Original Article

# Longitudinal Strain and Ischemic Stroke in the Absence of Known Heart Disease

***Strain Longitudinal e Acidente Vascular Encefálico Isquêmico na Ausência de Cardiopatia Conhecida***

*Jeova Cordeiro de Morais Junior[1,2]; Nayane Carolina Pertile Salvioni[1], Dannyl Roosevelt de Vasconcelos Lima[1]; Crissvânia Firmino Confessor[1]; Alexsandro Paulo Costa Galdino Junior[1]; Lara Sodré Cardoso[1]; Antônio Marconi Leandro da Silva[1]; Joao Lima[4]; Anderson da Costa Armstrong[1]; Luis Claudio Lemos Correia[2,3]*

*[1]Federal University of São Francisco Valley, Petrolina, Pernambuco Brazil; [2]Bahian School of Medicine and Public Health, Salvador, Bahia, Brazil; [3]São Rafael Hospital, Salvador, Bahia, Brazil; [4]Johns Hopkins Hospital, Baltimore, MD, USA.*

## Abstract

**Background:** Stroke is prevalent worldwide, and early recognition of subclinical cardiovascular (CV) disease could predict a first ischemic stroke (IS) episode. Speckle-tracking echocardiography (STE) allows the detection of early subclinical myocardial dysfunction.

**Aim:** To examine the association between myocardial deformation, evaluated by STE, and first episode of IS in a sample of otherwise healthy patients.

**Methods:** We included individuals between 40–80 years old, with a first incidence of IS, with no known CV disease, matched to healthy controls by sex, age, and hypertension at a 1:2 ratio. STE was used to assess LV global longitudinal strain (GLS), and traditional echocardiography was performed. Univariate and multivariable analyses were performed to assess the relationship among stroke, CV risk factors, and echocardiography-derived parameters.

**Results:** A total of 29 cases and 62 controls were included. The mean age of the patients was 60 ± 12 y/o, and 54% were males. Smoking was more prevalent in cases compared to controls (34% vs. 9%; p = 0.001), and there were no significant differences in the other examined risk factors. Cases had less myocardial deformation compared to controls (GLS: -16.7% ± 3.4% vs. -19.2 ± 2.8%; p < 0.001), and there was no significant difference regarding traditional echocardiography parameters. After adjusting for smoking and hyperlipidemia, GLS maintained an independent association with stroke (OR = 1.3; 95% CI, 1.1–1.6; p = 0.005). The area under the ROC curve for stroke significantly increased after adding GLS to smoking (0.65 to 0.78, p = 0.009).

**Conclusion:** GLS has a consistent and independent association with a first IS episode in middle-aged adults with generally normal hearts. Therefore, GLS may be a useful risk marker in this population.

**Keywords:** Stroke; Cardiovascular Disease; Echocardiography.

## *Resumo*

***Fundamento:*** *O acidente vascular encefálico (AVE) é prevalente no mundo. Reconhecimento precoce da doença cardiovascular subclínica pode predizer um primeiro episódio de AVE isquêmico; o speckle tracking associado à ecocardiografia (STE) permite detecção precoce da disfunção miocárdica subclínica.*

***Objetivo:*** *Provar a associação entre deformação miocárdica avaliada pelo STE e primeiro episódio de AVE em indivíduos saudáveis.*

***Método:*** *Incluímos participantes entre 40-80 anos com primeiro episódio de AVE isquêmico sem cardiopatia conhecida, pareados por sexo, idade e hipertensão com grupo controle saudável na proporção 1:2. STE avaliou strain longitudinal (SL) do VE, e ecocardiografia tradicional foi realizada. Análises univariada e multivariada avaliaram as relações do AVE com fatores de risco cardiovasculares e parâmetros derivados da ecocardiografia.*

***Resultado:*** *29 casos e 62 controles foram incluídos. Média etária foi 60 ± 12 anos; 54% eram homens. Tabagismo foi mais prevalente em casos do que em controles (34% vs. 9%; p=0.001). Nenhum outro fator de risco evidenciou diferença estatística. Casos tiveram menor deformação*

**Mailing Address: Nayane Carolina Pertile Salvioni •**
Rua Desembargador Eliseu Guilherme, 147, 3° subsolo, Paraíso. CEP: 04004-030, São Paulo, SP, Brazil.
E-mail: nayanepertile@gmail.com
Manuscript received 1/14/2020; revised 3/23/2020; accepted 7/9/2020

**DOI:** 10.47593/2675-312X/20203304eabc101

*miocárdica comparados aos controles (SL -16.7 ± 3.4% vs. -19.2 ± 2.8%; p < 0.001). Não houve diferença em relação aos parâmetros ecocardiográficos tradicionais. Após ajuste para tabagismo e hiperlipidemia, SL manteve-se independentemente associado com AVE (OR=1.3; 95% CI, 1.1 – 1.6; p=0.005). A área abaixo à curva ROC para AVE aumentou significativamente após adicionar SL ao tabagismo (0.65 para 0.78, respectivamente; p=0.009).*

***Conclusão:*** *SL tem independente associação com o primeiro episódio de AVE isquêmico em adultos de média idade com corações geralmente normais. SL pode ser potencial marcador de risco nesta população.*

***Palavras-chave:*** *Acidente Vascular Cerebral; Doenças Cardiovasculares; Ecocardiografia.*

## Introduction

Stroke is the leading cause of disability worldwide,[1] affecting approximately 15 million people per year.[2] The impact of stroke-related disability is a major health concern, particularly in the aging population.[3,4] Although the risk for cerebrovascular disease is well established among the elderly, the increase in stroke incidence among younger adults is a growing concern.[5] In fact, it is unclear how to prevent a first stroke event in a previously healthy young adult population.

