Subclinical Left Ventricular Dysfunction and Silent Cerebrovascular Disease: The Cardiovascular Abnormalities and Brain Lesions (CABL) Study

Running title: Russo et al.; LV function and subclinical brain disease

Cesare Russo, MD1; Zhezhen Jin, PhD2; Shunichi Homma, MD1; Mitchell S.V. Elkind, MD, MS3; Tatjana Rundek, MD, PhD4,5; Mitsuhiro Yoshita, MD, PhD8; Charles DeCarli, MD6; Clinton B. Wright, MD, MS4,5; Ralph L. Sacco, MD, MS, FAHA4,5,7; Marco R. Di Tullio, MD1

1Dept of Medicine; 2Dept of Biostatistics; 3Depts of Neurology and Epidemiology, Columbia University, New York, NY; 4Dept of Neurology; 5Dept of Epidemiology and Public Health; 7Human Genetics, Miller School of Medicine, University of Miami, Miami, FL; 6Dept of Neurology, University of California at Davis, Davis, CA; 8Dept of Neurology, Hokuriku National Hospital, Nanto, Japan

Address for Correspondence:
Marco R. Di Tullio, MD
Division of Cardiology
Columbia University Medical Center
630 West 168th Street
New York, N.Y. 10032
Tel: 212-305-8805
Fax: 212-342-6051
E-mail: md42@columbia.edu

Abstract:

Background—Silent brain infarcts (SBI) and white matter hyperintensities (WMH) are subclinical cerebrovascular lesions associated with incident stroke and cognitive decline. Left ventricular (LV) ejection fraction (LVEF) is a predictor of stroke in patients with heart failure, but its association with subclinical brain disease in the general population is unknown. LV global longitudinal strain (GLS) can detect subclinical cardiac dysfunction even when LVEF is normal. We investigated the relationship of LVEF and GLS with subclinical brain disease in a community-based cohort.

Methods and Results—LVEF and GLS were assessed by two-dimensional and speckle-tracking echocardiography in 439 participants free of stroke and cardiac disease from the Cardiovascular Abnormalities and Brain Lesions (CABL) study. SBI and WMH were assessed by brain magnetic resonance imaging. Mean age of the study population was 69±10 years, 61% were women, LVEF was 63.8±6.4%, GLS was -17.1±3.0%. SBI were detected in 53 participants (12%), WMH volume was 0.63±0.86%. GLS was significantly lower in participants with SBI vs. those without (-15.7±3.5% vs. -17.3±2.9%, p<0.01), whereas no difference in LVEF was observed (63.3±8.6% vs. 63.8±6.0%, p=0.60). In multivariate analysis, lower GLS was associated with SBI (odds ratio/unit decrease=1.18, 95% CI 1.05-1.33, p<0.01), whereas LVEF was not (odds ratio/unit increase=1.00, 95% CI 0.96-1.05, p=0.98). Lower GLS was associated with greater WMH volume (adjusted β=0.11, p<0.05), unlike LVEF (adjusted β=-0.04, p=0.42).

Conclusions—Lower GLS was independently associated with subclinical brain disease in a community-based cohort without overt cardiac disease. GLS can provide additional information on cerebrovascular risk burden beyond LVEF assessment.

Key words: silent brain infarction, white matter disease, left ventricular ejection fraction, speckle tracking echocardiography, magnetic resonance imaging
Stroke prevalence in the adult population of the United States is estimated at 3.0%, with an average of one person every 4 minutes dying of a stroke. The morbidity, mortality and economic burden associated with stroke is huge, making its prevention a public health priority. In population-based studies, the prevalence of asymptomatic vascular brain lesions is substantially higher than that of clinically overt disease. Silent brain infarcts (SBI) have been documented in 7% to 28% of subjects without prior stroke, with a steep increase in prevalence observed with aging. Cerebral white matter hyperintensities (WMH) have also been described in asymptomatic people in the general population. SBI and WMH are associated with an increased risk of future clinical stroke, cognitive impairment, and dementia.

