Role of echocardiography for silent cerebrovascular disease

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Abstract
Silent cerebrovascular disease, such as silent brain infarctions and white matter hyperintensities detected on magnetic resonance imaging is frequently observed in elderly individuals [1]. Although often called silent, because it occurs in the absence of clinically apparent neurological symptoms, SCD carries an increased risk of future stroke and dementia [4]. As conditions associated with poor brain health represent leading causes of global morbidity and mortality [5], identifying individuals at increased risk of SCD may allow for early and more effective prevention strategies. Echocardiography [both transthoracic (TTE) and transesophageal (TEE)] is a widely available, relatively inexpensive and non-invasive imaging modality that can play an important role for the detection of cardioembolic source for stroke [6]. In addition, the associations of abnormal echocardiographic findings with cognitive impairment have been recently shown [7]. Therefore, to understand the association between cardiac abnormalities assessed by echocardiography and silent cerebrovascular disease may provide cost-effective opportunities to detect abnormalities that may act on to try and decrease the risk of future adverse events. In the present mini review, we highlight the role of echocardiography in silent cerebrovascular disease.

Introduction
Silent cerebrovascular disease (SCD), such as silent brain infarctions (SBI) and white matter hyperintensities (WMH) on magnetic resonance imaging, is frequently observed in elderly individuals [1]. Although often called silent, because it occurs in the absence of clinically apparent neurological symptoms, SCD carries an increased risk of future stroke [2,3] and dementia [4]. As conditions associated with poor brain health represent leading causes of global morbidity and mortality [5], identifying individuals at increased risk of SCD may allow for early and more effective prevention strategies. Echocardiography [both transthoracic (TTE) and transesophageal (TEE)] is a widely available, relatively inexpensive and non-invasive imaging modality that can play an important role for the detection of cardioembolic source for stroke [6]. In addition, the associations of abnormal echocardiographic findings with cognitive impairment have been recently shown [7]. Therefore, to understand the association between cardiac abnormalities assessed by echocardiography and SCD may provide cost-effective opportunities to detect abnormalities that may be acted on to try and decrease the risk of future adverse events.

Left ventricular parameters and silent cerebrovascular disease

Left ventricular systolic function
Decreased cerebral blood flow subsequent to low cardiac output [8] and formation of left ventricular (LV) thrombus [9] are two potential pathophysiologic mechanisms accounting for SCD in patients with severe systolic heart failure (HF). Previous studies showed that a low LV ejection fraction was independently related to the presence of SCD in HF [10,11]. However, this relationship was not clearly observed in community-based participants whose LV ejection fraction was within the normal range [12-14]. Recently, Russo et al. [14] have shown that the early LV systolic dysfunction detected by lower global longitudinal strain, but not LV ejection fraction, was associated with the presence of SCD. Lower global longitudinal strain, which appears insufficient to result in both significant reduction in cerebral perfusion or be a source of thrombus formation and embolism, might in fact be a sensitive indicator of generalized atherosclerosis [15].

Left ventricular diastolic function
LV diastolic dysfunction evaluated by transmitral flow velocity and mitral annular tissue Doppler velocity is associated with the presence of SBI [13,16] and WMH [17,18] in community-based studies. The possible mechanism underlying the relationship between diastolic dysfunction and SCD may be multifocal. The early diastolic dysfunction may reflect generalized changes in the vascular system, which could contribute to subclinical atherosclerosis including endothelial dysfunction [13,19]. Moreover, the reduced systemic perfusion and thus impairment of the autoregulation of cerebral blood flow that may occur in LV diastolic dysfunction may affect the progression of WMH [17,20]. On the other hand, an association between LV diastolic dysfunction and SBI was also shown in patients with non-valvular atrial fibrillation [21] and HF [10]. In the advanced diastolic dysfunction observed in those patients, the elevated diastolic filling pressure may lead to blood stasis associated with spontaneous echo contrast and left atrial thrombus formation, which are known risk factors for embolic events [10,22]. Ishikawa et al showed that poor LV diastolic function assessed by TTE was significantly associated with a high prevalence of those left atrial (LA) abnormalities detected by TEE [21].

Left ventricular mass
Increased LV mass (LVM), particularly in the case of concentric LV hypertrophy (LVH), appears to be associated with the presence of SCD. LVM is a possible clinical marker of end-organ damage in the cerebral vasculature, as it provides a time-integrated summation of exposure to various cardiovascular risk factors [23-25]. Recently, Johansen et al found that greater LVM index was associated with the presence of SCD in a large community-based study [12]. Similar results were shown in

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Key words: silent cerebrovascular disease, echocardiography, silent brain infarction

Received: May 01, 2019; Accepted: May 10, 2019; Published: May 13, 2019
several cross-sectional studies [13,26,27]. Furthermore, the association between LV geometric patterns and the prevalence of SCD has been also investigated [28-30]. Nakanishi et al showed that concentric LVH carried the greatest independent risk for both SBI and WMH, followed by eccentric LVH, whereas concentric remodelling was not associated with SCD in the large cohort [29]. On the other hand, Haring et al recently demonstrated that higher LVM in midlife was associated with greater severity of WMH in later life [23]. Overall, it can be said that current evidence supports a strong relationship between LV mass and the presence of SCD.

**Left atrial parameters and silent cerebrovascular disease**

Several studies showed that LA enlargement is associated with both SBI [31] and WMH [32]. Recently, Russo et al. [33] demonstrated that greater LA volumes and smaller LA reservoir function assessed by real-time three-dimensional echocardiography were associated with SCD in a community-based cohort. Poor LA function can be an expression of long-standing hypertension, LVH, LV diastolic dysfunction and increased filling pressure which may lead to reduce cerebral perfusion [34] and is therefore considered as a powerful marker of cardiovascular diseases [35]. In addition, due to the strong association between increased LA size and incident atrial fibrillation [36], cardioembolism may be the other possible mechanism linking LA dysfunction and SCD. On the other hand, Sugioika et al found that LA abnormalities such as LA thrombus, spontaneous echo contrast and LA appendageemptying velocity, known risk factors for embolic stroke assessed by TEE, were associated with the presence of SBI in patients with atrial fibrillation [37].

**Aortic atherosclerosis and silent cerebrovascular disease**

Complex aortic arch plaques (AAP) are considered an important source of thromboembolic and ischemic stroke in the elderly [38]. Accordingly, the association between complex AAP detected by TEE and SBI were shown in patients with atrial fibrillation [37] and HF [10]. Recently, Tugcu et al. [39] showed an association of AAP assessed by TTE with WMH in a large community-based cohort. The presence of AAP, strongly associated with arterial stiffness [40], may be also considered as a marker of diffuse and subclinical atherosclerosis.

**Other findings**

Rodriguez et al. [41] showed an association between left-sided annular or valvular calcification and SCD in a large community-based elderly cohort, although it is still unknown whether such abnormalities are just markers of subclinical atherosclerosis [42,43]. Finally, Di Tullio et al. [44] reported that patent foramen ovale was not associated with SCD as well as future stroke in the general population.

**Conclusions**

Although the precise underlying mechanisms are unclear, current evidence shows that various cardiac abnormalities detected by echocardiography are associated with the presence of SCD. Therefore, primary prevention strategies resulting in reduced vascular risk-factors may concurrently improve both heart and brain health. Further prospective investigations are needed to refine the role of echocardiography for SCD in clinical settings.

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