001294.
- Park CM, Williams ED, Chaturvedi N, Tillin T, Stewart RJ, Richards M *et al*. Associations between left ventricular dysfunction and brain structure and function: findings from the SABRE (Southall and Brent Revisited) study. *J Am Heart Assoc* 2017;**6**:e004898.
- van den Hurk K, Reijmer YD, van den Berg E, Alsema M, Nijpels G, Kostense PJ *et al*. Heart failure and cognitive function in the general population: the Hoorn Study. *Eur J Heart Fail* 2011;**13**:1362–9.
- Stewart S, Chan YK, Wong C, Jennings G, Scuffham P, Esterman A *et al*. Impact of a nurse-led home and clinic-based secondary prevention programme to prevent progressive cardiac dysfunction in high-risk individuals: the Nurse-led Intervention for Less Chronic Heart Failure (NIL-CHF) randomized controlled study. *Eur J Heart Fail* 2015;**17**:620–30.
- Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I *et al*. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;**53**:695–9.
- Carrington MJ, Stewart S. Bridging the gap in heart failure prevention: rationale and design of the Nurse-led Intervention for Less Chronic Heart Failure (NIL-CHF) Study. *Eur J Heart Fail* 2010;**12**:82–8.
- Craig CL, Marshall AL, Sjoström M, Bauman AE, Booth ML, Ainsworth BE *et al*. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* 2003;**35**:1381–95.
- Mochari H, Gao Q, Mosca L. Validation of the MEDFICTS dietary assessment questionnaire in a diverse population. *J Am Diet Assoc* 2008;**108**:817–22.
- Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. *Appl Psychol Meas* 1977;**1**:385–401.
- Arroll B, Khin N, Kerse N. Screening for depression in primary care with two verbally asked questions: cross sectional study. *BMJ* 2003;**327**:1144–6.
- Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA *et al*. Recommendations for chamber quantification. *Eur J Echocardiogr* 2006;**7**:79–108.
- Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA *et al*. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr* 2009;**10**:165–93.
- Anstey KJ, Sargent-Cox K, Eramudugolla R, Magliano DJ, Shaw JE. Association of cognitive function with glucose tolerance and trajectories of glucose tolerance over 12 years in the AusDiab study. *Alz Res Therapy* 2015;**7**:48.

20. Ball J, Carrington MJ, Stewart S, SAFETY Investigators. Mild cognitive impairment in high-risk patients with chronic atrial fibrillation: a forgotten component of clinical management?. *Heart* 2013;**99**:542–7.
21. Cao L, Pokorney SD, Hayden K, Welsh-Bohmer K, Newby LK. Cognitive function: is there more to anticoagulation in atrial fibrillation than stroke? *J Am Heart Assoc* 2015;**4**:e001573.
22. Carvalho A, Rea IM, Parimon T, Cusack BJ. Physical activity and cognitive function in individuals over 60 years of age: a systematic review. *Clin Interv Aging* 2014;**9**:661–82.
23. Waldstein SR, Rice SC, Thayer JF, Najjar SS, Scuteri A, Zonderman AB. Pulse pressure and pulse wave velocity are related to cognitive decline in the Baltimore Longitudinal Study of Aging. *Hypertension* 2008;**51**:99–104.
24. Alves TC, Rays J, Fraguas R Jr, Wajngarten M, Meneghetti JC, Prando S et al. Localized cerebral blood flow reductions in patients with heart failure: a study using 99mTc-HMPAO SPECT. *J Neuroimaging* 2005;**15**:150–6.
25. Elias MF, Sullivan LM, Elias PK, D'agostino RB Sr, Wolf PA, Seshadri S et al. Left ventricular mass, blood pressure, and lowered cognitive performance in the Framingham offspring. *Hypertension* 2007;**49**:439–45.
26. Scuteri A, Coluccia R, Castello L, Nevola E, Brancati AM, Volpe M. Left ventricular mass increase is associated with cognitive decline and dementia in the elderly independently of blood pressure. *Eur Heart J* 2009;**30**:1525–9.
27. Russo C, Jin Z, Homma S, Elkind MS, Rundek T, Yoshita M et al. Subclinical left ventricular dysfunction and silent cerebrovascular disease: the Cardiovascular Abnormalities and Brain Lesions (CABL) study. *Circulation* 2013;**128**:1105–11.