Left ventricular (LV) systolic function measured as ejection fraction (LVEF) is strongly associated with incident stroke and with cognitive impairment in the setting of congestive heart failure and coronary artery disease. The prevalence of SBI in patients with heart failure is higher compared to that observed in unselected populations. LV dysfunction has also been found more often in patients with stroke compared to stroke-free controls. However, in the general population, and in the absence of heart disease, it is not known whether LV systolic function predicts subclinical brain disease. In a previous study, LVEF was not associated with WMH volume (WMHV) in the general population. LV global longitudinal strain (GLS) is an echocardiographic measure of LV function that can unmask subclinical systolic abnormalities, even when LVEF is in the normal range, in a variety of conditions that are also potent risk factors for stroke, such as arterial hypertension and diabetes mellitus. In fact, GLS has prognostic value for cardiovascular events and mortality that is independent and additive to that of LVEF. It is not known whether GLS is associated with the presence of subclinical brain disease in subjects without heart disease. If demonstrated, this association might be of value in the
identification of cerebrovascular disease at an asymptomatic stage. Accordingly, the aim of the present study was to investigate the association of LV systolic function, measured by LVEF and GLS, with subclinical cerebrovascular disease in a community-based cohort without clinical stroke or overt cardiac disease.

Methods

Study population

The Cardiovascular Abnormalities and Brain Lesion (CABL) study is a community-based epidemiologic study designed to investigate the cardiovascular predictors of silent cerebrovascular disease in the community. CABL based its recruitment on the Northern Manhattan Study (NOMAS), a population-based prospective study that enrolled 3,298 participants from the community living in northern Manhattan between 1993 and 2001. The study design and recruitment details of NOMAS have been described previously.24 Beginning in 2003, participants were invited to participate in an MRI substudy if they: 1) were at least 55 years of age; 2) had no contraindications to MRI; and 3) did not have a prior diagnosis of stroke. From September 2005 to July 2010, NOMAS MRI participants that voluntarily agreed to undergo a more extensive cardiovascular evaluation including transthoracic echocardiography were included in CABL. Participants for whom echocardiography and brain MRI information were available constitute the sample of the present study. Participants with non-sinus rhythm at the time of the echocardiogram, history of atrial fibrillation or atrial flutter, significant mitral or aortic valve disease, and coronary artery disease were excluded from the present analysis.

Written informed consent was obtained from all study participants. The study was approved by the Institutional Review Boards of Columbia University Medical Center and of University of
Miami.

**Risk factors assessment**

Cardiovascular risk factors were ascertained through direct examination and interview by trained research assistants. Systolic (SBP) and diastolic blood pressure (DBP) were measured at the non-dominant arm in a sitting position after 5 minutes of rest, using a mercury sphygmomanometer and a proportioned arm cuff. Study participants were not asked to discontinue anti-hypertensive medications on the day of the visit. Two BP measurements were performed and averaged. Hypertension was defined as SBP $\geq 140$ mm Hg or DBP $\geq 90$ mm Hg, or the participant’s self-reported history of hypertension or use of anti-hypertensive medication. Diabetes mellitus (DM) was defined as fasting blood glucose $\geq 126$ mg/dL or the participant’s self-reported history of DM or use of diabetes medications. Hypercholesterolemia was defined as total serum cholesterol $>240$ mg/dL, a patient’s self-report of hypercholesterolemia or use of lipid-lowering treatment. Cigarette smoking, either at the time of the interview or in the past, was recorded. Coronary artery disease (CAD) was defined as a history of myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, typical angina or use of anti-ischemic medications. Atrial fibrillation was defined from ECG at the time of echocardiography or from self-reported history. The race-ethnicity classification was based on self-identification, and categorized as black, Hispanic and white.

**Echocardiographic assessment**

**Two-dimensional echocardiography**

Transthoracic echocardiography was performed using a commercially available system (iE 33, Philips, Andover, MA) by a trained, registered cardiac sonographer according to a standardized protocol. Interventricular septum and posterior wall thickness, LV end-diastolic diameter, and
left atrial antero-posterior diameter were measured from a parasternal long-axis view according to the recommendations of the American Society of Echocardiography.\textsuperscript{25} LV end-diastolic diameter and left atrial diameter were indexed by body surface area. LVEF was calculated using the biplane modified Simpson’s rule, replaced by semi-quantitative method or visual estimation in case of technically suboptimal images. LV mass was calculated with a validated method\textsuperscript{26} and indexed by body surface area. LV relative wall thickness was calculated as: 2 x posterior wall thickness / LV end-diastolic diameter. LV diastolic function assessment has been previously described in detail.\textsuperscript{27} Briefly, color Doppler imaging was used to visualize the trans-mitral flow from an apical 4-chamber view; the pulsed-wave Doppler sample volume was placed perpendicular to the inflow jet at the level of mitral valve leaflet tips. The peak early velocity (E), late velocity (A), and deceleration time of the mitral inflow were measured, and the E/A ratio was calculated. Mitral annular velocities were evaluated by pulsed-wave tissue-Doppler imaging and sampled on the longitudinal axis from the apical 4-chamber view. The peak early diastolic velocity (e’) of the lateral and the septal mitral annulus were measured and the average value was calculated. Diastolic dysfunction definition was published previously.\textsuperscript{27}

