ASSESSMENT AND INVESTIGATION OF CEREBRAL LARGE AND SMALL VESSEL DISEASES AND COEXISTING CARDIOVASCULAR DYSFUNCTION AMONG MIDDLE-AGED AND OLDER ADULTS

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Assessment and Investigation of Cerebral Large and Small Vessel Diseases and Coexisting Cardiovascular Dysfunction among Middle-Aged and Older Adults

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CERTIFICATE OF ORIGINALITY

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it reproduces no material previously published or written, nor material that has been accepted for the award of any other degree or diploma, except where due acknowledgement has been made in the text.

_____ (Signed)

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Publications and Presentations

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2. **Yangyang Cheng,** Lihua LAI, Jieqi LUO, Michael YING. Exploring Association between Daytime Heart Rate Variability and Intracranial Atherosclerosis Identified by High Resolution MRI in Middle-aged or over Community-Dwelling Adults. Diagnostics, 2025, Volume 15, Issue 21, 2731.

3. **Cheng, Yangyang**, Aidi Wu, Michael Ying, Xiangyan Chen. The updated roles of new ultrasound imaging techniques in assessing carotid vulnerable plaques. WFUMB Ultrasound Open, 2023. p. 100023.

4. **Yangyang Cheng**, Lihua LAI, Jieqi LUO, Michael YING. Correlation between Myocardial Micro-ischemic Metabolic Changes from ECG Dispersion Mapping and MRI-defined White Matter Hyperintensities and Cerebral Microbleeds in Middle-Aged or Over Community Dwelling Adults. *(In preparation)*

Other Publications

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2. Du H, Zheng J, Li X, Dong Y, **Cheng Y**, Liu C, Hu J, Chen X. The correlation between medial pattern of intracranial arterial calcification and white matter hyperintensities. Atherosclerosis. 2023 Sep; 381:117247.

3. Du H, Zheng J, Li X, Bos D, Yang W, **Cheng Y**, Liu C, Wong LKS, Hu J, Chen X. The correlation between intracranial arterial calcification and the outcome of reperfusion therapy. Ann Clin Transl Neurol. 2023 Jun;10(6):974-982.

Conference Presentations

1. **Yangyang CHENG**, Xiangyan Chen. Associating Intracranial Atherosclerosis with White Matter Disease in Middle-Aged and Older Community-Dwelling Adults. Asia Pacific Stroke Conference (APSC 2023). In-person conference, oral presentation (13 December 2023).

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Abstract

Background and purpose

Brain vascular diseases, including intracranial atherosclerosis (ICAS) and cerebral small vessel disease (cSVD), a highly prevalent observation on head magnetic resonance imaging (MRI), have been demonstrated to be associated with cardiovascular disease.[1-3] However, certain physiological mechanisms between cardiac dysfunction and cerebral vascular diseases have not been clarified, and much less is known about the clinical value of typical cardiac metrics for identifying people who are at a higher risk of cerebrovascular events.

Atherosclerosis is a systemic disease that typically affects the cardiac and cerebral vasculatures. For the brain, being the end-organ of cumulative vascular damage, is profoundly influenced by cardiac function, evidence indicates that heart rate variability and autonomic dysregulation contribute to cerebral hypoperfusion, endothelial dysfunction, and subsequent vascular cognitive impairment. Given this intrinsic link, this thesis aims to elucidate the interplay between cardiac dysfunction indicated by ECG dispersion mapping and cerebral large- and small-vessel diseases revealed through 3.0T MRI, while exploring novel cardiac metrics as potential early biomarkers for cerebrovascular diseases, offering opportunities for timely intervention and prevention.

Methods and Materials

This community-based study consecutively recruited dwelling individuals aged more than 45 years or older. All of the study participants had no history of stroke or other severe vascular disease and completed all the examination processes of the study, including baseline questionnaire, MRI examinations-magnetic resonance angiography (MRA), and high-resolution MRI (HR-MRI), and 3-minute ECG dispersion mapping (ECG-DM). The detailed

imaging features of intracranial atherosclerotic lesions were assessed by MRA and HR-MRI, including irregularity and smooth plaque, eccentricity or concentricity, positive or negative plaque burden, luminal stenosis, *etc*. The association between ICAS features and cSVD imaging markers was assessed to stratify risk factors in sub-healthy community-dwelling adults. The extent of cardiac dysfunction was evaluated by ECG-DM monitoring. Cardiac function was classified as either heart rate variability (HRV) or myocardium micro-ischemic metabolic impairment. HRV was assessed by frequency-domain (high-frequency, HF; and low-frequency, LF) and time-domain (the standard deviation of the NN intervals, SDNN; and the root mean square successive difference of intervals, RMSSD). The myocardium function was assessed using a series of metrics, including the myocardial micro-alteration index (MMI), atrium deviation, and ventricle deviation, which were automatically evaluated by ECG-DM monitoring.

Results

This study investigated the relationship between intracranial atherosclerotic stenosis (ICAS), cerebral small vessel disease (cSVD), and cardiac dysfunction in 272 community subjects. Non-stenotic ICAS was found in 65.8% of the 272 participants, with the middle cerebral arteries (MCAs) being the most frequent site, followed by the basilar and vertebral arteries. Moreover, our results demonstrated that the prevalence and severity of ICAS positively correlated with the presence and burden of cSVD imaging markers. Specifically, eccentric plaque morphology on vessel wall imaging was identified as an independent risk predictor of higher burden of white matter hyperintensities (OR, 1.47; 95% CI,1.04 – 2.10; p= 0.036). In terms of cerebral large and small vessel diseases and cardiac dysfunction, the study also revealed that lower HRV (OR, 1.55; 95% CI,1.10 – 2.18; p=0.012) and atrium deviation (OR, 1.85; 95% CI,1.10 – 3.14; p=0.022) were predictive risk factors for the presence of ICAS.

Lastly, in the analysis of the correlations between cSVD (WMHs and CMBs) and cardiac dysfunction, independent associations were found between WMH burden and both ventricle(OR 3.1, 95% CI 1.37 – 7.29, p= 0.007) and atrium (OR 2.1, 95% CI 1.07 – 4.21, p= 0.030) myocardial metabolic oxygen impairment; whereas the presence of CMBs were independently predicted by a higher myocardial micro-alteration index (MMI, OR 1.69, 95% CI 1.18 – 2.41, p= 0.004) and lower HRV (time-domain SDNN, OR 0.56, 95% CI 0.35 – 0.91, p= 0.019).

Conclusions

The study findings addressed three research questions related to cerebral large arteries and small vessel disease. Firstly, the study findings indicated a potential correlation between ICAS and cSVD, and the results further elucidated that eccentric atherosclerotic plaque is an independent risk factor for a greater burden of WMH. This highlights a distinction and correlation between two types of intracranial vascular lesions and suggests the potential for targeted prevention of lesion formation and cerebrovascular diseases. Secondly, the associations with cardiac dysfunction between cerebral large-arterial atherosclerosis and small vessel disease are different. Irregular heart rate variability and atrium hypoxia were more closely associated with features indicative of a higher risk of large artery atherosclerosis. These cardiac indicators are crucial for the early identification of adults who are at high risk for ICAS, thereby enabling clinicians to prioritize early diagnosis, optimize treatment strategies, implement preventive measures, and minimize adverse outcomes of cerebrovascular events. Thirdly, the study showed a robust dose-response relationship of the presence and burden of white matter hyperintensities and cerebral microbleeds with abnormal variation in heart rate and myocardial micro-alteration impairment. Myocardial oxidative metabolic impairment is significantly associated with the severity of WMHs, and reduced heart rate and myocardial

micro-alteration abnormalities could be considered risk predictors for the incidence of CMBs. Overall, this PhD study elucidated that cardiac dysfunction may have distinct pathophysiological roles in both cerebral large and small vessel diseases by influencing the cerebrovascular beds.

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List of Abbreviations

ACA, anterior cerebral artery

ANS, autonomic nervous system

BA, basilar artery

BMI, body mass index

CMB, cerebral microbleed

cSVD, cerebral small vessel disease

DBP, diastolic blood pressure

ECG, electrocardiogram

ECG-DM, electrocardiogram dispersion mapping

ePVS, enlarged perivascular space

HF, high-frequency power

HR-MRI, high-resolution magnetic resonance imaging

ICA, internal carotid artery

ICAD, intracranial atherosclerotic disease

ICAS, intracranial atherosclerosis

LF, low-frequency power

LF/HF, the ratio of LF to HF power

MCA, middle cerebral artery

MMI, myocardial micro-alteration index

MRI, magnetic resonance imaging

PCA, posterior cerebral artery

RMSSD, the root mean square successive difference of interval

SBP, systolic blood pressure

SDNN, the standard deviation of the NN interval

TOF-MRA, time-of-flight magnetic angiography

VA, vertebral artery

VWMRI, vessel-wall magnetic resonance imaging

WMH, white matter hyperintensity

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Chapter 1. Introduction of The Thesis

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1.1 Background

Cardiac-cerebrovascular disorders are common middle-aged and elderly diseases worldwide that pose significant threats to public health and the global economy.[4] Reports indicated that cerebrovascular and cardiovascular diseases accounted for the highest mortality prevalence worldwide, with approximately 15 million deaths annually.[5] According to the World Health Organization (WHO), in 2019, around 17.9 million people died from cardiovascular diseases, accounting for 32% of global deaths, with 85% of these fatalities resulting from heart attacks and strokes.[3] Approximately 2% to 6% of patients who experienced the onset of ischemic stroke may occur cardiovascular-related fatal events within three months reported in previous reports.[3, 6, 7] Both disorders are often interrelated due to sharing common risk factors and underlying pathological mechanisms such as atherosclerosis, arrhythmias, hypertension, diabetes mellitus, etc.[8] For example, atrium fibrillation (AF), one type of arrhythmia, markedly increases the risk of cerebrovascular events by promoting the embolization of thrombi from the atria and ventricles to the brain. Thus, cardiovascular disease is a prevalent source of cerebrovascular impairment, and vice versa. This PhD study aimed to explore the characteristics of these diseases and their interrelationships.

1.1.1 Cerebrovascular Diseases

Cerebrovascular diseases are defined as cerebral ischemic infarction and hemorrhage. Ischemic stroke is a major cerebrovascular event with poor prognosis, which can affect individuals of any age, although the incidence and prevalence of this condition increase sharply with age. [9, 10] Over 50% of cerebrovascular accident survivors still lack the ability to perform self-care despite substantial advancements in diagnostic and therapeutic technologies that can be used to achieve some effects.[11] Previous literature shows that among all the identified etiologies of stroke, intracranial atherosclerosis (ICAS) is a leading cause of ischemic stroke

and is associated with an increased risk of stroke recurrence with aging.[7, 12-14] Prior studies reported that the prevalence of ICAS takes up over 50% of stroke or transient ischemic attack (TIA) cases in Asia, which is a higher rate than those among African descent (29%) or Caucasians (15%).[15, 16] Even worse, the incidence of patients with stroke attributed to intracranial atherosclerosis persists in an upward trend rather than showing signs of amelioration. Therefore, in this PhD study, the focus was on ICAS.

Additionally, cerebrovascular diseases predominantly include both cerebral large and small vessel disease (SVD).[17] Recently, the burden of intracranial atherosclerosis and SVD has been severe in China, and both brain lesions have been significant contributors to acute stroke and physical disability in the elderly.[18] Cerebral small vessel disease(cSVD) is the most common, progressive vascular disease with no optimal treatment option till now. Commonly, cSVD presents as a variety of clinical symptoms such as headache, gait disturbances, dementia[19] and is typically detected by neuroimaging modalities such as computed tomography (CT) and Magnetic resonance imaging (MRI). However, due to the heterogeneity in cSVD lesions, conventional MRI reveals only the tip of the iceberg of the total cSVD-related brain damage. Despite some studies having shown possible associations and underlying mechanisms between these two brain vascular disorders in stroke patients[20-23], comprehensive evidence remains limited, especially on brain-heart interactions in sub-healthy populations. Hence, it is necessary to elucidate both the distinct characteristics of these disorders and their interrelationships.