Therefore, early recognition of subclinical cardiovascular (CV) disease that could predict a first episode of ischemic stroke is of major clinical importance, especially in patients who appear to have no significant risk. Speckle tracking echocardiography (STE) allows for accurate detection of early subclinical myocardial dysfunction, beyond traditional echocardiography-derived parameters.[6] Indeed, STE has been validated in several clinical settings as a useful tool for assessing CV events.[7–9] However, how subclinical cardiac abnormalities might relate to incidents of cerebrovascular disease is less well understood.

In the current study, we explore the hypothesis that the reduction of the STE-derived LV global longitudinal strain (GLS) (as early subclinical cardiac dysfunction) is associated with the first episode of stroke in a sample of otherwise healthy patients. To this end, we utilized a comprehensive echocardiography protocol, and compared the sample population to healthy matched controls.

## Material and methods

### Study design and population

Men and women, 40 to 80 years old, with a first ischemic stroke and no prior known CV disease, were recruited from a single center from January 2015 to September 2016. Ischemic stroke was established following the validated National Institutes Health (NIH) Scale,[10] and confirmed by brain imaging. Individuals were excluded if they had a history of heart failure, coronary artery disease, atrial flutter or atrial fibrillation, abnormalities detected by electrocardiography that suggested structural cardiac change, or structural echocardiographic changes (left ventricular hypertrophy, increased chamber volumes, wall motion abnormality, or moderate/severe valvular dysfunction).

Control participants were healthy individuals, recruited in the proportion of 2:1, preferably relatives of included cases or recruits from the outpatient facility of the same institution. All controls were paired by sex, age, and previous diagnosis of hypertension. We chose to pair for hypertension to avoid confusion, as hypertension has been shown to reduce GLS[11] and is also a strong risk factor for cerebrovascular disease.[12]

Finally, cases and controls were excluded if they had poor quality images, when they or their caregivers refused to participate in the study, or when there was an absence of physical and mental conditions necessary to provide consent. Informed consent was obtained for all participants.

### Clinical parameters

When self-reported, hypertension was defined if using anti-hypertensive medication, or following two blood pressure measurements of ≥ 140 (systolic blood pressure) or ≥ 90 mmHg (diastolic blood pressure). When self-reported, diabetes mellitus was defined if using hypoglycemic medication, or if two fasting blood glucose levels were ≥ 126 mg%, or if hemoglobin A1c (HbA1c) levels were > 6.5%. Dyslipidemia was defined when there was a self-reported history of hypercholesterolemia, use of lipid-lowering treatment, or total serum cholesterol > 200 mg/dL. Patients who had smoked cigarettes during the last 6 months were defined as current smokers. Body mass index (BMI) was calculated by dividing weight by the square of the height.

## Traditional echocardiography protocol

Echocardiography images were acquired using a Vivid S6 scanner (General Electric Health; Jardim, São Paulo, Brazil), 2 to 14 days after the ischemic stroke event, in order to avoid the acute phase. A single reader then blindly analyzed the images.

Traditional echocardiography-derived parameters followed current American Society of Echocardiography (ASE) recommendations.[13,14] Left ventricular end-diastolic diameter, interventricular septum, posterior wall thickness, left atrial diameter, and aortic root diameter were measured from a parasternal long-axis view in two-dimensional images. The LV mass was then calculated and indexed by body surface area. The left ventricular ejection fraction (LVEF) was calculated using the biplane modified Simpson's rule. The left atrial volume (LAV) biplane was calculated with apical four- and two-chamber images, using the area-length method and indexing to the body surface area. The E/e' ratio was calculated from the peak early diastolic velocity of the E wave in the transmitral flow, evaluated by pulsed-wave Doppler imaging, divided by the average between the peak early diastolic velocity of the e' lateral and e' septal waves, and evaluated by pulsed-wave tissue Doppler imaging. The tricuspid annular plane systolic excursion was obtained in M-mode at the level of the tricuspid annulus in the four-chamber image.

### Speckle tracking echocardiography protocol

The STE protocol followed the previously published protocol used for the CARDIA study.[15] Images were acquired in two-dimension mode, in grayscale, in which at least three cycles were recorded at a frame rate of ≥ 50 fps. To analyze myocardial deformation (global longitudinal systolic strain, GLS), we calculated the average negative peak of the longitudinal strain from 12 ventricular segments assessed in the apical four- and two-chamber views. The number of segments excluded in the speckle tracking analysis was very low, with an average of below one segment per participant; significantly, more negative values indicate more myocardial deformation.

