Enhancing Detection of Subclinical End-Organ Damage:
Echocardiographic Left Ventricular Strain Holds Up a Mirror to the Brain

Running title: Kizer; LV strain and subclinical cerebrovascular disease

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The turn of the 21st century marked an unprecedented achievement in the health of the U.S. and other developed countries, with the extension of life expectancy to over 75 years, as compared with approximately 45 years recorded at the start of the previous century.1 This accomplishment, however, and the promise of further increases in longevity as the present century marches on, has brought to the fore a daunting new challenge posed by the burgeoning of chronic disabling conditions affecting our aging populations. Indeed, morbidity and chronic disability now account for almost half of the U.S. health burden.2 Yet among such chronic conditions, a foremost concern is the rising epidemic of cognitive impairment and dementia.3 With a prevalence in developed countries of roughly 7% among adults aged 60 and older, as many as half of whom require resource-intensive home or institution-based care, dementia alone imposes an outsized societal toll.3 At the economic level, health care expenditures in 2010 for the estimated 35.6 million people affected with dementia worldwide run to an astounding $604 billion, a figure that will push far higher with the disorder’s projected tripling in prevalence by 2050.3

Against this backdrop, studies of dementia have led to the growing recognition that vascular disease and its risk factors play a major role in pathogenesis.4 The most common cause of dementia is Alzheimer’s disease, a neurodegenerative disorder characterized pathologically by the accumulation of β-amyloid plaques and neurofibrillary tangles, followed in frequency by vascular dementia, which is defined pathologically by detection of extensive ischemic lesions in the brain.3 But an autopsy series showed that although 86% of patients with dementia exhibited pathology related to Alzheimer’s disease, only half had pure Alzheimer’s disease, and over one-quarter had mixed Alzheimer’s disease and cerebrovascular pathology.5 Furthermore, another large post-mortem study found the presence of cerebrovascular disease, detected in 32% of patients with Alzheimer’s disease, to be associated with a lower burden of Alzheimer’s disease
lesions for a comparable severity of dementia at death. These data support the view that cerebrovascular disease may be an important co-factor in Alzheimer’s disease, acting to lower the threshold for dementia in this disorder.

Beyond such neuropathological evidence, advances in neuroimaging have been pivotal in defining the true scope of cerebrovascular disease by allowing its pre-mortem identification and study. Magnetic resonance imaging (MRI) of the brain in epidemiological cohorts has shown that the incidence of silent infarcts and hemorrhages is far more common than clinically overt stroke, exceeding the latter by as much as 10-fold. Notably, epidemiological studies have documented that these silent strokes are not inconsequential, but instead confer a heightened risk of cognitive decline and dementia. MRI also led to the more frequent and incidental discovery of white matter lesions (WML), or leukoaraiosis, in subcortical and periventricular areas of the brain. These findings were initially thought to be benign, but their clinical and pathological correlates strongly suggest that they are the consequence of small vessel disease. In fact, like covert brain infarcts, clinically silent WMLs have been shown to increase with age, and to herald the future onset of dementia.

In parallel with such progress in neuroimaging, and the detection of subclinical vascular damage, major strides have been made in non-invasive approaches to evaluate cardiac structure and function. Along with other modalities, echocardiography has remained on the leading edge in the quest to better assess cardiac mechanics, and to yield improved measures of ventricular systolic and diastolic function. Such efforts have focused fruitfully on myocardial deformation, described by the physical terms “strain” and “strain rate (SR)”, referring, respectively, to the fractional change in myocardial length, and to the magnitude of fractional length change per unit time. Strain and SR have an important advantage over traditional measures of ventricular
performance, which are predicated on displacement of myocardial structures, in that they assess regional function independently of translational motion, and have been found to be less influenced by loading conditions.\textsuperscript{10} Traditionally the preserve of cardiac MRI, non-invasive assessment of strain/SR has received a major boost with the development of speckle-tracking echocardiography (STE).\textsuperscript{10} This technique tracks the motion of intramyocardial speckles, acoustic signatures of focal tissue characteristics visible on B-mode imaging, in a manner that circumvents the angle-dependency problems associated with its forerunner, Doppler-tissue imaging (DTI).\textsuperscript{10}

STE can be applied to generate a global measure of systolic longitudinal strain (GLS) by averaging the regional strain values of the 12 to 16 left ventricular (LV) segments that can be evaluated from the 2 or 3 different apical views.\textsuperscript{11,12} Using this approach, different groups have demonstrated the stronger and independent prognostic value of GLS over LV ejection fraction (EF) or wall motion score index for adverse cardiovascular outcomes or mortality in cohorts referred for echocardiographic evaluation\textsuperscript{11} or with chronic systolic heart failure.\textsuperscript{12} Previous studies have documented a close link between depressed LVEF and clinical or subclinical stroke in the setting of coronary heart disease (CHD) or heart failure (HF).\textsuperscript{13,14} Whether novel indices of myocardial systolic function might offer earlier insights into shared vascular damage of the heart and brain among apparently healthy individuals has not, however, been previously studied.

In this issue of Circulation,\textsuperscript{15} Russo and colleagues address this very question in a subset of the population-based Northern Manhattan Study (NOMAS) prospectively enrolled in the Cardiovascular Abnormalities and Brain Lesion (CABL) study. As part of CABL, participants aged 55 or older with no clinical history of stroke underwent brain MRI and transthoracic echocardiograms nearly concurrently. The present study focused on participants (n=439) free of
known atrial fibrillation/flutter or CHD who completed both tests, and had no important left-sided valvular disease. Lower GLS, but not LVEF, was associated with the presence of subclinical brain infarcts and higher WML volume both as a continuous and categorical variable independently of clinical and other echocardiographic parameters, including LVEF itself. The magnitude of the association for participants (11.8%) with GLS values below, as compared to above, the study-specific lower limit of normal and presence of silent brain infarcts was especially pronounced, with an over three-fold increase in the relative odds of subclinical cerebral infarction.