1.1.2 Cardiovascular Dysfunction

Cardiovascular dysfunction refers to any condition that affects the effective function of the heart or blood vessels. The onset of acute cardiac symptoms with functional impairment often signifies progression to an irreversible disease stage. Subclinical cardiac dysfunction

often goes undetected due to inadequate screening paradigms and insensitive diagnostic tests, thereby facilitating the progression of severe cardiovascular-cerebrovascular disorders. [24] Among numerous traditional biomarkers such as smoking, age, gender, hypertension, and diabetes, recently, heart rate variability (HRV), an ingenious marker, is a reliable reflection for assessing various physiological factors modulating the normality of cardiac rhythm.[25] HRV has been extensively proven as an early metric for subclinical cardiac dysfunction by indirectly evaluating the balance between the sympathetic and parasympathetic branches of the autonomic nervous system (ANS) and differentiating among various risk stratification protocols for an at-risk patient. [26-29] It has been illustrated that individuals presented with diminished or abnormal HRV tended to face an increased risk of mortality in the subsequent years following heart and stroke.[30] Recent studies have explored the association between HRV and cerebrovascular events and reported that lower HRV has been related to a higher risk of cerebrovascular diseases, such as incident stroke, and secondary ischemic events, even though there still exist controversies about these associations [31, 32], and much less is known about the clinical value of cardiac electrophysiological indicators in identifying people at higher risk of cerebrovascular events. Given the close interaction and complex pathological distinctions between cerebrovascular disease and cardiac function, further research is warranted to elucidate their latent associations in imaging diagnostics, mechanistic pathways, and clinical risk stratification within community-based populations.

1.2 Objectives and Organization of the Thesis

1.2.1 Objectives

This PhD research aimed to investigate neuroimaging features identified by vessel wall imaging and multiple-sequence MRI as novel biomarkers for cerebrovascular disease, along with cardiac electrophysiological metrics automatically recorded through optimized ECG

dispersion mapping (ECG-DM) technology to explore the relationships between autonomic regulation pathogenesis and hemodynamic effects related to both two brain lesions (ICAS, cSVD) and cardiac dysfunction in middle-aged and older adults in Hong Kong. It consisted of four major objectives:

1) To investigate the potential correlation between cerebral large and small vessel disease among community adults in a local population.
2) To determine whether neuroimaging morphological features of ICAS identified by HR-MRI as predictors for early identification of the presence and severity of cerebrovascular small vessel disease (white matter hyperintensities and cerebral microbleeds), which could highlight early risk stratification and improve their clinical diagnostic values.
3) To explore the correlation of cardiac function based on some ECG markers, which are related to microcirculatory function and autonomic regulation in distinct ICAS imaging features, and small vessel disease markers (WMHs and microbleeds) in a local community-based population.
4) To understand the roles of both HR-MRI and ECG dispersion mapping technologies and to promote these novel examinations for widespread use in clinical early diagnosis and treatment interventions.

1.2.2 The Organization of the Thesis

This study is divided into seven chapters. Chapter 1 provides the general introduction of this thesis that summarizes the background and objectives of the study. Chapter 2 is a literature review, in which two brain vascular diseases (ICAS and cerebral SVD) and cardiac function (heart rate variability and myocardium micro-ischemic alteration) are systematically introduced based on the differentiation of histopathology, definitions, physiological

mechanisms, distinct radiological features, and clinical relevance. In this chapter, the introduction of cutting-edge diagnostic methodologies is also summarized through the available literature. Chapter 3 presents a scientific study that investigated the potential correlation between ICAS and cSVD and the correlations of the distribution and progress of ICAS with the presence and severity of each cSVD imaging phenotype. Chapter 4 shows a research study that investigated the role of HR-MRI-validated different imaging features of intracranial atherosclerotic plaques in risk stratification by assessing their association with the presence and severity of WMHs on 3.0T brain MRI. The causal relationship between cerebral large arteries and small vessel diseases (WMHs and CMBs) and cardiac dysfunction is explored in studies presented in Chapters 5 and 6. In Chapter 5, based on previous radiological methods and cardiac metrics recorded by a novel short-term ECG dispersion mapping technique, the study presented in this chapter investigated the relationship between ICAS with distinct plaque imaging features and cardiac dysfunction. The study presented in Chapter 6 investigated the association between myocardium microcirculatory function and sub-cSVD markers (WMHs and CMBs) and validated the independent cardiac risk proxies for early screening of the presence and severity of both cSVD imaging phenotypes. Chapter 7 is the conclusion of this PhD thesis and provides perspectives for future studies. In summary, this PhD study aimed to determine the relationship between both cerebral vascular disorders and cardiovascular dysfunction, which provides critical clinical insights for identifying high-risk populations susceptible to heart-brain disorders within the general population, enhances the understanding of underlying pathological mechanisms, and optimization of prevention strategies.

Chapter 2. Literature Review

Chapter 2. Literature Review

2.1 Anatomy of the Major Cerebral Large Arteries

Atherosclerosis is known as a systemic disease that commonly involves both intracranial and extracranial arteries. However, the features of ICAS are distinctly different from those of ECAS and may be attributable to the unique structure of intracranial cerebral arteries and their hemodynamics. In the brain, the circle of Willis, an anatomically significant structure in the evaluation of neurovascular diseases, encircles the stalk of the pituitary gland and divides into anterior and posterior circulation, contributing to the brain's blood supply. [33] As the primary cerebral circulatory structure, the main intracranial arteries of the circle of Willis include the bilateral anterior cerebral arteries (ACAs), internal carotid arteries (ICAs), and middle cerebral arteries (MCAs) for anterior circulation, as well as the bilateral posterior cerebral arteries (PCAs), vertebral arteries (VAs), and a single basilar artery (BA) for posterior circulation. Intracranial atherosclerotic disease (ICAS) exhibits the highest prevalence in the internal carotid artery (ICA) (60-80%), followed by the vertebral artery (VA) (17-35%), with lower rates in the basilar artery (BA) (2.5-7%) and middle cerebral artery (MCA) (5%).[34-36] Histological data indicate a prevalence of intracranial atherosclerosis of 3% in Caucasian populations[37], whereas Chinese adults show significantly higher rates of 27.9% in the MCA [38]and 39% in major intracranial arteries. [39] **Figure 2-1** Shows Willis circle anatomy. (a.) schematic diagram of intracranial arterial distribution and (b.) corresponding MRA manifestations.

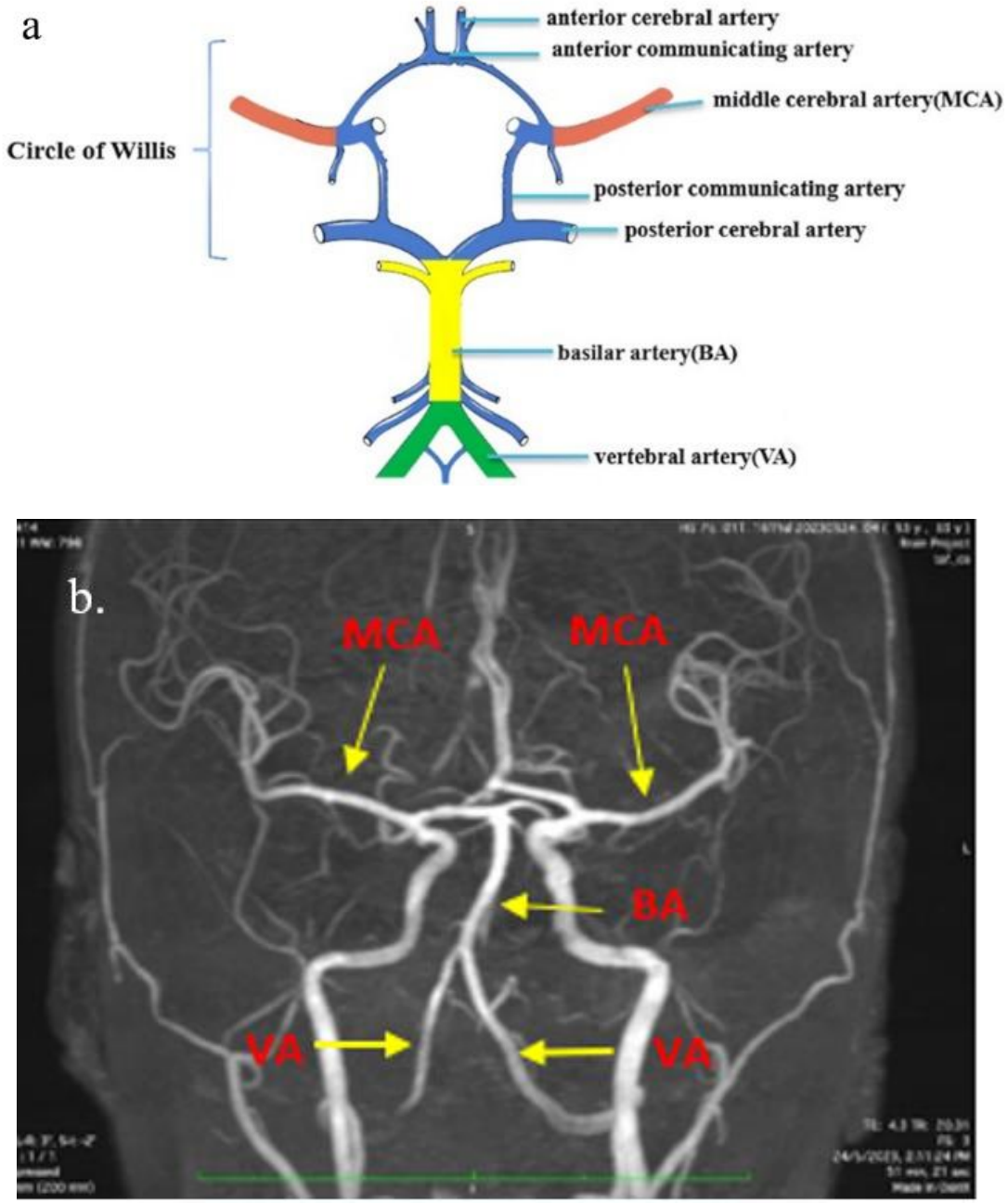


Figure 2-1 Willis' circle anatomy. (a) Schematic diagram of intracranial arterial distribution. (b) MRA manifestations.

2.2 Overview of Intracranial Atherosclerosis

Large artery intracranial atherosclerosis disease (ICAD) is more commonly affected in Oriental Asian (up to 50%) rather than Whites or Blacks. [40, 41] Atherosclerotic lesions develop

silently and systematically affect all vascular beds over the years until they become symptomatic. [40] ICAS starts late in life and is known as a key factor to variations in stroke morbidity and mortality. [42] In the past, ICAS received less attention relative to extracranial atherosclerosis, such as carotid or coronary artery disease, in stratifying stroke-free elderly populations, probably because of the difficulty in obtaining observation of cerebral arteries and latent status. Based on our prior autopsy studies, luminal stenosis and plaque histological characteristics (intraplaque hemorrhage and lipid core) were proven as independent predictors for ischemic stroke events.[38, 43] Nevertheless, these efforts are insufficient, and the studies of radiologic features of ICAS patterns from the asymptomatic stage are limited. Despite previous studies on intracranial atherosclerosis having primarily focused on patients with ischemic vascular events, and various independent risk factors for ICAS having been examined [44], it is important to note that the association between silent ICAS and micro-alteration in cardiac dysfunction is not undisputed, and these findings have never been pooled before.