A sample of images from 30 participants (1:1 cases and controls) was randomly selected to be re-assessed by the same reader, and by a second reader to evaluate intra- and inter-reader reproducibility. The intra-class correlation coefficient (ICC) was 0.8 ($p < 0.001$) for both intra- and inter-reader assessment. Details of the reproducibility assessment are shown in Figure 1.

### Statistical analysis

The clinical and echocardiography-derived parameters were compared for cases and controls using t-test or chi-squared test. All variables that had a p-value below 0.1 in the univariate analyses were included as covariates in the final multivariable logistic regression model (with stroke as a dependent variable). ROC curves of the final logistic regression models were also compared in order to evaluate the discrimination for stroke; initially, only including CV risk factors related to stroke in the univariate analysis, and then also including GLS.[16] Analyses were performed using STATA 14.2 and IBM SPSS Statistics version 18.1.

## Results

Of the 330 recruited cases, 104 had previous ischemic stroke, 77 had heart disease, 71 had hemorrhage stroke at the moment of hospital admission, and 43 refused to participate in the study, or were unable to provide information. One case had wall motion abnormality and five had poor image quality. Of the 76 controls who were initially recruited, six refused to participate in the study, one had wall motion abnormality, one had left ventricular hypertrophy, and six had poor quality images. In total, 29 cases and 62 controls were included in the final analysis. Figure 2 details the recruiting process.

The clinical characteristics of the participants are shown in Table 1. Both cases and controls had similar mean ages and sex (predominantly male). There was no significant difference between cases and controls in univariate analysis regarding hypertension, diabetes mellitus, and BMI. Smoking was more prevalent in cases compared to controls (34% vs, 9%, $p = 0.001$), and dyslipidemia had a higher prevalence in cases compared to controls (54% vs. 37%, $p = 0.09$).

Individuals with a first ischemic stroke showed less myocardial deformation (less negative mean GLS) than healthy controls (mean GLS, -16.7% ± 3.4% vs. -19.2% ± 2.8%, respectively; $P < 0.002$), as shown in Figure 3. Cohen's d was used to evaluate the magnitude of the difference, and an index of 0.80 was obtained. However, there was no significant difference in the traditional echocardiography parameters between cases and controls (Table 2).

After adjustment for smoking and hyperlipidemia, GLS maintained an independent association with stroke (OR = 1.3; 95% CI, 1.1–1.6; $p = 0.005$) (Table 3 and Figure 4). There was a significant increase in the area under the ROC curve for stroke compared to the model that only included current smoking (a clinical variable that was associated with stroke) after adding GLS (0.65 vs. 0.78, $p = 0.009$).

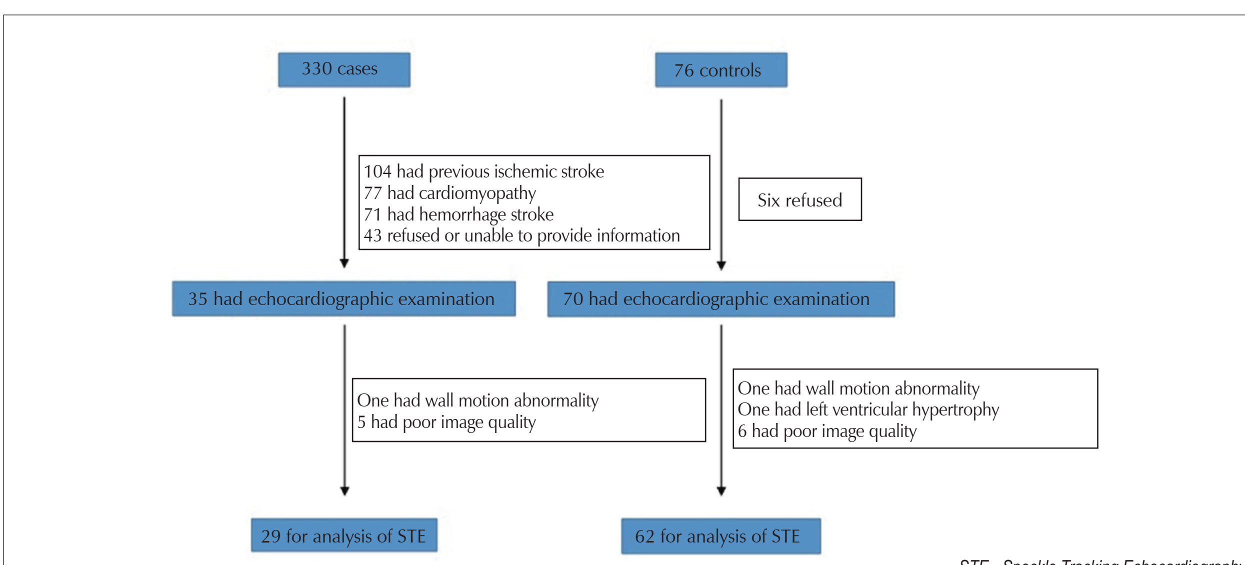
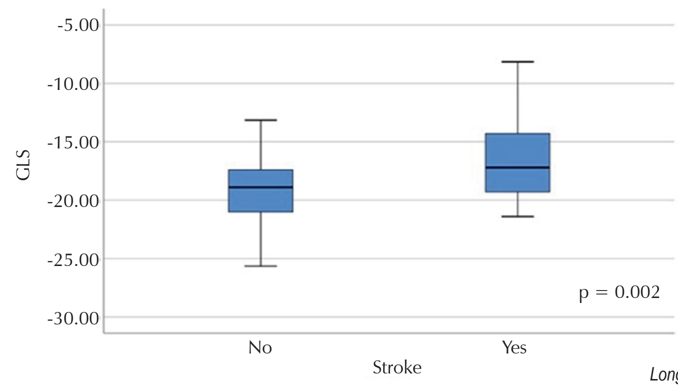