The present findings are important, and the study’s strengths rest with its prospective, community-based design, and with its novel application of state-of-the-art echocardiographic assessment of global myocardial mechanics. The cross-sectional and observational nature of the work does not, however, allow conclusions about the causal basis for the association, leaving room for several potential explanations. Cerebral hypoperfusion, such as occurs in advanced HF, can cause cerebral ischemia and cognitive impairment, but the early abnormalities in LV systolic function detected by GLS are insufficient to result in meaningful reductions in global cerebral perfusion. Undetected atrial fibrillation leading to thromboembolism also needs to be considered, although as noted by the authors, the predominance of subcortical lesions argues against its under-recognition as a major cause.

The most tenable explanation for the current findings may instead lie in the common risk factors that adversely influence microvascular and macrovascular function, and on the relatedness or interdependence of vascular abnormalities across different vascular beds. Among risk factors for small-vessel arterial disease, hypertension, diabetes, and aging are paramount. These conditions are associated with inflammation, increased oxidative stress, and endothelial
Moreover, their histopathological hallmarks include basement membrane thickening, smooth muscle cell hyperplasia of the tunica media, and perivascular fibrosis of small arteries and arterioles. These changes are well described in neuropathological specimens. But they are also a feature of cardiac (and renal) histopathology in these disorders, where they are associated with ischemia and interstitial fibrosis occurring preferentially in the ventricular subendocardium. Furthermore, hypertension and diabetes are associated with insudation of fibrin into the arteriolar media and degradation of extracellular matrix components, leading histopathologically to lipohyalinosis and fibrinoid necrosis. These alterations, along with formation of miliary aneurysms, are typical of cerebral small-artery disease. Either through vascular occlusion, breakdown of the blood-brain barrier, or increased vascular fragility with microhemorrhages, these changes are believed responsible for the WML and lacunar infarcts enriched in the setting of aging and its associated vascular risk factors.

What is more, the microvasculature of the brain, retina, heart and kidneys may be particularly vulnerable to such damage through large and small artery cross-talk. Stiffening of the central arteries – likewise a consequence of aging, hypertension, and diabetes – leads to pulse pressure amplification, exposing these characteristically high-flow arterial beds to accentuated blood pressure oscillations, which could compound the underlying microvascular abnormalities. Understood in this context, the early development of systolic dysfunction in the longitudinally arrayed subendocardial myocyte layer would be a particularly sensitive barometer for cerebral small-vessel disease by dint of its own particular susceptibility to microvascular injury in the presence of aging-associated risk factors.

Still, the findings of the present study must be interpreted in the context of certain limitations. The clinical details of NOMAS participants who declined participation are not
provided, precluding characterization of possible selection bias. While the study cohort is of considerable size, only 53 participants had silent brain infarction. This modest number of outcomes could lead to model instability while adjusting for 12 or 13 covariates, although there was no obvious increase in the 95% confidence bounds with adjustment to suggest this problem. Furthermore, adjustment for cholesterol did not include lipid fractions, nor was estimated glomerular filtration rate considered as a factor in the analyses. In terms of echocardiographic parameters, diastolic dysfunction was entered as a binary variable in multivariable models, which may have led to a loss of information. Moreover, left atrial volume and measures of annular calcification were not included.

These limitations notwithstanding, the strength and independence of the associations documented for GLS here and elsewhere,11 provide additional evidence favoring the possible use of this measure of subclinical LV systolic dysfunction for global vascular risk stratification, and for potential intensification of prevention strategies involving blood pressure control, glycemic and LDL targets, and antiplatelet therapy in appropriate candidates. With respect to cerebrovascular disease in particular, the present data suggest that this technique could aid in identification of patients at heightened risk, particularly at younger ages, for entry into intervention trials to lower incidence of cognitive impairment and dementia. This concept will require additional data on the usefulness of GLS for the prediction of new-onset cerebral small-vessel disease in middle-aged patients.

With ongoing improvements in post-processing packages by different vendors, the ease of GLS analysis now makes it practicable for clinical use, adding <20 seconds of interpretation time in experienced research settings.11 But lack of harmonization for these packages across different vendors remains a problem, with different values obtained by different proprietary
software. Yet incorporation of GLS to routine clinical practice will require demonstration of its incremental predictive value relative to additional standard parameters, including left atrial volume, mitral annular calcification, and graded diastolic assessment, in other populations, and should rely on formal indices of discrimination and reclassification. In this regard, the relative performance of GLS over promising SR-based indices of global LV diastolic function, will likewise merit evaluation.

In conclusion, the study by Russo and colleagues demonstrates for the first time the primacy of global longitudinal systolic strain over global LVEF for detecting cerebral small-vessel disease in individuals without clinically overt cardiovascular disease. In so doing, Russo and colleagues have made a substantial contribution to the emerging picture linking microvascular disease and subclinical target-organ damage of major organs such as the heart and brain. No less important, their findings hold out the prospect that with earlier detection of the underlying disease processes, major gains against the scourge of vascular and cognitive disorders afflicting our aging societies, may now be closer within reach.

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