2.2.1 Atherosclerotic Plaque Formation

Given the diverse nature of vascular changes in brain disorders, describing multiple characteristics of high-risk intracranial plaques, including the degree of luminal stenosis, plaque burden, morphological features, and distribution patterns, is important and necessary. Based on a culmination of pathologic findings of plaque morphology identified specific parameters indicating plaque rupture.[45] The process of atherosclerosis is a dynamic, complex, multifactorial inflammatory and immune process that affects arterial walls in a heterogeneous manner. It may partially lead to blood flow reduction and occlusion in the lumen artery, which provokes the onset of characteristic clinical manifestations. Hence, the term 'atherosclerotic plaque' refers to a crucial factor in the pathophysiology of disorders that develop as a result of atherosclerosis.[46] Historically, atherosclerotic plaque is characterized by a localized buildup of subintimal lipid deposition and

macrophage accumulation that progressively forms within the arterial lumen and extends to at least 0.5 millimeters or half of the thickness of the adjacent intima-media layer.[47] The intimal layer is composed of a combination of subendothelial connective tissue and endothelial cells. During atherosclerosis, inflammation intrudes into the intimal layer and gradually thickens with calcified formation.[48] Calcified granules will turn into larger clusters with a continuous fusion of adjacent granules.[49] Sometimes, large calcifications may ulcerate the intima and disrupt the surface, leading to subsequent thrombus or occlusion.[50, 51] **Figure 2-2** shows the method of plaque formation.

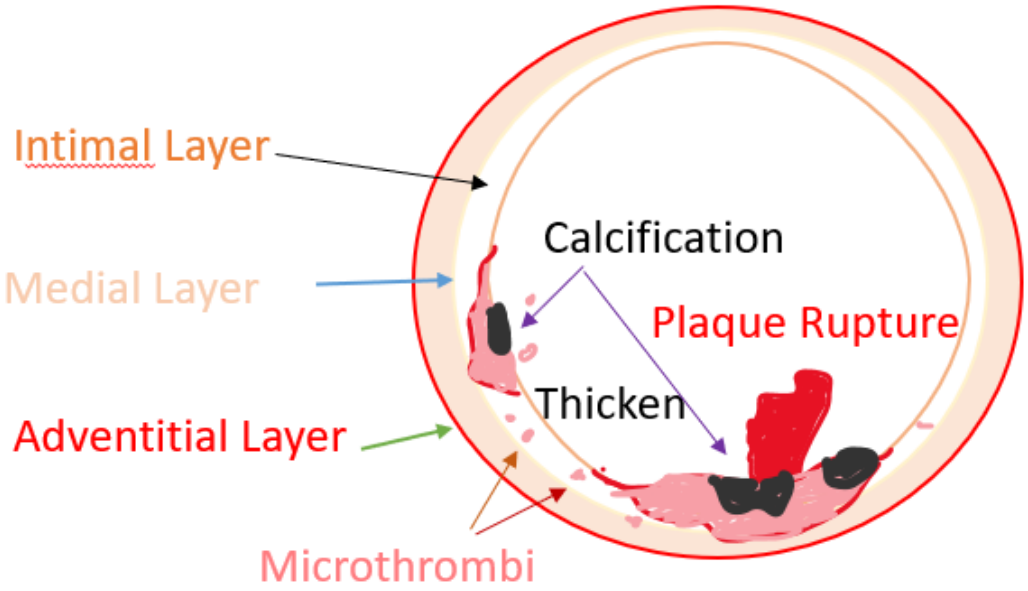


Figure 2-2 The method of plaque formation.

2.2.2 Histopathological Features of Atherosclerotic Plaque Vulnerability

Till now, previous pathological research has illustrated that both plaque components and morphological features indicating plaque vulnerability play an important role in leading to ischemic events.[52, 53] Spontaneous regression may commonly occur in early-stage lesions, whereas in the natural development of atherosclerosis, the intermediate and advanced stages frequently exhibit the appearance of continuous progression. Prior studies have revealed thin fibrous cap, a large lipid core, and an amount of infiltration of inflammatory cells are classified as the most important

components of vulnerable atherosclerotic plaque, which are the main causes that attribute to thrombotic events. [54] Hence, most atherosclerotic lesions remain in a stable status with no severe clinical events throughout an individual's life, but only those lesions deemed at high risk for triggering life-threatening thrombi are accountable for the eventual vascular diseases. For clinicians and researchers, the challenge lies in identifying lesions that are prone to be thrombosis, commonly referred to as “vulnerable plaques”. Besides the major histopathological characteristics that define a vulnerable plaque, there are also minor criteria based on imaging features, such as severe stenosis, eccentricity, and expansive (positive) remodelling.[55, 56] Nevertheless, these criteria may be helpful to define vulnerable atherosclerotic plaques within the intracranial vasculature; however, they are inadequate in current research due to the acute onset and irreversible prognosis of this disease. Therefore, our study aims to explore more effective imaging indicators for the risk stratification of intracranial atherosclerosis.

2.2.3 Atherosclerotic Plaque Formation

By comparing the autopsy and multimodal MRI, Jiang, et al.[57] accomplished a remarkable differentiation of atherosclerotic plaque components between lipid core (isointense/hyperintense on T1 sequence), calcification (hypointense) on T1 sequence, and hemorrhage, commonly presents as a hypersignal on TOF and T1-weighted images, while fibrous tissues show enhancement on T1-enhanced images.[45] In line with the modified American Heart Association (AHA) classification for MRI[58], each lesion was morphologically categorized as either: (1) stable plaques exhibiting near-normal vessel wall thickness or diffuse wall thickening with regular eccentricity, or (2) unstable plaques demonstrating complex morphology with irregular/patchy surfaces.

2.3 Neuroimaging Modalities of Assessing Intracranial Atherosclerosis

In the past, various conventional imaging modalities and techniques have been used to identify

atherosclerotic lesions, like computed tomographic angiography (CTA), transcranial Doppler (TCD), digital subtraction angiography (DSA), and magnetic resonance angiography (MRA), through an indirect visualizing way to provide information about the vessel lumen lesions. [59] However, these common imaging modalities can only detect intracranial plaques if they represent marked luminal narrowing. The fact is that the diameter of the lumen can be maintained even though intracranial arterial walls became thickened, caused by atherosclerotic plaques, presumably because of an outward ‘‘positive,’’ remodeling of the vessel wall, leading to an underestimation of the presence of intracranial atherosclerotic lesions identified by lumen-based methods. [60]

Nowadays, high-resolution MRI (HR-MRI) has been applied to evaluate lesions of intracranial vessel walls. [61] Compared with conventional imaging modalities, by presenting hypointensity, IACS can be directly visualized by HR-MRI.[62] Revealing the ultrastructure of the vessel wall, HR-MRI is more suitable for radiologists to accurately delineate the specific sites and morphological patterns of lesion manifestation (e.g., superficial and deep; focal or eccentricity) and their positional relationships with intracranial atherosclerotic plaque components, owing to its non-invasive nature and superior ability to differentiate tissue characteristics. [45, 63-65]

2.4 Risk Factors in Cerebral Large and Small Vessel Disease

Age, gender, hypertension, diabetes, hyperlipidaemia, and atrium fibrillation are defined as independent risk factors for cerebrovascular disease.[66] A growing number of evidences report that aging represents the most dominant determinant for the development of cardio and cerebrovascular diseases.[67] The widespread influence of age on cardio and cerebrovascular diseases arises not only from an increase in risk factors in the elderly but also from the intrinsic and unavoidable effects of aging itself. In 2014, epidemiological and neuroimaging studies demonstrated a high prevalence of ICAS and cSVD, with patients aged 65 years and older showing prevalence rates of ICAS(taking up 40-60%)[68] and cSVD (more than 50%) [69, 70]. Uncontrolled hypertension accounts for about

70% of patients with cerebral events, and up to 83% of individuals have cSVD. [71] Diabetes mellitus (OR value 1.3 to 2.2 in different cohorts reported by Meta-analysis in 2006)[72], and hyperlipidemia [73] are closely associated with ICAS [74-76] and cSVD[77], but these findings are inconsistent with some studies. [78, 79]

2.5 Introduction of Cerebral Small Vessel Disease (cSVD)

Prior studies have reported cerebral small vessel disease (cSVD) frequently coexists with ICAS [23, 80] and is associated with a higher risk of stroke recurrence [81, 82] as well as less favorable stroke outcomes. [83] According to epidemiology, cSVD has a 2 to 3-fold increased stroke risk[84], including 25% of ischemic strokes and about 50% of vascular impairments.[85-87] Cerebral small vessel disease, the most common chronic vascular disease, affects the smallest vessels in the brain, such as small arteries, arterioles, venules, capillaries, and other vessels that branch off from large intracranial arteries.[23, 85, 87] Over a 5-year follow-up, traditional vascular risk factors like age, hypertension, diabetes, hypercholesterolemia, and smoking are independently associated with cSVD progression.[67, 88-90] Due to the smaller morphology and complex pathogenesis in the intracranial vasculature, conventional diagnostic imaging modalities encounter difficulties in detecting these indistinct pathological processes.[91] In fact, there is a persistent controversy surrounding the observation that patients with comparable degrees of cerebral vascular disease on brain imaging frequently exhibit inconsistent levels of clinical symptoms. [92] With different mechanisms, CSVD and ICAS serve as two distinct entities that may present separate vascular pathologies, prevention, and treatments of brain accidents, and play different roles in divergent effects across various organ systems. Li X *et al*. identified an independent association between worse renal impairment and two patterns of intracranial arterial calcification.[93] Moreover, the meta-analysis showed worse renal function preferentially associated with stroke-free populations rather than lacunar stroke patients[94], and fibrotic non-alcoholic fatty liver disease was

independently correlated with a higher burden of WMHs reported by Jang H *et al*.[95] Although accumulating evidence has documented associations of hepatorenal dysfunction in both macrovascular (large artery) and microvascular cerebral pathologies, their cardiocerebral axis remains terra incognita. The question of whether, in what aspect and at what level, CSVD and ICAS are associated with each other and correlated with cardiac dysfunction remains unanswered. To provide clarity, we aim to investigate the specific relationships between the two types of brain vascular disease detected by MRI and heart dysfunction revealed by daytime ECG-DM in a community population.

2.6 Classification of Different Neuroimage Phenotypes of Cerebral Small Vessel Disease

Cerebral small vessel disease is a common term that groups various neuroimaging changes inferred from prominent white matter hyperintensities (WMHs), enlarged perivascular spaces (ePVs), lacunar infarcts, cerebral microbleeds (cMBs), and brain atrophies (BAs).[82, 96] These pathological changes are strongly linked to each other and often incidentally found on brain scans.[82, 96] Studies have proposed that a modified total 6-point cSVD burden score defined by MRI provides greater sensitivity and specificity by counting the presence of the overall profile of cSVD imaging markers (1 point for any present CMBs, moderate to severe BG-PVS, or Fazekas grades 2-3 of WMHs) and is associated with vascular dementias.[22, 97] This quantitative and qualitative evaluation can stratify the different severities of subtypes of cSVD, showing better predictive value for risk stratification in patients with TIA or ischemic stroke.[98]

2.6.1 White Matter Hyperintensity (WMH)

WMH, referred to as leukoaraiosis, is a general neuroimaging marker of cSVD.[99] It is of presumed vascular origin and commonly visible on conventional MRI and CT examinations. Prior studies reported that WMH is closely correlated with cognitive decline[100], and increased risk of

cerebral events like stroke [101] and all-cause dementia.[102] Moreover, they vary depending on the family longevity being, which is less frequent in subjects with long-lived parents due to its high heritability.[103] WMH plays an important role in clinic and risk factors association, and should not be overlooked as mere "silent" effects of the aging brain. Large evidence supports that various risk factors frequently worsen the severity and prevalence of WMH, including aging,[104] diabetes mellitus,[105, 106] hypertension[107] or higher blood pressure within normal range[107, 108], alcohol drinking,[109] insufficient physical exercise,[110, 111] and other undetermined risk factors.[112] A large sample of 1748 community studies in Caucasians reported a close relationship between the burden of WMH volume with higher prevalence of cardiovascular disorders and poorer memory.[113] Vaccarino V, et al., demonstrated that cardiovascular disease was a more important risk factor for increased burden of WMH under the episodes of acute or sustained mental stress.[114] Cerebral and cardiovascular diseases mutually influence each other, particularly when the balance of the autonomic nervous system (ANS), cerebral circulation regulation, and neuroendocrine stress systems is compromised. The current study aimed to examine associations between WMH and cardiac dysfunction using various cardiac metrics by novel ECG dispersion mapping.