**Figure 1 –** *Recruitment of cases and controls.*




*Longitudinal Strain; p value by Mann-Whitney test.*

**Figure 2 –** *Distribuition of global longitudinal strain (GLS) between cases (n=29) and controls (n=62).*

**Table 1 - Clinical characteristics for controls and cases.**

| Variables | Controls (68) Mean (±DP) | Cases (34) Mean (±DP) | P value |
|---|---|---|---|
| Age,years | 59 (12) | 60 (12) | 0.85 |
| Male sex, % | 54 | 54 | 1.0 |
| Hypertension, % | 64 | 65 | 0.89 |
| Diabetes Mellitus, % | 16 | 20 | 0.58 |
| Dyslipidemia, % | 37 | 54 | 0.09 |
| Current smoking, % | 9 | 34 | 0.001 |
| BMI, kg/m$^2$ | 26.3 (4) | 27.2 (5) | 0.32 |

*BMI - body-mass index; SD - Standard Deviation.*

## Discussion

In the current study, we demonstrate that reduced longitudinal myocardial deformation is associated with a first ischemic stroke in individuals with a generally healthy heart, independent of known CV risk factors, and before identifiable changes in traditional echocardiography-derived parameters. For this purpose, we carefully excluded individuals with a history of known CV diseases, as well as those with electrocardiographic and echocardiographic abnormalities. Moreover, we paired the participants for sex, age, and hypertension, all of which may influence myocardial deformation. Our findings show that GLS is associated with a first episode of stroke, and that GLS could help to predict a first episode of ischemic stroke in a low risk population.

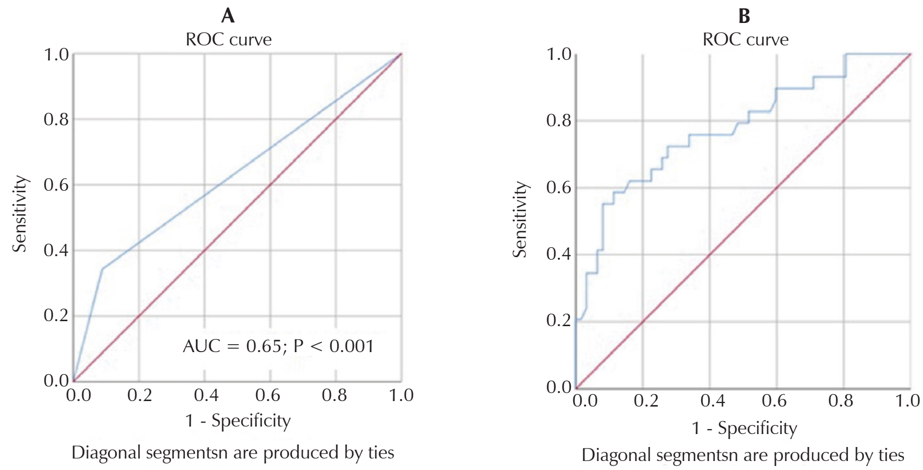
There is evidence of increasing stroke rates in young adults,[5] which frequently present as a first CV event. Importantly, stroke is related to high rates of death and disability,[1,2,17] and has a considerable impact on healthcare costs.[18] Therefore, the identification of an early marker for stroke is important, especially in apparently low-risk younger populations. Our population had a mean age of 60 ± 12 years, which was younger than that in other studies assessing stroke and subclinical CV disease. For instance, the Northern Manhattan Study (NOMAS), which demonstrated an association between GLS and silent cerebral ischemia, had an average age of 69 ± 10 years.[19]

The relationship between clinically evident heart failure and stroke is well established.[20,21] However, how subclinical cardiac changes relate to stroke is less clear. LVEF is an important marker in patients with known heart disease, but it was not associated with stroke in our study. In fact, the heart apparently has compensatory deformation mechanisms that allow for a stable LVEF in subclinical phases of cardiac dysfunction.[22,23] STE is more sensitive to early myocardial dysfunction because this new technique analyzes motion-tracking speckles in the ultrasonic image in two dimensions.[24]