**Speckle-tracking strain imaging**

Speckle-tracking analysis was performed off-line using commercially available software (QLAB Advanced Quantification Software version 8.1, Philips) as previously described.\textsuperscript{28} Briefly, speckle-tracking analysis of LV myocardial deformation over the longitudinal axis was performed from two-dimensional gray-scale loops by automatic tracking of myocardial speckles after manual selection of landmark points. Global longitudinal systolic strain (GLS) was calculated averaging the negative peak of longitudinal strain from 12 ventricular segments from the apical 4-chamber and 2-chamber views. At least two cardiac cycles were recorded at a frame
rate ≥ 45 fps, and were averaged for strain analysis. Aortic valve opening and closing times were measured from the LV outflow Doppler profile and were incorporated in the speckle-tracking strain profile in order to exclude post-systolic components. Because GLS is represented by negative values, with more negative numbers expressing greater systolic shortening and therefore better function, we adopted the terminology “lower GLS” referring to higher, less negative values, therefore expressing smaller systolic shortening. Abnormal GLS was defined as a GLS lower than the 95th percentile of the GLS distribution in the healthy subgroup of subjects free of hypertension, diabetes mellitus, coronary artery disease, arrhythmias, and with body mass index ≤ 25 kg/m², corresponding to a GLS > -14%. Reproducibility of speckle-tracking measurements has been reported previously.²⁹

**Brain Magnetic Resonance Imaging**

A detailed description of the assessment of subclinical cerebrovascular lesions has been published previously.²⁹,³⁰ Briefly, brain imaging was performed on a 1.5-T MRI system (Philips Medical Systems). Median time between MRI and echocardiographic examination was 2 days (75th percentile: 5 days). SBI were rated by two of the authors (C.D. and M.Y.) and defined as either a cavitation on the fluid-attenuated inversion recovery sequence of at least 3 mm in size, distinct from a vessel (due to the lack of signal void on T2 sequence), and of equal intensity to cerebrospinal fluid in the case of lacunar infarction, or as a wedge shaped cortical or cerebellar area of encephalomalacia with surrounding gliosis consistent with infarction due to distal arterial branch occlusion. Inter-observer agreement for SBI detection was 93.3%.³⁰ WMHV analysis was based on a FLAIR (Fluid Attenuated Inversion Recovery) image and performed using the Quantum 6.2 package on a Sun Microsystems Ultra 5 workstation. WMHV was expressed as proportion of total cranial volume to correct for differences in head size, and log-transformed.
(log-WMHV) to achieve a normal distribution for analysis as a continuous variable. All measurements were performed blinded to participant identifying and clinical information.

**Statistical analysis**

Data are presented as means ± standard deviation (SD) for continuous variables and as percentages for categorical variables. Student’s t-test was used to assess differences in GLS, LVEF, and WMHV between groups (presence/absence of SBI; normal/abnormal GLS and LVEF). Logistic and linear regression models were used to test the association of demographic and clinical variables with parameters of LV function, and the association of LV function parameters with SBI and log-WMVH. Unstandardized (B) and standardized (β) parameter estimates, standard errors (SE), Pearson’s partial correlation coefficients, odds ratios (OR) and 95% confidence intervals (CI) were calculated and reported. Covariates for multivariate models were selected based on their univariate association with LV function parameters, with a threshold for entry in the multivariate models set at a p-value less than 0.2. For all statistical analyses, a two-tailed p<0.05 was considered significant. Statistical analyses were performed using SAS software version 9.2 (SAS Institute Inc., Cary, NC).