2.6.1.1 Prevalence and Pathogenesis

The prevalence of WMH varies and increases with age, particularly in the elderly aged over 60 years old.[115] It has been reported that the prevalence of WMH has been estimated to reach 20% to 50% in the general population in midlife, increasing to >90% with advanced age. [6, 116] Typically, WMHs affect the deep(D-WMH) and perivascular(PV-WMH) regions of the brain, with pathogenic mechanisms involving varying degrees of demyelination, endothelial cell activation, gliosis, and fiber loss, contributing to increased vascular resistance and collagen deposition in venules. [117] Thus, these different pathogeneses may lead to a spectrum of vessel wall thickening, perivascular space enlargement, and the presence of plasma proteins, revealing extensive WMHs abnormalities

manifested as more severe and confluent imaging features. [92]

2.6.1.2 Medical Imaging Assessment Methods

Based on the imaging assessment, white matter changes are commonly shown as bright signal on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences.[118] The severity of WMH was scored according to the Fazekas scale[119], from absent to severe. Mild WMHs were calculated with a total score ≤ 2 (including PV-WMH and D-WMH scores), moderate WMHs were 3-4 points of the total WMH score, and severe WMHs were a total of 5-6 scores.[97, 98] **Figure 2-3** shows cases of different distributions of moderate WMHs: (c) Moderate PV-WMH. (d) Moderate D-WMH. We agree that volumetric quantification is more advantageous than a visual Fazekas rating scale. However, volumetric measurement often costs a lot of time, and special software packages are required. Therefore, a notable strength of our study is the adoption of the Fazekas rating scale—a reliable, quantitative, and internationally accepted method.

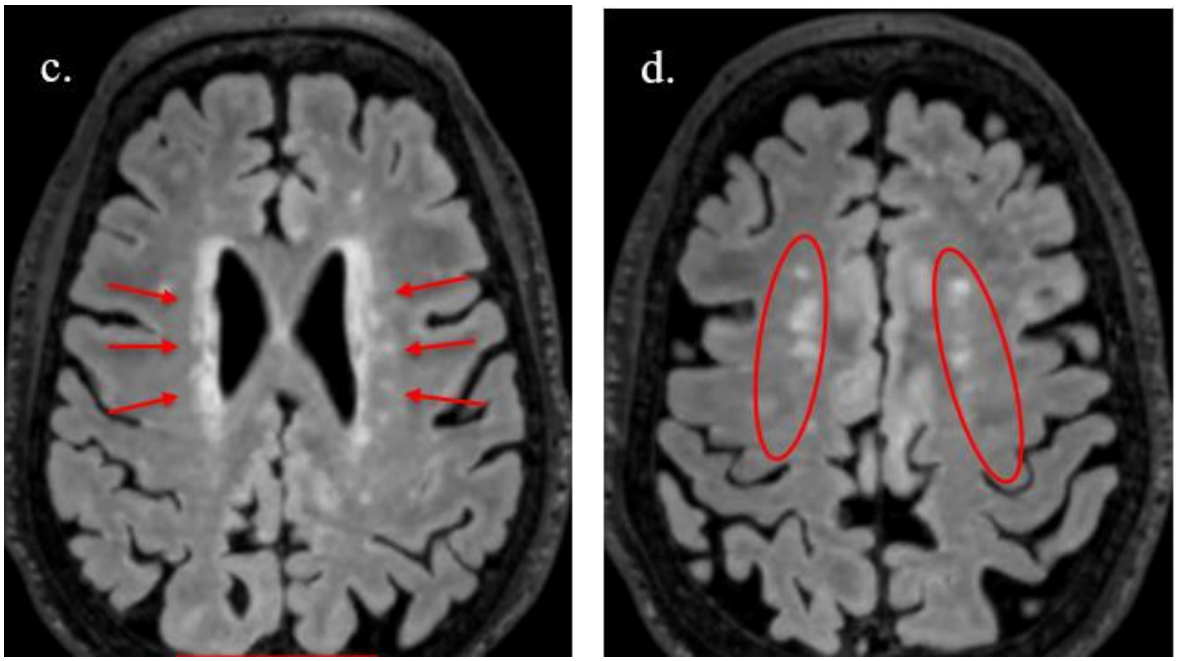


Figure 2-3 Cases of different distributions of moderate WMHs: (c) Moderate PV-WMH. (d) Moderate D-WMH. Case 1, a 72-year-old man with mild hypertension, FLAIR images showed partial confluence of WMH at the sites of the brain periventricle and deep regions.

2.6.2 Cerebral Microbleed

Cerebral microbleed (CMB) is one of the most important imaging markers of cSVD. According to prior research, CMB is a contributor to an increased risk of ischemic stroke, cognitive impairment[120], and death.[121] Well-documented risk factors for microbleeds include gender, age, and hypertension.[122-124] CMB is caused by microangiopathic processes and is correlated with other cSVD markers such as WMH and lacune infarction. [125, 126] Cardiovascular disease has also been related to increased risk of the development of microbleeds,[127, 128] but few population-based studies have evaluated this association, and these studies have not included ECG dispersion mapping.

2.6.2.1 Prevalence and Histopathology

Cerebral microbleeds (CMBs) pose a risk for the occurrence of intracerebral hemorrhage (ICH) [129], and the prevalence increases to over 40% in advanced age. [130] Histopathological evidence revealed that most microbleeds are caused by perforating arteries or capillaries disruption.[131] It reflects a vasculopathy rather than a parenchymal hemorrhage, including vessel wall dissection, microaneurysms or vessel wall thickening due to accumulation of fibrin and red blood cells in the vessel wall.[131, 132]

2.6.2.2 MRI-defined Microbleeds Features

MRI-identified CMBs represent areas of old microhemorrhage, which are generally displayed as small and round hypointense foci on the sensitive T2-weighted gradient-recalled echo (GRE) or susceptibility-weighted sequences(SWI).[133] Evidence from the radiological studies indicated that CMBs are more likely to occur in the lobar region(the highest prevalence, about 44%)[133], followed by the deep area(up to 38%), rather than the brain stem or cerebellum(approximately 9%).[134] Despite associations of CBMs with other pathological subtypes of cSVD, such as WMHs, lacunar

infarction, and cognitive decline[124, 135], what lies beneath the surface of this radiographic marker of abnormality is thought to be multifactorial in the aging brain and an active area of research.

Figure 2-4 MRI-defined CMB.

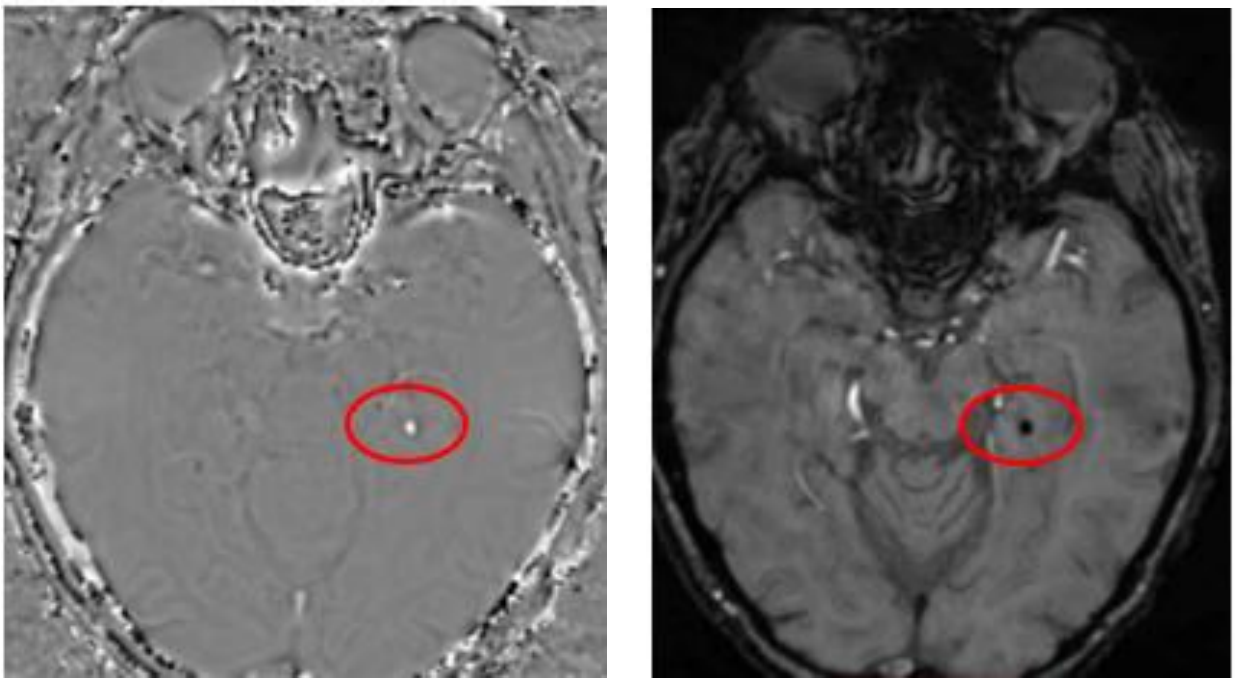


Figure 2-4 A case of MRI-defined CMB. Lt. single CMB in the hippocampal region presents small and round hypointense foci on the sensitive T2-weighted gradient-recalled echo (GRE) or susceptibility-weighted sequences (SWI).

2.6.3 Imaging Characteristics of cSVD Hallmarks: Enlarged Perivascular Spaces, Lacunes, and Brain Atrophy

Aside from WMHs and CMBs as described before, the remaining three imaging subtypes—enlarged perivascular spaces (ePVS), lacunes, and brain atrophy (BA)—are also defined radiological hallmarks of CSVD. These are typically regarded as normal, clinically silent degenerative changes associated with brain aging till apparent symptom onset [136], and their accumulation subsequently increases the risk of stroke. [137]

Enlarged perivascular spaces (ePVS) or Virchow-Robin spaces, an important drainage conduit

for cerebral interstitial fluid [138, 139], are commonly found in increased numbers in older individuals.[140] Histopathologically, cerebrospinal fluid fills the enlarged perivascular space and follows the course of the penetrating arterioles. However, although a few are normal at any age, large numbers are not. [141] Hence, despite being recently considered to represent normal degeneration with no severe clinical consequences, it is often overlooked in many studies of brain events. According to their different distribution and quantity, ePVS are commonly detected on T2-weighted as well-defined, small, dotted, and/or linear hyperintensities in the centrum semiovale or basal ganglia regions on the same side of the brain. **Figure 2-4** A case of MRI-defined ePVS.