We found that GLS could be used as a consistent risk marker for first ischemic stroke in a population free of known CVD. Russo C et al.[19] have shown that brain and cardiac subclinical abnormalities were simultaneously present in the participants of the abovementioned study, while Armstrong et al. demonstrated in the 25-year CARDIA study[25] that reduced GLS was associated with microscopic, macrostructural, and subclinical cerebral perfusion changes. These findings reinforce the hypothesis that brain and cardiac subclinical changes are present at the same time, before clinically manifested CV disease. In our study, the data collection for exposure (GLS) and outcome (stroke) was performed simultaneously. This leads us to the discussion of which comes first, because we know that cerebrovascular impairment may cause subclinical cardiac changes.[26] Therefore, the findings of the NOMAS and CARDIA studies reinforces the hypothesis that GLS is a good subclinical cardiac marker for ischemic stroke and not the cause of event. Some studies have demonstrated an association between abnormalities on electrocardiography with stroke and subclinical cerebrovascular changes.[27,28]

Although GLS showed an independent association with stroke, no association was found for LVEF and the first cerebrovascular event in this middle-aged adult population. In fact, it has been shown that GLS values relate to stroke after myocardial infarction.[29] In addition, GLS was superior to LVEF as a predictor of CV mortality (including stroke) in patients with advanced chronic kidney disease.[30] However, the relationship between myocardial deformation and stroke are still not entirely clear, particularly when considering stroke as the first manifestation of CV disease in generally healthy middle-aged adults.

Other traditional echocardiography-derived parameters




*A – Model with current smoking; B – Model with smoking and global longitudinal strain. Hosmer and Lemeshow test with p value = 0.86; p value for AUC comparison = 0.009.*

**Figure 3 –** *ROC curve of final logistic regression models (n=91).*

**Table 2 - Description of the traditional echocardiography parameters in controls and cases.**

| Parameters | Controls (66) Mean (±DP) | Cases (32) Mean (±DP) | P value |
|---|---|---|---|
| LAV, ml/m$^2$ | 30 (8) | 28 (8) | 0.21 |
| LV mass, g/m$^2$ | 78 (18) | 84 (23) | 0.11 |
| E/e' ratio | 7.1 (2.3) | 6.7 (1.9) | 0.37 |
| LVEF, % | 63 (6) | 61 (7) | 0.11 |
| LVDD, mm | 47 (4) | 47 (4) | 0.86 |
| LAD, mm | 34 (3) | 34 (4) | 0.41 |
| Ao root, mm | 33 (3) | 33 (4) | 0.82 |
| TAPSE | 34 (3) | 34 (4) | 0.11 |

*LAV - left atrial volume indexed by BSA; LV mass - left ventricular mass indexed by BSA; E - Pulse-waved Doppler-derived peak diastolic velocity in transmitral inflow; é - tissue Doppler imaging-derived peak diastolic velocity (average for lateral and septal assessments); LVEF - left ventricular ejection fraction; LVDD - left ventricular diastolic diameter; LAD - left atrial diameter; Ao - aortic; TAPSE - tricuspid annular plane systolic excursion; BSA - body surface area.*

**Table 3 - Multivariable logistic regression models (n = 91).**

| Variables | Model 1 OR (CI 95%) | Model 2 OR (CI 95%) | P value |
|---|---|---|---|
| Age | 1.0 (0.97 - 1.04) | | |
| Male sex | 1.0 (0.44 - 2.26) | | |
| Hypertension | 1.1 (0.48 - 2.62) | | |
| Diabetes Mellitus | 1.5 (0.50 - 4.21) | | |
| Dyslipidemia | 2.04 (0.98 - 4.67) | 1.66 (0.58 - 4.64) | 0.34 |
| Current smoking | 5.39 (1.81 - 16) | 7.13 (1.88 - 26.9) | 0.004 |
| BMI | 1.05 (0.96 - 1.16) | | |
| GLS | 1.35 (1.13 - 1.61) | 1.31 (1.10 - 1.57) | 0.005 |

*BMI - body-mass index; GLS - global longitudinal strain; OR - Odds Ratio. Model 1 - univariate analysis; Model 2 - multivariate analysis.*

had no significant association with stroke in our study. The relations between LV mass, LA size, and aortic root with CV risk factors and events among middle-aged adults is well known.[31, 32] In our study, we aimed to address the risk in otherwise healthy patients, therefore excluding participants with ECG and major echocardiography abnormalities. This strict patient selection, in addition to controls matched by hypertension, age, and sex, probably attenuated the relations between stroke and these traditional echocardiography-derived parameters. Based on our findings, GLS may have a higher magnitude impact when assessing risk for patients who would be classified as having a normal heart based on traditional echocardiography.