IMAGE FOCUS

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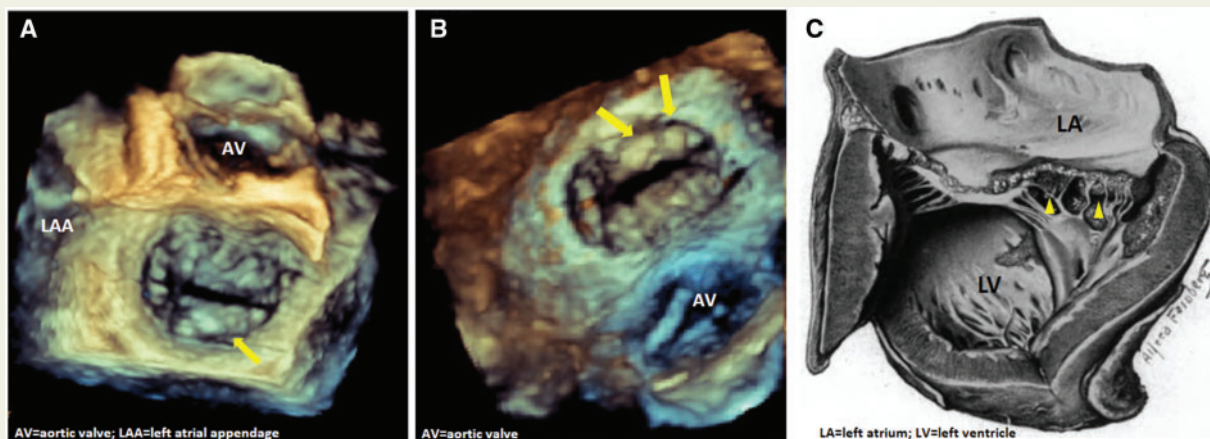
Libman–Sacks vegetations detected by 3D echocardiography

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A 35-year-old woman with a history of systemic lupus erythematosus presented with symptoms of congestive heart failure. She was treated with diuretics with resolution of her dyspnoea. Laboratory testing revealed a white-cell count of 7300/mm³, creatinine was 2.2 mg/dL, and C-reactive protein level was 10.2 mg/L (normal < 5). Repeated blood cultures were negative. Transthoracic echo demonstrated thickened mitral valve leaflets and severe mitral regurgitation. On 3D transoesophageal echocardiography, vegetations were observed on the atrial (Panel A, arrow) as well as the ventricular aspect (Panel B, arrows) of the posterior mitral leaflet, consistent with Libman–Sacks endocarditis (LSE).



In their 1924 seminal paper Libman and Sacks described four patients with a new form of endocarditis identified at autopsy. It was characterized as ‘. . . free from demonstrable micro-organisms’, emphasizing that ‘. . . the lesions on the posterior cusp of the mitral valve were situated chiefly on the ventricular aspect of the valve’. 2D echocardiography primarily images the atrial aspect of the mitral valve leaflets and is limited in its ability to image the valve from the ventricular side (see [Supplementary data](#) online, *Videos S1 and S2*). Hence LSE vegetations have been described on echocardiography as being on the atrial surface of the mitral valve leaflets. 3D echocardiography allows the visualization of the undersurface of the mitral valve. This enables the detection of vegetations on the ventricular aspect of the mitral valve (*Panel B* and [Supplementary data](#) online, *Video 3*) as originally described in Libman and Sacks’ autopsy case series (*Panel C*, *arrowheads*). This patient was discharged home for future surgical re-evaluation.

[Supplementary data](#) are available at *European Heart Journal—Cardiovascular Imaging* online.

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