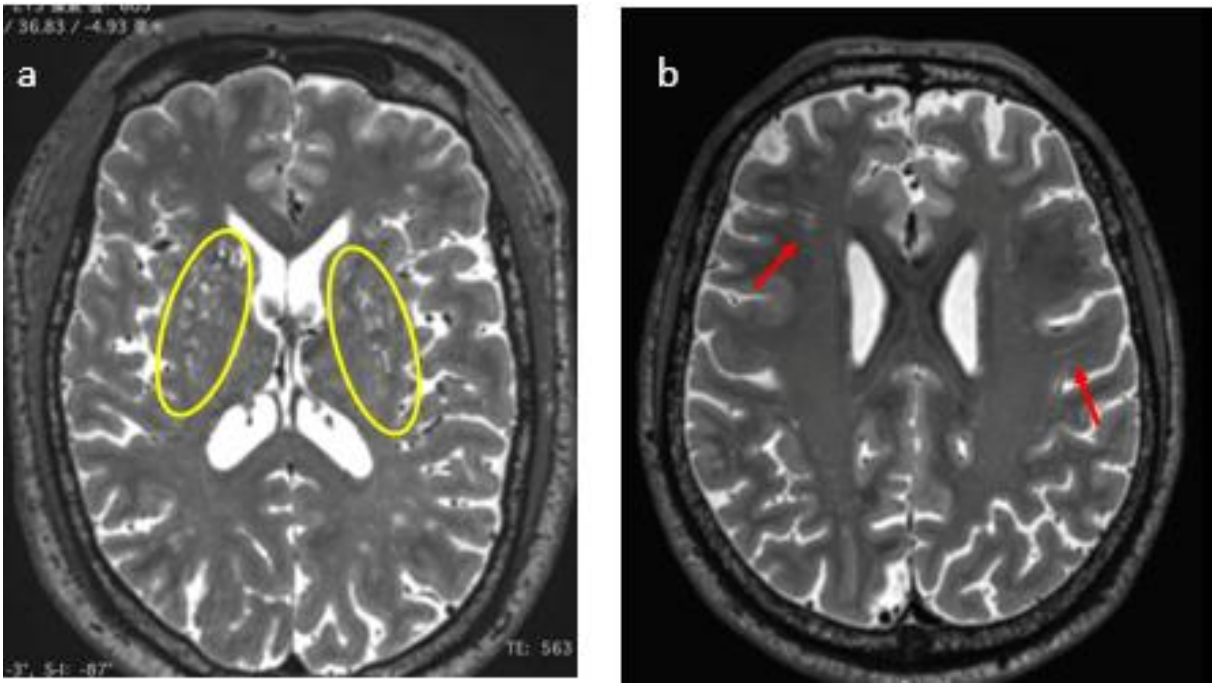


Figure 2-5 A case of MRI-defined ePVS. Figure 2-5(a) presents bilateral dotted, round, hyperintensities in the basal ganglia region, Grade 2>20 ePVS. Figure2-5(b) presents bilateral linear hyperintensities in the centrum semiovale region, ePVS Grade 1<10 ePVS.

Lacune infarcts are small cerebrospinal fluid-filled cavitated lesions, which typically affect the subcortical white matter, deep gray matter, and brainstem[142] It has been frequently served as an important pathological substrate of vascular dementia and are more likely to be detected in individuals aged 60 and older, even the prevalence varies.[143] Based on different pathological and

neuroimaging findings, lacunar infarcts are caused by the occlusion of small penetrating end arteries and fibrinoid degeneration, and they present as round or oval foci with hypointensity seen with T1-weighted imaging or fluid signal intensity on T2-weighted or FLAIR imaging. [21] Generally, an MRI-defined cerebral infarct is no larger than 2cm in diameter and classified by various distributions, morphologies, number, and size.[144] **Figure 2-6** MRI-defined lacune infarct.

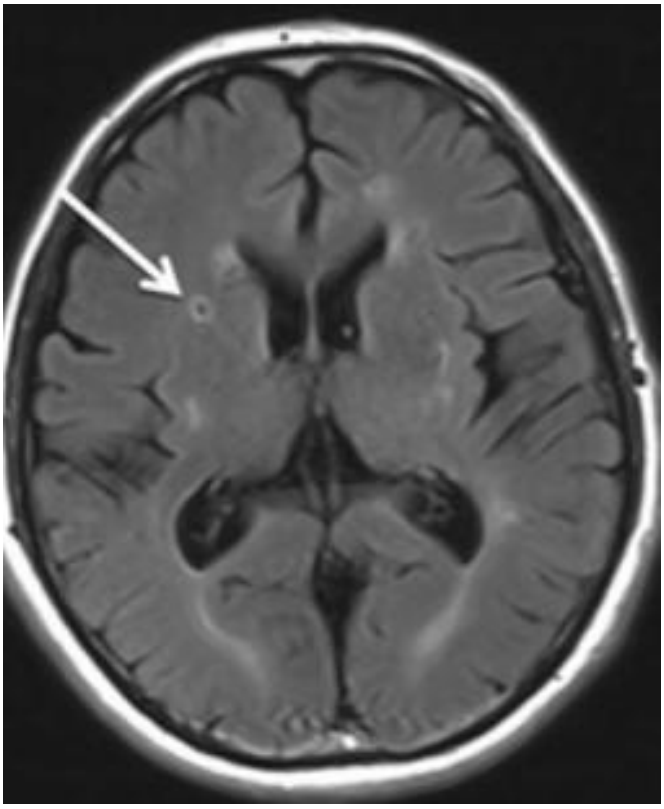


Figure 2-6 MRI- defined lacunar infarct with ring of hyperintensity and core of hyperintensity (white arrow). Reference form Norrving B. Pract Neurol. 2008 Aug;8(4).

Brain atrophy, also known as cerebral shrinkage, is described as the dynamic process of individual aging. Apart from natural degeneration, other factors such as vascular disease, cognitive impairment, and neuropathologic lesions also result in the extent of brain atrophy. Hence, brain atrophy is the most common but complex feature of many brain disorders.[145] It can occur only in focal or whole-brain regions, either symmetrical or asymmetrical. The pathological characteristics

of atrophy are heterogeneous due to the loss of various connections between neurons in the brain, which affects a specific tissue class.[146, 147] Currently, based on the global cortical atrophy (GCA) imaging scale, lower brain volume with sulci and ventricles enlargement has played an essential role in assessing the burden of brain atrophy.[148] **Figure 2-7** MRI-defined brain atrophy.

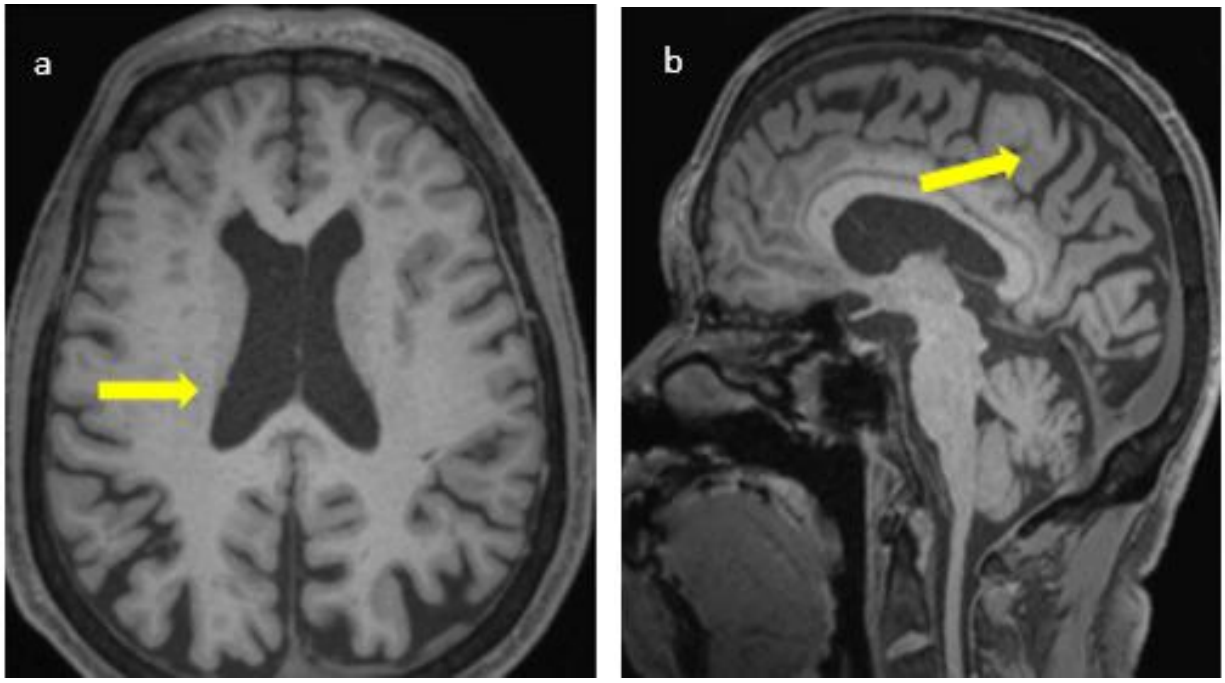


Figure 2-7 An example of focal brain atrophy. These two figures show signs of cortical atrophy with widened gyri on occipital and parietal T1-weighted images marked with arrows, rated moderate atrophy according to the Global Cortical Atrophy Scale.

Previous studies have investigated the etiology and underlying relationship between these subtypes of cSVD, such as WMHs and lacunar ischemic stroke, BAs, and vascular cognitive impairment.[149] Only a few studies have demonstrated its inflammatory correlation in multiple sclerosis[105], and the association with ICAS remains limited among Hong Kong community-dwelling residents with underlying cardiac dysfunction. Therefore, in our study, we tested the association between cSVD and ICAS, as well as other common vascular risk factors in the sub-healthy general population.

2.7 The Role of Brain-Heart Axis Interconnection in Cardiovascular Disease

Cardiovascular disease (CVD) is the number one cause of morbidity and mortality in the world, despite extraordinary advances in our understanding of the risk factors and treatment strategies.[114] The brain-heart axis(BHA), as a syndrome rather than isolated diseases affecting the brain and heart, is involved in a series of physiological functions. At the pathway level, this interaction is mediated by the sympathetic nervous system (SNS), parasympathetic nervous system (PNS), renin-angiotensin-aldosterone system (RAAS), and the hypothalamic-pituitary-adrenal (HPA) axis, while at the molecular level, it is facilitated through miRNAs, cytokines, and neurotransmitters. Research advancements over the past two decades have revealed the complex interaction between these two organ systems, including autonomic regulation, immune-hormonal modulation, and the influence of cytokines, as well as metabolic syndrome.[150] For example, nervous dysregulation could trigger cardiac function [151], leading to stress response or emotion-related cardiac dysfunction and stroke-induced cardiac syndrome.[152] Conversely, cardiac disturbances may also compromise neurological function, as seen in arrhythmia-related neurological complications, myocardial ischemia-associated neurological disorders, and systemic microvascular dysfunction. [153, 154] While the coexistence of cardiac and neurological disorders has been known for decades, the response of acute transient cardiac dysfunction to intracranial large and small vessel abnormalities has not been studied. Future research needs to focus on investigating the associations and risk factors between cardiac and cerebrovascular disorders, exploring how these organ systems interact and influence each other.

2.7.1 Autonomic Nervous System Mechanisms and Cardiac Physiological Regulation

Autonomic dysfunction is correlated with varying degrees of severity in different cerebrovascular diseases, primarily due to the anatomical and pathological features of the cerebrovascular system, and it indirectly reflects the balance between the sympathetic and parasympathetic structures. The parasympathetic nervous system (PNS) responds an instantaneous

response, whereas sympathetic activation results in an elevation of heartbeat rhythm and a decrease in inter-beat interval variability.[155] However, when the balance is broken, autonomic dysfunction resulting from sympathetic-vagal dysregulation can cause inaccurate responses or progressively delayed reactivity, ultimately leading to stress-related disorders such as cerebrovascular disease.[26] Moreover, cardiovascular ailments and various bodily functions, including heart rate, blood pressure, digestion, and respiration, are also controlled by ANS [156, 157] and can be detected both clinically and electrophysiologically. [158] Since the 1980s, pathological activation of the sympathetic nervous system has been observed in cerebral events like ischemic and hemorrhagic lesions. [159] This activation has been associated with multiple pathological conditions, including severe cardiac arrhythmias[160], complications of myocardial damage, heart failure, paroxysmal arterial hypertension, neurogenic pulmonary edema, and other forms of autonomic dysfunction. [159] Cardiac dysfunction is likely to be influenced after a vascular brain incident in patients without any pre-existing heart diseases, as reported by several studies.[161] From another aspect, baroreflex sensitivity (BRS) dysfunction is considered a critical outcome of dysregulation within the central autonomic network and plays a pivotal role in the autonomic cardiovascular disturbances observed after acute stroke, serving as an independent predictor of both mortality and the occurrence of adverse cardiovascular events. Therefore, the autonomic nervous system (ANS) serves a dual role as both a modulating cerebral autoregulator and a contributing risk factor in the pathogenesis of various neurological disorders.