Smoking was also an independent predictor of stroke in our study, after controlling for age, sex, and hypertension. In fact, smoking is a known strong risk factor for stroke,[33, 34] and has also been shown to be associated with cryptogenic stroke in patients of similar ages.[35] However, we did not assess the predictive value of CV risk factors for stroke, as the controls were matched for hypertension, age, and sex. It is known that smoking relates to inflammatory and pro-thrombotic states,[36] which may present a higher impact in otherwise healthy younger patients.

This study has several limitations. First, self-referred information was used to address risk factors, which may have been subject to errors. Second, we followed the CARDIA speckle tracking protocol, which is a validated protocol tested in a substantial number of patients, but did not include three-chamber views for strain analysis. Third, and importantly, we did not include participants with known CV events, abnormal EKG findings, nor abnormal traditional echocardiography-derived parameters. Therefore, it is unlikely that the average GLS would suffer significant changes when adding three-chamber data in this sample of participants with generally normal hearts.

In patients without previous cardiac disease, we showed that myocardial dysfunction, as assessed by decreases in longitudinal deformation, is a promising marker of the first episode of stroke. However, longitudinal studies are needed

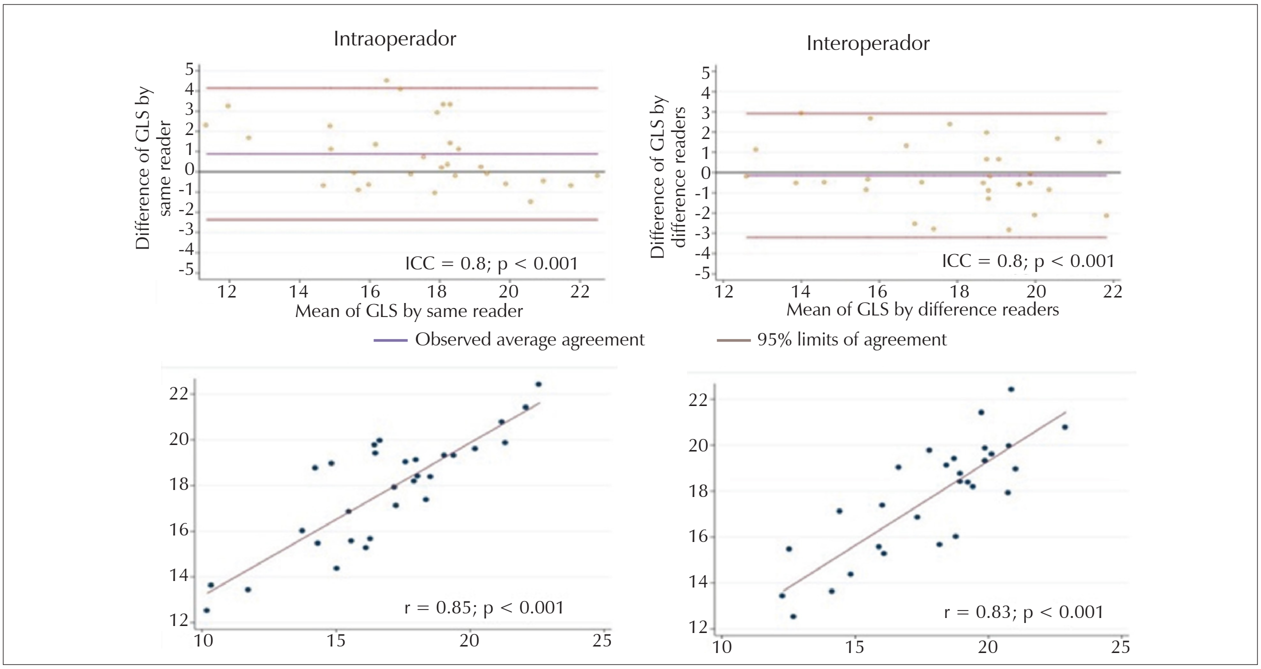



**Figure 4 –** *Intra and inter-reader evaluation of reproducibility.*

to further address this predictive potential. The ability to assess the early risk of stroke may aid policy planning to reduce the burden of this disease, particularly among younger patients.

## Conclusion

GLS has a consistent and independent association with a first episode of ischemic stroke in middle-aged adults with generally normal hearts, after controlling for age, sex, and hypertension. Longitudinal deformation may be a potential risk marker in people without obvious cardiac structure or functional abnormalities.

## Acknowledgments

Dr. Morais Jr. was funded by UNIVASF.

## Authors' contributions

Research creation and design:: Armstrong AC; Morais Júnior JC; Data acquisition: Morais Júnior JC; Salvioni NCP; Cardoso LS; Confessor CF; Silva AML; Lima DRV; Galdino Júnior APC; Data analysis and interpretation: Morais Júnior JC; Salvioni NCP; Cardoso LS; Armstrong AC; Statistical analysis: Armstrong AC; Writing: Morais Júnior JC; Critical revision for important intellectual content: Lima DRV; Silva AML; Lima J; Armstrong AC; Correia LCL

## Conflict of interest

The authors have declared that they have no conflict of interest.