**Results**

**Study population**

Clinical and demographic characteristics of the study population are shown in Table 1. We detected SBI in 53 study participants (12%); in 9 cases (17%), the SBI were located in cortical areas and 44 (83%) were subcortical. Mean WMHV was 0.63±0.86% (median=0.32%, interquartile range=0.47%). Echocardiographic data, including LVEF and GLS of the study population are shown in Table 2.
Factors Associated with LV Function

Table 3 shows the univariate associations of LVEF and GLS with demographics, risk factors, and echocardiographic variables. Lower LVEF was significantly associated with male sex, greater LV mass index, smaller relative wall thickness (all p<0.01), and higher body mass index (p<0.05). Lower GLS was significantly associated with older age, higher SBP and DBP, hypertension, diabetes, greater LV mass index, LV diastolic dysfunction (all p<0.01), and greater relative wall thickness (p<0.05).

LV systolic function and subclinical cerebrovascular disease

GLS was significantly lower in participants with SBI compared to those without (-15.7±3.5% vs. -17.3±2.9%, p<0.01), whereas LVEF was not significantly different in the two groups (63.3±8.6% vs. 63.8±6.0%, p=0.60). Data on the association between measures of LV systolic function and presence of SBI are shown in Table 4. LVEF showed no association with SBI in either univariate analysis (OR per unit increase of LVEF=0.99, 95% CI 0.95-1.03, p=0.53) or after adjustment for relevant covariates (adjusted OR=1.00, 95% CI 0.96-1.05, p=0.98). A LVEF<55% also did not show any significant relationship with SBI (adjusted OR=0.64, 95% CI 0.19-2.16, p=0.47). Lower GLS was significantly associated with SBI in univariate analysis (OR per unit decrease of GLS=1.21, 95% CI 1.10-1.34, p<0.01), and this association was confirmed after adjusting for covariates (adjusted OR=1.16, 95% CI 1.04-1.30, p<0.01). The addition of LVEF to the model did not affect the significant relationship between GLS and SBI (adjusted OR=1.18, 95% CI 1.05-1.33, p<0.01). An abnormal GLS was associated with a greater prevalence of SBI both in univariate (OR=4.44, 95% CI 2.24-8.81) and in multivariate analysis (adjusted OR=3.56, 95% CI 1.62-7.83, p<0.01).

WMHV was not significantly different in subjects with normal vs. low LVEF.
(0.62±0.85% vs. 0.76±0.81%, p=0.39), whereas it was significantly greater in subjects with abnormal vs. normal GLS (1.15±1.46% vs. 0.56±0.71%, p<0.001) (Figure). The association between LV systolic function and log-WMHV is shown in Table 5. LVEF was not associated with log-WMHV in either univariate analysis (β=-0.06, p=0.25) or after adjustment for covariates (β=-0.04, p=0.42). Lower GLS was significantly associated with greater log-WMHV both in univariate (β=0.18, p<0.01) and multivariate analysis (β=0.11, p<0.05). In a model further adjusted for LVEF, a lower GLS remained significantly associated with greater log-WMHV (β=0.10, p<0.05). No significant interaction was found between GLS and LVEF in the association with either SBI or log-WMHV.

Discussion

In this study, we demonstrated for the first time that GLS is associated with subclinical brain disease in a community-based cohort free of stroke and of overt cardiac disease. This association was significant for both SBI and WMHV, and was independent of confounders, cardiovascular risk factors, and of LVEF.

The mechanism underlying the association between a lower GLS and subclinical brain disease is not known. It is important to note that the vast majority (93.4%) of the study participants had a normal LVEF, making cerebral hypoperfusion, one of the proposed etiologic mechanisms for white matter lesions,$^{31,32}$ an unlikely contributor to our findings. In this respect, we confirm the findings of the Framingham Heart Study, which showed no association between LVEF and WMHV in a large sample of subjects free from clinical stroke and with largely normal LVEF.$^{21}$ GLS, however, is an indicator of myocardial deformation that has a different meaning and behaves differently from LVEF, especially in the early subclinical stages of LV.
dysfunction. GLS is mainly a measure of the contraction of the longitudinally oriented myocardial fibers, that are mostly located in the LV subendocardium. Since the LV subendocardium is especially vulnerable to hypoperfusion and hemodynamic overload, GLS can be a sensitive maker of LV ischemia. In previous studies, a lower GLS has been shown to be associated with several traditional cardiovascular risk factors such as hypertension, LV hypertrophy, and diabetes. Furthermore, in a previous study we demonstrated that GLS, but not LVEF, was reduced in subjects with increased arterial stiffness. The association of GLS with the aforementioned risk factors and with increased arterial stiffness, in otherwise asymptomatic subjects, may suggest GLS as an indicator of subclinical atherosclerosis.

