Left Atrial Dysfunction in the Pathogenesis of Cryptogenic Stroke: Novel Insights from Speckle-Tracking Echocardiography

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Background: Myocardial strain analysis by speckle-tracking echocardiography, which can detect subtle abnormalities in left atrial (LA) function, may offer unique insights into LA pathophysiology in patients with cryptogenic stroke (CS). The aim of this study was to investigate whether LA reservoir strain by speckle-tracking echocardiography, as a measure of LA compliance, is impaired in patients with CS and no history of atrial fibrillation.

Methods: A retrospective case-control study of 742 patients (mean age, 59 ± 13 years; 54% men; 371 with CS and 371 control subjects) was conducted. LA reservoir strain was quantified using speckle-tracking echocardiography.

Results: LA strain was significantly lower among patients with CS than control subjects (30 ± 7.3% vs 34 ± 6.7%, $P < .001$). Current smoking (odds ratio [OR], 2.6; 95% CI, 1.7–4.0; $P < .001$), systolic blood pressure (OR, 1.17 per 10 mm Hg increase; 95% CI, 1.06–1.29; $P = .001$), antihypertensive treatment (OR, 0.45; 95% CI, 0.30–0.66; $P < .001$), larger indexed left ventricular end-systolic volume (OR, 1.04; 95% CI, 1.01–1.07; $P = .02$), higher E/E′ ratio (OR, 1.06; 95% CI, 1.01–1.11; $P = .01$), mitral regurgitation (OR, 1.8; 95% CI, 1.2–2.7; $P = .003$), and lower LA reservoir strain (OR, 1.07 per 1% reduction; 95% CI, 1.05–1.10; $P < .001$) were independently associated with CS. Importantly, LA reservoir strain conferred incremental discriminatory value in the identification of patients with CS (likelihood ratio $P < .001$).

Conclusions: Subtle LA dysfunction, as assessed by LA reservoir strain with speckle-tracking echocardiography, is associated with CS independent of other cardiovascular risk factors. These findings suggest a potential role for LA strain to risk-stratify patients in the prevention of stroke. (J Am Soc Echocardiogr 2017;30:71-9.)

Keywords: Stroke, Echocardiography, Left atrium, Strain, Deformation

Stroke remains of unresolved etiology in a large proportion of patients despite extensive investigation (so-called cryptogenic stroke [CS]).[1,2] Research to identify individuals at high risk for CS is crucial to characterize the disease better and improve approaches to primary and secondary prevention. Potential mechanisms underlying CS may include unrecognized atrial fibrillation (AF)[3,4] and subclinical atherosclerotic disease.[2] Frequently these two conditions accompany each other,[5] as they share common risk factors, such as age and hypertension.

Both AF[6] and atherosclerotic risk factors[7] have been associated with abnormalities of left atrial (LA) mechanical function. The emergence of speckle-tracking echocardiographic imaging allows sensitive assessment of myocardial deformation (strain), including the analysis of LA function.[8] Impaired LA strain has been described in patients with hypertension and/or diabetes but with normal LA size.[7] Furthermore, a significant relationship between increasing LA myocardial fibrosis, increasing AF burden, and reduced LA strain by speckle-tracking analysis has been demonstrated.[9] These studies suggest that LA strain might be a sensitive marker of structural and functional LA abnormalities in cardiovascular disease and AF. Therefore, we investigated the relationship between LA strain in patients who experienced CS or transient ischemic attacks (TIAs) (collectively

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Abbreviations

AF = Atrial fibrillation

BP = Blood pressure

CS = Cryptogenic stroke

LA = Left atrial

LV = Left ventricular

LVESVI = Indexed left ventricular end-systolic volume

MR = Mitral regurgitation

PFO = Patent foramen ovale

ROC = Receiver operating characteristic

TIA = Transient ischemic attack

referred to as patients with CS) and a control cohort. We hypothesized that LA strain would be reduced in patients with CS compared with control subjects, because LA speckle-tracking strain is a sensitive marker of chronic cardiovascular disease and AF, either or both of which may cause CS.

METHODS

The study design entailed a retrospective case-control analysis of patients who had undergone thorough clinical and echocardiographic evaluation. Patients with CS were identified by screening the indication for all referrals for transthoracic echocardiography at a tertiary referral center between 2000 and 2012 as part of the evaluation for ischemic stroke or TIA. Patients were considered for inclusion only in the presence of brain imaging to exclude primary intracerebral hemorrhage, with the diagnosis confirmed by a neurologist. Stroke was defined as rapidly developing clinical signs of cerebral disturbance lasting >24 hours or featuring cerebral imaging evidence of brain infarction, with no apparent nonvascular cause.[10] TIA was diagnosed if these clinical signs persisted up to 24 hours with no indication of brain infarction on neuroimaging.[10] Stroke or TIA was considered cryptogenic in keeping with contemporary approaches,[11] defined by the absence of (1) large-vessel arterial stenosis >50% of the vessel's reference diameter, (2) arterial occlusion or dissection, (3) cardioembolic source (see the subsequent exclusion criteria for a detailed description), and (4) other recognized causes of stroke, including but not limited to polycythemia vera, cerebral vasculitis, and antiphospholipid syndrome.