2.7.2 Pathological Change of Cardiac Vascular Function

The adverse brain environment can affect vascular function, autonomic activation, and the constriction of coronary and peripheral microvessels, which is associated with increasing coronary artery atherosclerosis and endothelial dysfunction reported by comprehensive studies.[162-164] Specifically, cardiovascular disease patients experience stress-induced peripheral vasoconstriction due to α-adrenergic activation, leading to reduced microvascular dilation and impaired blood

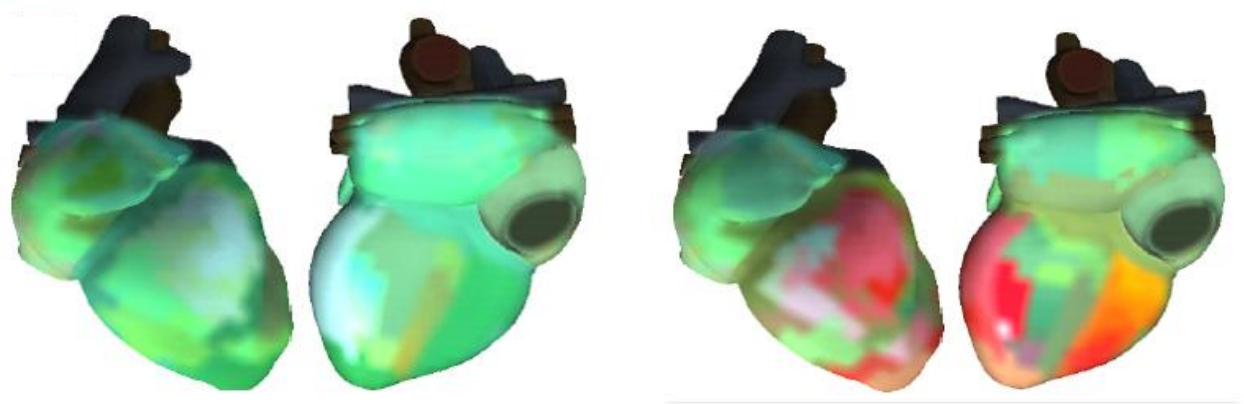
circulation regulation, along with cardiac dysfunction.[165] Additionally, inflammatory and oxidative pathways may play a role in the connection between cardiac and cerebral vascular functions.[166]There is significant crosstalk between the sympathetic nervous system and the immune system, with transient inflammatory responses partially triggered by sympathetic activation, resulting in increased reactive oxygen species (ROS) and subsequent lipid peroxidation and DNA damage.[167] These oxidative changes occur in peripheral nerves and the brain, particularly through microglial activation. Consequently, oxidative damage plays a critical role in endothelial dysfunction.[166] Given the importance of endothelial function in microvascular responses, ROS may serve as a significant intermediary linking cerebrovascular and cardiovascular diseases.

2.8 Methods of Assessing Cardiac Function

The evaluation of cardiac function currently relies on multiple imaging and electrophysiological modalities, each with inherent advantages and limitations. Cardiac MRI provides excellent soft-tissue characterization and volumetric measurements, yet its high cost, time-consuming nature, and inability to capture real-time electrophysiological data restrict routine clinical application.[168] Computed tomography angiography (CTA) for the management of patients with stable ischaemic heart disease offers superior coronary artery visualization but involves ionizing radiation and an invasive procedure. [169] Conventional 12-lead electrocardiography (ECG), while widely available and cost-effective, suffers from low spatial resolution and limited capacity to detect subtle electrophysiological disturbances. Although these techniques serve distinct diagnostic purposes across heterogeneous cardiac conditions, none can concurrently evaluate autonomic nervous system activity and myocardial repolarization heterogeneity with high spatiotemporal resolution—a capability now enabled by novel dispersion mapping technology. [170, 171]

2.8.1 Innovative ECG Technology for Cardiac Function Assessment

The standard ECG is known to be a screening tool for detecting the transient electrical activity of patients.[172, 173] However, in most cases, a conventional 12-lead electrocardiogram provides incomplete information with a lower sensitivity of 20% to 70%, and often misses subtle amplitude changes that may not be detectable in standard ECG recordings, even though it is convenient and cheaper. [174, 175] A 24-Holter is a wearable detector derived from the standard ECG and recognized as the gold standard to continuously record your heart rate and rhythm irregularities for 24 hours.[176] Nevertheless, the system is complex, and it is necessary to establish a special monitoring station for real-time processing. Hence, it is a challenge for us to explore a simple and reliable non-invasive ECG to address this issue. Nowadays, the new electrocardiographic dispersion mapping(ECG-DM) serves as an innovative "cardiovisor" with higher sampling frequencies to monitor myocardial electric instability and offer more comprehensive and robust data, which is especially important for capturing subclinical myocardium and heart rate micro-alteration during dynamic movements.[29, 177] Moreover, compared to traditional ECG and 24-Holter, the dispersive map can be classified into nine groups (G1-G9), quantitatively characterizing regional electric myocardial instability.[178, 179] Furthermore, the scatter diagram directly visualizes myocardial anatomical distribution and injury severity of pathological changes through color coding: red indicates severe ischemia/hypoxia, yellow represents borderline status, and green denotes normal status. However, this technology's application is limited in patients with arrhythmias due to insufficient validation data. **Figure 2-8** (**a. b**) are examples of imaging provided by dispersive mapping.



(a) **(b)**

Figure 2-8 A graduated color-coded heart dispersion mapping: green denotes healthy myocardial tissue, while red indicates pathological alterations. (a) Normal cardiac physiology. (b) Bilateral ventricular ischemic impairment

2.8.2 Novel Cardiac Biomarkers for Cardiac Function

From the aspect of cardiac autonomic dyshomeostasis, heart rate variability(HRV), a sophisticated metric of sympathovagal balance, describes a series of automatic calculations for psychophysiological responses between consecutive heartbeats.[25, 180] Parameters were classified as time and frequency domains that can be obtained through 3-minute, 5-minute, or 24-hour continuous ECG recordings.[181] The standard deviation of the NN intervals (SDNN, normal range: 17.9~40.1 ms) and the root mean square successive difference of intervals (RMSSD, healthy level, 20-89 ms) are the predominant indicators of the time domain. The frequency domain parameters are responsible for ANS, including high-frequency (HF; range 0.15–0.4 Hz), low-frequency (LF; range 0.04–0.15 Hz), very-low-frequency (VLF; <0.04 Hz), and the ratio of LF to HF power (LF/HF).[161, 182] Previous studies have reported that SDNN comprehensively responds to autonomic nervous system function.[183] RMSSD and high-frequency(HF) reflect the status of the parasympathetic nervous system (PNS) activity. LF is a mediator that is modulated by both the sympathetic nervous system (SNS) and PNS. Furthermore, the ratio between LF and HF represents the sympathetic-vagal balance.[183] Thus, various stressors consequently lead to ANS dysfunction

and unstable changes in sympathetic-vagal balance, which can result in normal HRV index changes. (**Figure 2-9 & 2-10** Spectral analysis of heart rate)

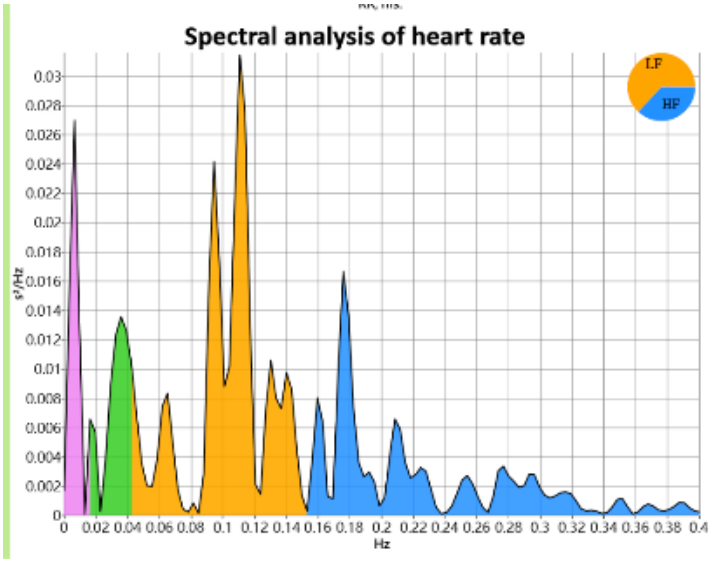


Figure 2-9 LF/HF>1~ sympathetic activity.

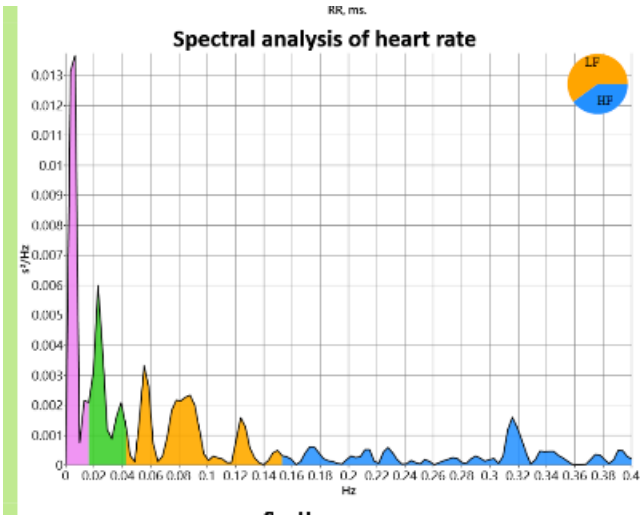


Figure 2-10 The sympathetic-vagal homeostasis.

2.9 Heart Rate Variability in Chronic Cerebrovascular Disease

As detailed before, HRV reflects the dynamic process in the nervous system, which could be applied in the multi-risk stratification of cardiovascular and cerebrovascular events.[184, 185]

Evidence from extensive studies has proven that HRV, as a "mediator" with high sensitivity(71.4%) and specificity(81%), could classify hypertensive patients at high risk in vascular events.[186] More recently, some studies have reported that HRV decline has increased the risk probability of cerebrovascular diseases, such as incident stroke and secondary cerebral events.[31] In the Atherosclerosis Risk Community study, HRV was evaluated in 12550 middle-aged resident adults, and Cox regression analysis revealed a robust association of low HRV index with a modest risk of incident stroke in patients with diabetes mellitus.[31] A prior study has proven that a higher heart rate (odds ratio = 1.041; 95% IQR=1.006 - 1.078; p=0.023) is independently associated with WMH in stroke patients, thereby suggesting that autonomic nervous system decline is related to CSVD progress.[183] Paradoxically, Del Brutto OH. *et al.* reported that low HRV has positively increased the CSVD burden.[187] Yu Tian et al. indicated that HRV was not validated as associated with heterogeneous phenotypes of cerebral SVD, such as brain atrophy and lacunes.[133] Despite evidence from prior studies demonstrating a causal relationship between heart rate variability and both cerebral large and small vessel disease, conflicting results persist, and these relationships remain unclear. Hence, in our study, these uncertain correlations warrant further exploration.