Consistent with this hypothesis, a study in asymptomatic diabetic patients with normal LVEF showed that a reduced GLS was associated with higher coronary artery calcium score, a direct marker of coronary atherosclerosis. This association might therefore provide a pathophysiological explanation for the association between GLS and subclinical brain disease shown in the present study. Indeed, several studies showed that SBI and WMHV are associated with atherosclerotic and cardiovascular risk factors, such as hypertension, LV hypertrophy, diabetes, cigarette smoking, hyperhomocysteinemia, carotid plaque, and intima-media thickness. The fact that the association between GLS and subclinical brain disease persisted after adjusting for many known risk factors for atherosclerotic disease may be compatible with the concept that, once atherosclerosis has developed, adjusting for these factors may no longer affect the risk estimates, or not as much. Furthermore, it is also possible that other unmeasured factors may be involved in mediating the observed associations.

While in patients with overt heart failure the presence of SBI has been hypothesized to be in part of thromboembolic origin (because of the low cardiac output favoring blood stasis in the
cardiac chambers), in the present study population this does not appear to be a likely cause, given the largely normal LVEF, the exclusion of participants with history of CAD, and the absence of LV thrombus in all study participants. Cardioembolism from paroxysmal atrial arrhythmias can theoretically be another mechanism for SBI occurrence. Although we excluded participants with history and ECG evidence of atrial arrhythmias, the presence of undocumented episodes of paroxysmal atrial fibrillation that may have contributed to our findings in participants with lower GLS cannot be excluded. It is known that patients with isolated paroxysmal atrial fibrillation but normal LVEF may have lower GLS compared to healthy controls, and that catheter ablation of the atrial fibrillation restores GLS to normal levels. Additionally, we have previously demonstrated that a lower GLS is associated with reduced left atrial reservoir function, which in turn is associated with the development of both atrial arrhythmias and subclinical brain disease. Although cardioembolism may be a theoretically possible link between lower GLS and SBI, it is unlikely that it played a significant role in explaining our findings. In fact, the number of cortical brain infarcts, generally considered of more likely embolic origin, in our study population was very low.

Our study has potential clinical implications. For the first time, we show that an echocardiographic parameter of LV systolic function can provide useful information about the risk of subclinical brain disease. We found that an abnormal GLS was associated with an over three-fold increase in risk of having a SBI in multivariate analysis, and, importantly, this association was independent of LVEF. The negative prognostic value of a reduced LVEF has been well documented in patients with heart failure, dilated cardiomyopathy, and in patients surviving myocardial infarctions. It is also known that lower LVEF is associated with subclinical brain disease in the context of heart failure; however, probably because of our
study sample’s mostly normal LVEF values, LVEF did not provide useful information on stroke risk stratification, nor did it show a significant interaction with GLS on the risk of subclinical brain disease. GLS, on the other hand, may detect the rearrangement in LV mechanics described in the early stages of LV remodeling, when a reduction in longitudinal shortening can be compensated by either an increase in circumferential strain or the development of myocardial hypertrophy, both resulting in a preserved LVEF; hence, the use of speckle-tracking echocardiography might be of help in the early identification of subjects with subclinical LV dysfunction and who might also be at higher risk of developing cerebrovascular disease. Whether more aggressive treatment strategies and risk factors control may reduce the future incidence of clinical stroke and cognitive decline in those individuals is a hypothesis that deserves further investigation.

**Strengths and limitations**

The main strengths of our study are the large number of subjects studied with advanced imaging techniques (speckle-tracking echocardiography and brain MRI), the wide range of cardiovascular risk profiles present in our study population, and the confirmation of our findings in multivariable models. However, our study also has limitations. The study sample included subjects over age 55 with a large representation of Hispanic ethnicity, which might preclude the generalization of our findings to populations with different demographic composition. However, since silent brain disease is more commonly found in the elderly, our study cohort was the ideal setting for this study. Furthermore, the cross-sectional design of our study allows us to document associations that do not necessarily imply direct cause-effect relationships. Finally, although we performed multivariate analyses adjusted for many known risk factors for atherosclerosis and brain disease, the possibility that unmeasured confounders might be involved in the observed
associations cannot be excluded.