## References

1. Zhang Y, Chapman AM, Plested M, Jackson D, Purroy F. The Incidence, Prevalence, and Mortality of Stroke in France, Germany, Italy, Spain, the UK, and the US: A Literature Review. Stroke Res Treat.. 2012;2012:436125. doi: 10.1155/2012/436125.

2. Berzina G, Paanalahti M, Lundgren-Nilsson A, Sunnerhagen KS. Exploration of some personal factors with the International Classification of Functioning, Disability and Health core sets for stroke. J Rehabil Med. 2013 Jul;45(7):609-15. doi: 10.2340/16501977-1171..

3. 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 Nov;18:41-52. doi: 10.1016/j.arr.2014.07.003.

4. Lo Coco D, Lopez G, Corrao S. Cognitive impairment and stroke in elderly patients. Vasc Health Risk Manag. 2016;12:105-16. doi: 10.2147/VHRM.S75306.

5. Bejot Y, Bailly H, Durier J, Giroud M. Epidemiology of stroke in Europe and trends for the 21st century. Presse medicale. 2016;45(12 Pt 2):e391-e98. doi: 10.1016/j.lpm.2016.10.003.6. Geyer H, Caracciolo G, Abe H, Wilansky S, Carerj S, Gentile F, et al. Assessment of myocardial mechanics using speckle tracking echocardiography: fundamentals and clinical applications. J Am Soc Echocardiogr 2010;23(4):351-69; quiz 453-5. doi: 10.1016/j.echo.2010.02.015.

7. Joyce E, Hoogslag GE, Leong DP, Debonnaire P, Katsanos S, Boden H, et al. Association between left ventricular global longitudinal strain and adverse left ventricular dilatation after ST-segment-elevation myocardial infarction. Circulation Cardiovascular imaging. 2014;7(1):74-81. doi: 10.1161/CIRCIMAGING.113.000982.

8. Cong T, Sun Y, Shang Z, Wang K1, Su D1, Zhong L, et al. Prognostic Value of Speckle Tracking Echocardiography in Patients with ST-Elevation Myocardial Infarction Treated with Late Percutaneous Intervention. Echocardiography. 2015;32(9):1384-91. doi: 10.1111/echo.12864.

9. Lacalzada J, de la Rosa A, Izquierdo MM, Jiménez JJ, Iribarren JL, García-González MJ, et al. Left ventricular global longitudinal systolic strain predicts adverse remodeling and subsequent cardiac events in patients with acute myocardial infarction treated with primary percutaneous coronary intervention. The international journal of cardiovascular imaging 2015;31(3):575-84 Int J

Cardiovasc Imaging. 2015;31(3):575-84. doi: 10.1007/s10554-015-0593-2.

10. Meyer BC, Lyden PD. The modified National Institutes of Health Stroke Scale: its time has come. Int J Stroke. 2009 Aug;4(4):267-73. doi: 10.1111/j.1747-4949.2009.00294.x.

11. Galderisi M, Lomoriello VS, Santoro A, Esposito R, Olibet M, Raia R, et al. Differences of myocardial systolic deformation and correlates of diastolic function in competitive rowers and young hypertensives: a speckle-tracking echocardiography study. J Am Soc Echocardiogr. 2010 Nov;23(11):1190-8. doi: 10.1016/j.echo.2010.07.010..

12. Kjeldsen SE, Narkiewicz K, Burnier M, Oparil S. The INTERSTROKE Study: hypertension is by far the most important modifiable risk factor for stroke. Blood Press. 2017 Jun;26(3):131-2. doi: 10.1080/08037051.2017.1292456.

13. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1):1-39.e14. doi: 10.1016/j.echo.2014.10.003.

14. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular. Eur Heart J Cardiovasc Imaging. 2016 Dec;17(12):1321-1360. doi: 10.1093/ehjci/jew082.

15. Armstrong AC, Ricketts EP, Cox C, Adler P, Arynchyn A, Liu K, et al. Quality Control and Reproducibility in M-Mode, Two-Dimensional, and Speckle Tracking Echocardiography Acquisition and Analysis: The CARDIA Study, Year 25 Examination Experience. Echocardiography.2015;32(8):1233-40. doi: 10.1111/echo.12832.

16. Cleves MA. From the help desk : Comparing areas under receiver operating characteristic curves from two or more probit or logit models. The Stata Journal 2002;2(3):301-13.

17. Saposnik G, Del Brutto OH. Stroke in South America: a systematic review of incidence, prevalence, and stroke subtypes. Stroke. 2003;34(9):2103-7. doi: 10.1161/01.STR.0000088063.74250.DB.

18. Ovbiagele B, Goldstein LB, Higashida RT, Howard VJ, Johnston SC, Khavjou OA, et al. Forecasting the future of stroke in the United States: a policy statement from the American Heart Association and American Stroke Association. Stroke 2013;44(8):2361-75. doi: 10.1161/STR.0b013e31829734f2.

19. 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(10):1105-11. doi: 10.1161/CIRCULATIONAHA.113.001984.