2.10 Summary

Cerebrovascular disease includes two major vasculopathy types: cerebral large arteries and small vessels, in which the territorial domains and histopathological features are different from each other. **Table 2-1** summarizes the main different features between cerebral large arteries and small vessel lesions. Cerebral large arterial lesions are responsible for the blood supply to the brain, while cerebral small vessel diseases tend to involve arterioles, capillaries, and small veins, are account for the exchange of oxygen, nutrients, and waste products between blood and brain cells. Intracranial large arterial lesions are often associated with plaque vulnerability and the hemodynamic impact in advanced atherosclerotic stages, while small vessel lesions are frequently connected to arteriolar stiffness and microangiopathy. Due to the different histological features of

large and small vessel diseases, the traditional diagnosis and management could be limited to reflect accurate clinical information, indicating a demand for new qualitative and quantitative assessments by MRI.

Intracranial plaque vulnerability plays a critical role in hemodynamic impact and luminal stenosis, even though they are non-culprit plaques that may also lead to the development of ischemic cerebral events.[188] By characterizing plaque features beyond luminal stenosis, vessel wall MRI is a promising technique to detect specific plaque features associated with cerebral infarct microangiopathy, like WMHs, lacune infarction, and cerebral microbleeds. Furthermore, cardiac damage is prevalent in patients with cerebrovascular disease and may serve as a risk biomarker for assessing the severity of cerebrovascular conditions. [189, 190] Broadly, brain injury that induces cardiac dysfunction may disrupt brain-heart interaction and impair ANS balance, even in cases of mild or recoverable impacts, such as neurogenic stress cardiomyopathy. Heart rate fluctuation is known as an assessment tool for autonomic cardiac control. Changes in HRV may represent an inadequate response of the autonomic nervous system to the stress associated with a more severe condition. [191] The causal correlation of cerebrovascular disease and cardiac dysfunction, and the influence of separate atherosclerotic plaque imaging features, is unknown. Plaque radiological features have been recently found to be a potential risk factor for cSVD, most likely due to the hemodynamic change. The pathophysiology underlying the vasculopathy-inducing heart rate dysfunction is still unclear. Further imaging, electrophysiology, and clinical evidence that are based on different brain vascular lesions with cardiac micro-alteration are required in future studies.

Table 2-1. Summary of the main differences between cerebral large arteries and small vessel lesions.

Cerebral vascular types	Pathological feature		Risk factor (difference)	Clinical impact	
	Formation	Distribution/Morphology		Relevance and mechanism	Treatment
Large arteries	(1) Driven by atherosclerotic processes (2) Inflammation associated (3) Granules initially, fuse into large plaque formation and potential occlusion (4) May ulcerate and rupture	Willis' circle, thicker walls and larger lumens	Aging, gender, smoking;	(1) Main cause of stroke and transient ischemic attacks (2) Hypoperfusion (luminal stenosis and occlusion)	Surgical interventions such as angioplasty or stenting
Small vessels	(1) Related to chronic hypertension, diabetes, and other metabolic disorders, affecting the vessel wall directly (2) Lipohyalinosis, fibrinoid necrosis, and microangiopathy (3) Involving small parenchymal arteries and arterioles	Smaller, more delicate structures	Aging, diabetes mellitus, hypertension;	(1) 1/5 cause of stroke and 45% of dementias; Arterial stiffness and vascular dementia (2) Possibly worse cerebral perfusion in microvascular beds	Controlling underlying conditions (e.g., hypertension, diabetes) and anticoagulant.

Chapter 3. Study-1: Intracranial Atherosclerosis Defined by High-resolution Vessel Wall Imaging is Correlated with Cerebral Small Vessel Disease: A Community-based Cohort Study

Chapter 3. Study-1

3.1 Background

The relationship of extracranial atherosclerosis with cerebral small vessel disease (cSVD) has been widely studied. [192, 193] For instance, silent cSVD commonly coexists with the severity of carotid artery stenosis and is associated with the features of unstable carotid plaques demonstrated by previous studies.[194, 195] Apart from extracranial arteries, evidence of the association of intracranial large-artery atherosclerosis with cSVD has been also reported, but inconsistent findings were observed in previous studies, which might be due to their different pathogenetic mechanisms[196] and the diversity of ICAS assessments including intracranial arterial calcification by CT, blood flow velocity assessment by pulse wave ultrasound, or vessel wall assessment by MRI.[197, 198] Recently, more attention has been paid to high-resolution MRI (HR-MRI) examinations, which are capable of evaluating lesions within intracranial vessel walls by presenting hypointensity on MRI images.[199] This technique reveals the ultrastructure of the vessel wall and enables radiologists to identify calcium deposits at different arterial locations (e.g., M1 of the middle cerebral artery, V4 of the vertebral artery) and to assess varied imaging morphological characteristics of intracranial atherosclerotic plaques.[62, 200] By comparing autopsy findings with multi-contrast HR-MRI, Jiang *et al*[57] achieved a remarkable differentiation between lipid core (isointense/hyperintense), fibrous cap (isointense), and calcification (hypointense) on T1 sequences, which benefits both the diagnosis and differentiation of ICAS features and plaque vulnerability. Based on the previous investigation, ICAS is a major cause of stroke worldwide, accounting for 30-50% and 10% of ischemic cerebrovascular events in Asians and Whites, respectively.[201-203] In addition, ICAS and cSVD commonly coexist[23] and are jointly affected by intracranial hemodynamics [200], although they are different in geographic distribution and physiological function. Moreover, both cerebral vascular diseases, as demonstrated by prior investigations, contribute to stroke, cognitive

decline, permanent disability, and even mortality. [136, 204] Given their important roles in clinical outcomes, it is essential to further explore the potential correlation between ICAS and cSVD, particularly in Asian populations, which bear a higher burden of both conditions.[205-207] Previous evidence has demonstrated that there is an association between ICAS and CSVD in stroke patients. [20, 22] To date, however, there is scant information about whether such an association is present among community populations. Non-stenotic ICAS and cSVD may be asymptomatic or mild in the general population, yet they have a higher prevalence and are commonly associated with various cerebral adverse events and cognitive dysfunction.[205-207] Therefore, to fill in this research gap, the present study aimed to elucidate the association between ICAS and cSVD in community-dwelling adults based on a cohort in Hong Kong.

3.2 Materials and Methods

3.2.1 Participants and Baseline Characteristics

The study was approved by the Institutional Review Board of the Hong Kong Polytechnic University, and all subjects gave written informed consent. Consecutive Hong Kong local community inhabitants from November 2022 to December 2024 were recruited. The inclusion criteria were as follows: 1) subjects aged 45 years or older, who were free from any prior stroke or transient ischemic attack (TIA); 2) Chinese origin; 3) subjects with high-quality MR imaging and full completion of the study protocol. Participants with the following conditions were excluded: 1) any contraindication for MRI; 2) history of severe cardiovascular disease; 3) subjects with critical medical conditions, such as malignancy, head trauma, or vasculopathies. 4) poor quality of imaging data and incomplete clinical and ECG data because of medical conditions or other reasons.

A baseline questionnaire was used to collect the demographic and vascular risk factors of

individual subjects. The clinical risk factors were recorded by performing a questionnaire on the same day as ECG and MRI examinations. Baseline characteristics including age, gender, and other vascular risk factors, including history of hypertension, diabetes mellitus, ischemic heart disease, current smoking, and drinking. Use of statins, antiplatelet, or cholesterol-lowering medications was recorded. We defined hypertension as blood pressure ≥140/90 mmHg or current use of an antihypertensive agent or a self-reported physician diagnosis of hypertension. The ischemic heart disease was defined as the use of oral anti-ischemic heart agents without percutaneous coronary stenting or a self-reported congenital heart disease. Diabetes mellitus and hyperlipidaemia were judged as present when a history of treatment was presented or self-reported. Smoking was defined as the current use of cigarettes. Drinking was defined as currently having a daily intake of alcohol. We reviewed prior medical treatments: antiplatelet, anti-coagulant, and statin use.

3.2.2 MRI Acquisition

MR imaging was performed by a 3.0-T scanner (Siemens Medical Systems, XR Numarism, Germany) with a 64-channel head coil. High-resolution vascular sequences (HR-MRI, a transverse 3D T1-weighted volumetric isotopically reconstructed turbo spin echo acquisition; detailed parameters were as follows: field of view: 53x 210 x 138mm3, acquired resolution 0.7x0.7x0.7mm3, repetition time [TR]/echo time [TE] 900/15ms, slice thickness 0.66mm, echo spacing 4.88ms, and scan duration 5.56minutes.

A standardized brain MRI protocol was used which consisted of a 3-dimensional (3D) time-of-flight MRA(TOF-MRA, field of view 263x 350x 350 mm3, acquired resolution 0.5x0.5x0.3mm3, repetition time/echo time 20.3/4.3ms, and scan duration 3.51minutes), conventional spin-echo mixed intensity and T2-weighted sequence (field of view: 263x 350 x 350mm3, repetition time [TR]/echo time [TE] 4100-6000/88 and 99msec, flip angle 150°, slice

thickness 4.0mm), FLAIR (Fluid Attenuated Inversion Recovery; the scanning parameters were set as follows: field of view: 230x 230 x 173mm3, acquired resolution 0.9x0.9x0.9mm3, repetition time [TR]/echo time [TE] 7000/395ms, slice thickness 0.90mm, flip angle 150°, and scan duration 3.46 minutes) and T1-weighted fat suppressed (field of view: 240x 256x 167mm3, acquired resolution 0.8x0.8x0.8mm3, repetition time [TR]/echo time [TE] 2500/2.22ms, slice thickness 0.80mm, flip angle 8°, and scan duration 6.54 minutes).

3.2.3 MRI Post-processing

MRI images were independently analyzed by two observers (LH. L. and YY. C.) with at least three years of experience in MRI image interpretation, who were both blind to the clinical data of the participants. In the case of disagreement between raters, a consensus reading was held by Dr. JQ. LUO (with more than ten years of neuroimaging experience). Intracranial artery segments including bilateral segment the cavernous segment (C4) and supraclinoid segment (C5) of internal carotid arteries (ICAs), M1 segment of middle cerebral arteries (MCAs), segment A1 of anterior cerebral arteries (ACAs), segment P1 of posterior cerebral arteries (PCAs), intracranial (V4) segment of vertebral arteries (VAs), the basilar artery (BAs), were examined. **Figure 3-1**

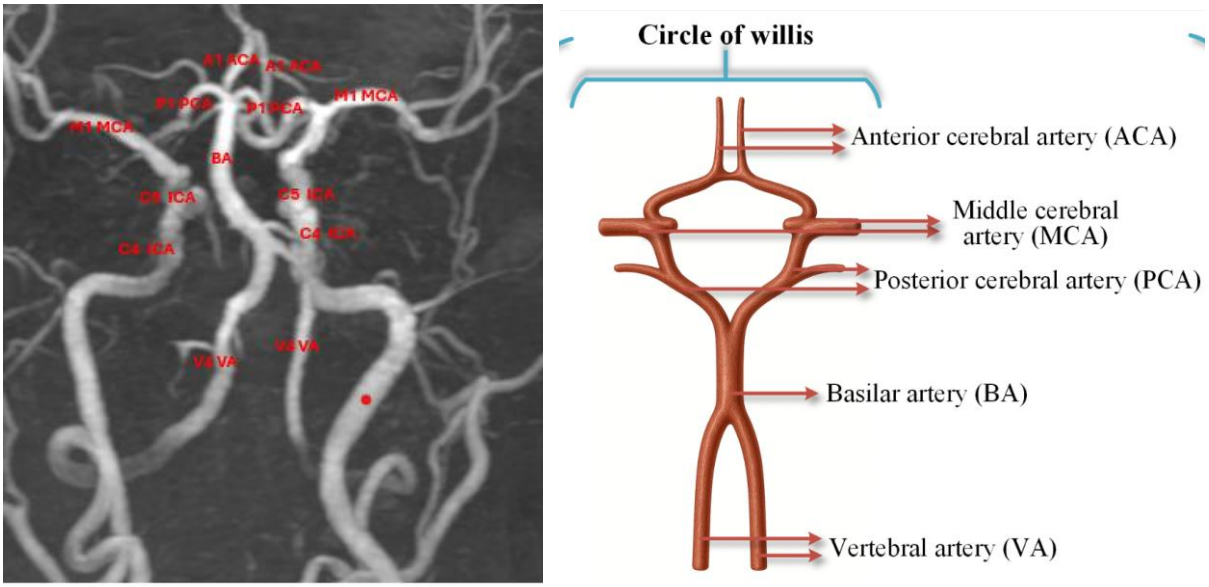


Figure 3-1 Intracranial artery segments on Willis' circle anatomy visualized on MRA image. The cavernous segment (C4) and supraclinoid segment (C5) of internal carotid arteries (ICAs), M1 segment of middle cerebral arteries (MCAs), segment A1 of anterior cerebral arteries (ACAs), segment P1 of posterior cerebral arteries (PCAs), intracranial (V4) segment of vertebral arteries (VAs), and the basilar artery (BAs).