Conclusions

A lower GLS was independently associated with subclinical brain lesions, both SBI and WMHV, in a stroke-free community-based cohort without overt cardiac disease. The traditional assessment of LV systolic function by LVEF was not associated with either SBI or WMHV. GLS can provide additional information on cerebrovascular risk even when LVEF is in the normal range. The early identification of subjects at higher risk for subclinical brain disease may be crucial for intervention aiming at reducing the global burden of clinical stroke and cognitive decline.

Acknowledgments: The authors wish to thank Janet De Rosa, MPH (project manager), Rafi Cabral, MD, Michele Alegre, RDCS, and Palma Gervasi-Franklin (collection and management of the data).

Funding Sources: This work was supported by the National Institute of Neurological Disorders and Stroke [grant number R01 NS36286 to MDT and R37 NS29993 to RLS/MSE].

Conflict of Interest Disclosures: None.

References:


2001;57:1222-1229.


25. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH,
Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr.* 2005;18:1440-1463.


46. Palmon LC, Reichek N, Yeon SB, Clark NR, Brownson D, Hoffman E, Axel L. Intramural


**Table 1.** General characteristics of the study population

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>439</td>
</tr>
<tr>
<td>Age, years</td>
<td>69.3±9.7</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>266 (60.6)</td>
</tr>
<tr>
<td>Race-ethnicity</td>
<td></td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>59 (13.4)</td>
</tr>
<tr>
<td>African-American, n (%)</td>
<td>70 (15.9)</td>
</tr>
<tr>
<td>Hispanic, n (%)</td>
<td>306 (69.7)</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>4 (0.9)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.8±4.5</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>133.8±16.8</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>78.4±9.3</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>319 (72.7)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>115 (26.2)</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>270 (61.5)</td>
</tr>
<tr>
<td>Smoking history, n (%)</td>
<td>238 (54.2)</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>32 (7.3)</td>
</tr>
</tbody>
</table>

SBP: Systolic blood pressure. DBP: Diastolic blood pressure.

**Table 2.** Echocardiographic data

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LV septal thickness, mm</td>
<td>11.3±1.7</td>
</tr>
<tr>
<td>LVEDi, mm/m²</td>
<td>25.6±2.9</td>
</tr>
<tr>
<td>LV posterior wall thickness, mm</td>
<td>11.0±1.5</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>102.5±23.8</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.49±0.08</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>63.8±6.4</td>
</tr>
<tr>
<td>LVEF &lt; 55%, n (%)</td>
<td>29 (6.6)</td>
</tr>
<tr>
<td>GLS, %</td>
<td>-17.1±3.0</td>
</tr>
<tr>
<td>GLS &gt; -14%, n (%)</td>
<td>52 (11.8)</td>
</tr>
<tr>
<td>Left atrial diameter, mm/m²</td>
<td>21.9±2.7</td>
</tr>
<tr>
<td>LV diastolic dysfunction, n (%)</td>
<td>240 (54.7)</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>70.3±11.2</td>
</tr>
</tbody>
</table>

LV: Left ventricular. LVEDi: LV end-diastolic dimension index. LVEF: LV ejection fraction. GLS: Global longitudinal strain.
Table 3. Factors univariately associated with LV function