Control subjects were selected according to published comparability principles, in that they were representative of the same base experience as patients.[12] These control subjects included patients with no histories of stroke or TIA who were referred for echocardiography for the following clinical indications: evaluation of chest pain, dyspnea, syncope, palpitations, auscultatory murmur, or suspected structural heart disease or ventricular dysfunction. Screening for control subjects was performed by the indication for echocardiography. Control subjects were accepted only if there was no structural heart disease present. Consecutive eligible control subjects were included working backward chronologically from studies performed in 2012 until the same number of control subjects as patients was reached.

Exclusion criteria were (1) factors associated with medium or high risk as sources of cardioembolism in patients with stroke, such as aortic or mitral valvular prostheses, any history of AF or atrial flutter, known or suspected cardiomyopathy, infective endocarditis, atrial septal defect, and intracardiac tumor or thrombus,[13] and (2) potential confounders in the measurement of LA mechanical function, including the presence of significant (>50% luminal) coronary artery stenosis, previous myocardial infarction or regional wall motion abnormality, prior administration of cardiotoxic chemotherapeutic agents, sick sinus syndrome, any valvular lesion of >2+ severity, and pregnancy. These exclusion criteria were applied to both patients and control subjects. In addition, patients were not included in the absence of cerebrovascular imaging to rule out large-vessel arterial stenosis or occlusion. The performance of other investigations was driven by the treating physician, and in the patients with CS, exclusion of known causes of stroke was guided by individual clinical evaluation.

Comorbid conditions were recorded as of the time of echocardiography for control subjects and as of the time immediately preceding the index stroke or TIA for patients. In addition, hypertension, diabetes mellitus, and hyperlipidemia diagnosed within 12 months following the patient's index visit were included among their comorbidities, as these were likely to have been present before this index visit.

All clinical and echocardiographic data were collected in the departmental cardiology information system (EPD-Vision; Leiden University Medical Centre, Leiden, The Netherlands) and retrospectively analyzed. The institutional review board approved this retrospective analysis of clinically acquired data and waived the need for written informed consent.

Echocardiography

Patients underwent transthoracic echocardiography using a commercially available system equipped with a 3.5-MHz transducer (Vivid 7 or E9; GE Vingmed Ultrasound AS, Horten, Norway). Two-dimensional grayscale images and pulsed-wave, continuous-wave, and color Doppler data were acquired in the parasternal and apical views. Images were acquired in the left lateral decubitus position during quiet respiration, with a single focal zone and the sector width adjusted to achieve a frame rate of 40 to 80 frames/sec.

Patent foramen ovale (PFO) was evaluated in patients with CS by color Doppler imaging and by two-dimensional grayscale imaging before and during the Valsalva maneuver, following the administration of agitated saline contrast. Specifically, to assess the presence of a right-to-left shunt, color Doppler imaging was used, lowering the Nyquist limit and performing an agitated saline contrast study as currently suggested.[14] Agitated saline contrast (7–9 mL) was injected intravenously at rest and after the Valsalva maneuver (achieving deviation of the interatrial septum to the LA side). The presence of a PFO was presumed when agitated saline contrast was noted in the left atrium within three to five cardiac cycles after complete opacification of the right atrium. Systematic PFO evaluation was not a requirement among control subjects, because the study's aim was not to examine the relationship between PFO and CS. For patients undergoing transesophageal echocardiography, the ascending aorta, aortic arch, and descending aorta were imaged.

Images were recorded digitally in cine-loop format and analyzed offline using the commercial software package EchoPAC version 111.0.0 (GE Vingmed Ultrasound AS). All offline echocardiographic analysis was performed blinded to patient group.

Echocardiographic Measurements

Left ventricular (LV) volumes were measured from the apical two- and four-chamber views, and LV ejection fraction was calculated using the biplane Simpson technique. LA volume was also evaluated using the biplane Simpson technique. LV mass and relative wall thickness were estimated according to current recommendations.[15] Chamber volumes and LV mass were indexed to body surface area. Mitral regurgitation (MR) severity was graded according to current guidelines.[16] Transmitral LV filling velocities (E and A waves) were measured at the mitral valve leaflet tips using pulsed-wave Doppler. E′ velocity was recorded as the peak early diastolic tissue velocity