20. Alberts VP, Bos MJ, Koudstaal P, Hofman A, Witteman JC, Stricker B, et al. Heart failure and the risk of stroke: the Rotterdam Study. Eur J Epidemiol. 2010 Nov;25(11):807-12. doi: 10.1007/s10654-010-9520-y.

21. Cuadrado-Godia E, Ois A, Roquer J. Heart failure in acute ischemic stroke. Curr Cardiol Rev. 2010 Aug; 6(3): 202–213. doi: 0.2174/157340310791658776.

22. Kerkhof PL, Yasha Kresh J, Li JK, Heyndrickx GR. Left ventricular volume regulation in heart failure with preserved ejection fraction. Physiol Rep. 2013;1(2):e0007. doi: 10.1002/phy2.7..

23. Holst JM, Kilker BA, Wright S, Hoffmann B. Heart failure with preserved ejection fraction: echocardiographic VALVE protocol for emergency physicians. Eur J Emerg Med. 2014 Dec;21(6):394-402. doi: 10.1097/MEJ.0000000000000093.

24. Perk G, Tunick PA, Kronzon I. Non-Doppler two-dimensional strain imaging by echocardiography--from technical considerations to clinical applications. J Am Soc Echocardiogr. 2007 Mar;20(3):234-43. doi: 10.1016/j.echo.2006.08.023.

25. Armstrong AC, Muller M, Ambale-Ventakesh B, Halstead M, Kishi S, Bryan N, et al. Association of early left ventricular dysfunction with advanced magnetic resonance white matter and gray matter brain measures: The CARDIA study. Echocardiography. 2017. 34(11): 17–1622. doi: 10.1111/echo.13695

26. Cuisinier A, Maufrais C, Payen JF, nottin S, Walther G, Bouzat P. Myocardial function at the early phase of traumatic brain injury: a prospective controlled study. Scand J Trauma Resusc Emerg Med. 2016;24(1):129. doi.org/10.1186/s13049-016-0323-3

27. Kamel H, Soliman EZ, Heckbert SR, Kronmal RA, Longstreth WT Jr, Nazarian S, et al. P-wave morphology and the risk of incident ischemic stroke in the Multi-Ethnic Study of Atherosclerosis. Stroke. 2014;45(9):2786-8. doi: 10.1161/STROKEAHA.114.006364.

28. Kamel H, Bartz TM, Longstreth WT, Jr., Okin PM, Thacker EL, Patton KK, et al. Association between left atrial abnormality on ECG and vascular brain injury on MRI in the Cardiovascular Health Study. Stroke. 2015;46(3):711-6. doi: 10.1161/STROKEAHA.114.007762.29. Olsen FJ, Pedersen S, Jensen JS, Biering-Sørensen T. Global longitudinal strain predicts incident atrial fibrillation and stroke occurrence after acute myocardial infarction. Medicine (Baltimore). 2016 Nov;95(44):e5338. doi: 10.1097/MD.0000000000005338.30. Krishnasamy R, Isbel NM, Hawley CM, Pascoe EM, Burrage M, Leano R, et al. Left Ventricular Global Longitudinal Strain (GLS) Is a Superior Predictor of All-Cause and Cardiovascular Mortality When Compared to Ejection Fraction in Advanced Chronic Kidney Disease. PloS one 2015;10(5):e0127044. doi: 10.1371/journal.pone.0127044.

31. Armstrong AC, Jacobs DR, Jr., Gidding SS, Colangelo LA, Gjesdal O, Lewis CE, et al. Framingham score and LV mass predict events in young adults: CARDIA study. Int J Cardiol. 2014 Mar 15;172(2):350-5. doi: 10.1016/j.ijcard.2014.01.003.

32. Armstrong AC, Liu K, Lewis CE, Sidney S, Colangelo LA, Kishi S, et al. Left atrial dimension and traditional cardiovascular risk factors predict 20-year clinical cardiovascular events in young healthy adults: the CARDIA study. Eur Heart J Cardiovasc Imaging. 2014 Aug;15(8):893-9. doi: 10.1093/ehjci/jeu018.

33. O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. Lancet. 2016;388(10046):761-75. doi: 10.1016/S0140-6736(16)30506-2.

34. Wang W, Jiang B, Sun H, Ru X, Sun D, Wang L, et al. Prevalence, Incidence, and Mortality of Stroke in China: Results from a Nationwide Population-Based Survey of 480 687 Adults. Circulation. 2017;135(8):759-71. doi: 10.1161/CIRCULATIONAHA.116.025250.

35. Leong DP, Joyce E, Debonnaire P, Katsanos S, Holman ER, Schalij MJ, et al. Left Atrial Dysfunction in the Pathogenesis of Cryptogenic Stroke: Novel Insights from Speckle-Tracking Echocardiography. J Am Soc Echocardiogr. 2017 Jan;30(1):71-79.e1. doi: 10.1016/j.echo.2016.09.013.

36. Arboix A. Cardiovascular risk factors for acute stroke: Risk profiles in the different subtypes of ischemic stroke. World J Clin Cases. 2015 May 16;3(5):418-29. doi: 10.12998/wjcc.v3.i5.418.