<table>
<thead>
<tr>
<th></th>
<th>LVEF (per % point)</th>
<th>GLS (per % point)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B (SE)</td>
<td>P value</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>-0.03 (0.03)</td>
<td>0.34</td>
</tr>
<tr>
<td>Male sex</td>
<td>-3.11 (0.61)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Body mass index (per kg/m²)</td>
<td>-0.17 (0.07)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SBP (per mmHg)</td>
<td>0.02 (0.02)</td>
<td>0.29</td>
</tr>
<tr>
<td>DBP (per mmHg)</td>
<td>0.02 (0.03)</td>
<td>0.61</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.37 (0.68)</td>
<td>0.59</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.27 (0.69)</td>
<td>0.70</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>0.73 (0.62)</td>
<td>0.25</td>
</tr>
<tr>
<td>Smoking history</td>
<td>-1.01 (0.61)</td>
<td>0.10</td>
</tr>
<tr>
<td>Current smoking</td>
<td>-0.56 (1.17)</td>
<td>0.64</td>
</tr>
<tr>
<td>LV mass index (per g/m²)</td>
<td>-0.04 (0.01)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>12.61 (3.56)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Left atrial diameter (per mm²)</td>
<td>0.06 (0.11)</td>
<td>0.61</td>
</tr>
<tr>
<td>LV diastolic dysfunction</td>
<td>-1.14 (0.61)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Values in table are parameter estimates (B) and relative standard error (SE). LV: Left ventricular. SBP: Systolic blood pressure. DBP: Diastolic blood pressure. LVEF: LV ejection fraction. GLS: Global longitudinal strain.
Table 4. Association of LV systolic function with silent brain infarcts.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Model 1 OR (95% CI)</th>
<th>P value</th>
<th>Model 2 OR (95% CI)</th>
<th>P value</th>
<th>Model 3 OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF*</td>
<td>0.99 (0.95-1.03)</td>
<td>0.53</td>
<td>1.00 (0.96-1.05)</td>
<td>0.98</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Abnormal LVEF (&lt;55%)†</td>
<td>1.20 (0.40-3.60)</td>
<td>0.75</td>
<td>0.64 (0.19-2.16)</td>
<td>0.47</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GLS‡</td>
<td>1.21 (1.10-1.34)</td>
<td>&lt;0.01</td>
<td>1.16 (1.04-1.30)</td>
<td>&lt;0.01</td>
<td>1.18 (1.05-1.33)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Abnormal GLS (&gt;14%)§</td>
<td>4.44 (2.24-8.81)</td>
<td>&lt;0.01</td>
<td>3.28 (1.53-7.03)</td>
<td>&lt;0.01</td>
<td>3.56 (1.62-7.83)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Values in table are odds ratios (OR) and 95% confidence intervals (CI). Each predictor is evaluated in a separate model. *OR per 1 LVEF unit increase. †Reference group: normal LVEF (≥55%). ‡OR per 1 GLS unit decrease (less negative values). §Reference group: normal GLS (≤-14%). Model 1: Unadjusted. Model 2: Adjusted for age, sex, body mass index, SBP, DBP, hypertension, diabetes, hypercholesterolemia, smoking history, LV mass index, relative wall thickness, and LV diastolic dysfunction. Model 3: Adjusted for covariates in model 2 plus LVEF.

Table 5. Association of LV systolic function with log-WMHV.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Model 1 β (SE)</th>
<th>P value</th>
<th>Model 2 β (SE)</th>
<th>Part. R</th>
<th>P value</th>
<th>Model 3 β (SE)</th>
<th>Part. R</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF</td>
<td>-0.06 (0.05)</td>
<td>0.25</td>
<td>-0.04 (0.04)</td>
<td>0.06</td>
<td>0.42</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GLS</td>
<td>0.18 (0.05)</td>
<td>&lt;0.01</td>
<td>0.11 (0.04)</td>
<td>0.12</td>
<td>&lt;0.05</td>
<td>0.10 (0.05)</td>
<td>0.11</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Values in table are parameter estimates per standard deviation increase (β), standard errors (SE), and partial correlation coefficients (Part. R). Each predictor is evaluated in a separate model. Model 1: unadjusted. Model 2: adjusted for age, sex, body mass index, SBP, DBP, hypertension, diabetes, hypercholesterolemia, smoking history, LV mass index, relative wall thickness, and LV diastolic dysfunction. Model 3: adjusted for covariates from model 2 plus LVEF.
Figure Legend:

**Figure 1.** Association between WMHV, expressed as % of the total cranial volume, and LV systolic function.
Subclinical Left Ventricular Dysfunction and Silent Cerebrovascular Disease: The Cardiovascular Abnormalities and Brain Lesions (CABL) Study
Cesare Russo, Zhezhen Jin, Shunichi Homma, Mitchell S. V. Elkind, Tatjana Rundek, Mitsuhiro Yoshita, Charles DeCarli, Clinton B. Wright, Ralph L. Sacco and Marco R. Di Tullio

Circulation. published online July 31, 2013;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/early/2013/07/31/CIRCULATIONAHA.113.001984

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/