The presence and severity of intracranial atherosclerotic lesions was identified by reconstructed HR-vessel wall images using OsiriX DICOM Viewer (Pixmeo SARL, Bernex, Switzerland. Any identified or suspected luminal stenosis was referenced against TOF-MRA, with only the most severe lesions chosen for MRI cross-sectional slice measurements. While the nearest plaque-free cross-section was selected as the reference site, if no segment without plaque was identified proximal to the plaque, the nearest distal cross-section was chosen as an alternative reference site. [208, 209] As demonstrate in **Figure 3-1**, the number of arteries involved by ICAS was categorized as absent, 1-2 ICAS, and ≥3 ICAS. Plaque burden was calculated by the formula: (plaque area/ OWA_{lesion}) x 100%.[209] Based on the plaque burden, ICAS severity is classified into three groups: none, pre-ICAS (plaque burden <75%), and progressive-ICAS (plaque burden ≥75%). The presence and burden of cSVD features, including the presence,

distribution, and severity of white matter hyperintensities (WMHs), enlarged perivascular space (ePVS), cerebral microbleeds (CMBs), lacune infarctions, and cerebral atrophy, were also assessed on standardized brain MRI. Based on the standards of Fazekas score of 0-6 in T2 and FLAIR sequences, the severity of deep and periventricleWMHs was assessed from absent to severe. [210] Mild WMHs were defined as a total score of ≤ 2 (punctate foci in PV-WMH and D-WMH regions), moderate WMHs as a total score of 3-4 (classified as beginning confluence in PV-WMH and D-WMH regions), and severe WMHs as a total score of 5-6 (characterized by large confluent bright signals extending from the PV-WMH area into the deep white matter region). [210] ePVS was identified as ovoid, round, or linear structures with a diameter of ≤3mm, showing hyperintense signals on T2 and FLAIR images. [211] In this study, a 4-level severity score assessed the severity of ePVS is based on the number of foci ePVS in the basal ganglia (BG-ePVS) and centrum semiovale (CS-ePVS). When ePVS were present in both hemispheres, the most severe manifestation on one side of the hemisphere was selected for analysis. Subjects were classified into Grade 0 (no ePVS, score 0), Grade 1 (number of ePVS≤10, score 1), Grade 2 (number of ePVS=11-20, score 2) or Grade 3 (number of ePVS≥21, score 3) to evaluate the impact of severe ePVS on ICAS. Chronic lacunes were visualized as one or more circular or ovoid lesions (3–15 mm in diameter) with a central CSF-like hypointensity with a surrounding rim of hyperintensity.[136] CMBs were defined as a small round signal void with less than 10 mm in diameter in SWI with associated blooming. [136] Total cSVD scores (ranged from 0 to 4) were calculated according to the scoring system described by Staals et al. 2014.[212] The criteria are detailed as below:

Moderate-to-severe WMH (including PVH):

- Defined as: Confluent deep WMH (Fazekas score 2 or 3) or irregular PVH extending into deep white matter (Fazekas score 3)
- Score: 1 point if present

Moderate-to-severe BG-PVS:

- Defined as ≥ 11 BG-PVS on one side
- Score: 1 point if present

CMBs or lacunae

- Defined as the presence of one or more foci
- Score: 1 point each if present

3.2.4 Statistical Analysis

IBM SPSS version 27.0 was performed for statistical analysis. Continuous variables were presented as mean ± standard deviation (SD), while categorical data, such as the presence and the severity of ICAS and cSVD features, were presented as percentages and numbers. Independent *T*-tests and *U*-tests were used for continuous variables. Pearson's chi-square test and Fisher's exact test were used to analyze categorical variables. Relationships of ordinal variables were analyzed by the Chi-square linear trend test. $p \leq 0.05$ was considered statistically significant. The inter-rater reliability of two observers was assessed by Cohen's kappa analysis.

3.3 Results

3.3.1 Baseline Characteristics

This study recruited 284 participants. Out of these 284 participants, a total of 12 individuals (5.3%) were excluded from the study due to either being below the age of 45 or having incomplete data. A total of 272 subjects were finally included in this study. There were 179 (65.8%) subjects identified to have one or more arteries involved with ICAS, and the remaining 93 (34.1% %) subjects had no ICAS. Subjects involved with ICAS were generally older (mean age, 64.39 ± 6.82 vs. 61.44 ± 6.33, $p<0.001$) and frequently had hypertension (36.9%

vs. 15.1%, p<0.001) and hyperlipidemia (45.8% vs. 23.7%, p<0.001) compared to those without ICAS. Among these subjects with ICAS, 86 out of 179 (48.0%) participants were men. Current smoking and drinking were found in 9 and 15 subjects, respectively, out of 179 subjects (5.0% and 8.4%). Moreover, 24 out of 179 (13.4%) subjects had diabetes. Among the 93 participants without ICAS, 32 (34.4%) were men. Of the 93 subjects, 5 (5.4%) and 5 (5.4%) subjects had history of smoking and drinking, 14 (15.1%) had hypertension, 22 (23.7%) had hyperlipidemia, and 9 (9.7%) had diabetes. **Table 3-1** shows the demographic and clinical baseline characteristics of the subjects with and without ICAS.

Table 3-1 The demographic and clinical baseline characteristics of the subjects with and without ICAS.

Characteristics	All subjects (n=272)	Participants without ICAS (n=93)	Participants with ICAS (n=179)	*p*-value
Male, n (%)	118(43.4)	32 (34.4)	86 (48.0)	0.031*
Age (mean ± SD, years)	63.38 ± 6.79	61.44 ± 6.33	64.39 ± 6.82	< 0.001*
Hypertension, n (%)	80 (29.5)	14 (15.1)	66 (36.9)	< 0.001*
Hyperlipidemia, n (%)	104 (38.4)	22 (23.7)	82 (45.8)	< 0.001*
Diabetes, n (%)	33(12.2)	9(9.7)	24 (13.4)	0.371
Ischemic heart disease, n (%)	17(6.3)	3(3.2)	14 (7.8)	0.137
Smoking, n (%)	14(5.2)	5 (5.4)	9 (5.0)	0.902
Drinking, n (%)	20(7.4)	5 (5.4)	15(8.4)	0.368

Abbreviations: ICAS, intracranial atherosclerosis; SD, standard deviation. *: p<0.05

3.3.2 Distribution of Cerebral SVD Phenotypes

3.3.2.1 Imaging Characteristics of ICAS with the Burden of Sub-cSVD Markers

The frequency of sub-CSVD markers in three groups categorized by the number of arteries involved by ICAS is presented in **Table 3-2**. The Chi-square linear trend test showed the

number of ICAS-involved arteries was related to a higher prevalence of cSVD phenotypes. Among these subjects, those involved by more than three ICAS arteries presented a greater total WMH score (43.9% vs. 16.1%, p=0.001), a higher prevalence of enlarged perivascular spaces in basal ganglia (68.5% vs. 44.1%, p=0.048), and moderate to severe brain atrophy (46.3% vs. 13.0%, p<0.001), compared to those with no ICAS involvement. However, this correlation was not found in the number of ICAS-involved arteries with the presence of lacunar infarcts and cerebral microbleeds (all p>0.05).

Furthermore, a similar trend was detected in the correlations between the progress of ICAS and the severity of imaging features of cSVD markers (**Table 3-3**). Among 272 subjects, 65 (23.8%) were categorized as having progressive intracranial atherosclerotic conditions with a plaque burden >75%. The more severe ICAS burden had a noticeably higher total WMH score ≥3 points (p=0.019), more severe ePVS in the basal ganglia (number > 10 ePVS, p=0.041), and higher grade of brain atrophy (p<0.001) than those in the normal and mild ICAS groups. There were no significant differences in the presence of CMBs and chronic lacunes among the three groups of patients with no ICAS, mild ICAS (plaque burden <75%), and severe ICAS (plaque burden ≥75%), all p>0.05.

Table 3-2 Comparison between the number of arteries involved by intracranial atherosclerosis (ICAS) and the imaging features of cerebral small vessel disease.

	ICAS-involved arteries			*p*-value
	None (n=93)	1-2 arteries (n=138)	≥3 arteries (n=41)	
WMH presence, n (%)	64(68.8)	114(82.6)	38 (92.7)	0.003*
Deep WMH, n (%)				
Absent	32 (34.4)	28 (20.3)	4 (9.8)	
Punctuate	46 (49.5)	83 (60.1)	22 (53.7)	0.003*
Confluent	15 (16.1)	27 (19.6)	15 (36.6)	
PeriventricleWMH, n (%)				
Absent	47 (50.5)	37 (26.8)	6 (14.6)	
Thin	37 (39.8)	82 (59.4)	23 (56.1)	<0.001*
Extending	9 (9.7)	19 (13.8)	12 (29.3)	
Total WMH score, n (%)				
0 points	28 (30.1)	24 (17.4)	3 (7.3)	
1-2 points	50 (53.8)	82 (59.4)	20 (48.8)	0.001*
≥3 points	15 (16.1)	32 (23.2)	18 (43.9)	
EPVS presence, n (%)	93 (100)	138 (100.0)	41 (100.0)	
Basal ganglia EPVS number, n (%)				
≤10	52 (55.9)	71 (51.4)	17(41.5)	0.048*
11-20	36 (38.7)	48 (34.8)	18 (43.9)	

≥21	5 (5.4)	19 (13.8)	6 (14.6)	
Centrum semiovale EPVS number, n (%)				
≤10	59 (63.4)	82 (59.4)	28(68.3)	
11-20	24 (25.8)	45 (32.6)	9 (22.0)	0.630
≥21	10 (10.8)	11 (8.0)	4 (9.8)	
CMBs presence, n (%)	17 (18.3)	27 (19.6)	11 (26.8)	0.506
CMBs number, n (%)				
0	75 (81.5)	112(81.2)	30 (73.2)	
1	12 (13.0)	20 (14.5)	3 (7.3)	0.039*
≥2	5 (5.4)	6 (4.3)	8 (19.5)	
Lacune presence, n (%)	21 (22.6)	37 (26.8)	14 (34.1)	0.373
Atrophy, n (%)				
Normal	34 (37.0)	26 (18.8)	5 (12.2)	
Mild atrophy	46 (50.0)	76 (55.1)	17 (41.5)	<0.001*
Moderate atrophy	12 (13.0)	33 (23.9)	18 (43.9)	
Severe atrophy	0 (0.0)	3 (2.2)	1 (2.4)	

*: $p<0.05$. WMH, white matter hyperintensities; EPVS, enlarged perivascular space; CMBs, cerebral microbleeds.

Table 3-3 Comparison between the severity of intracranial atherosclerosis (ICAS) and the imaging features of cerebral small vessel disease.

	Participants with different severities of ICAS			*p*-value
	No ICAS (n=93)	Pre-ICAS (n=114)	Prog-ICAS (n=65)	
WMH presence, n (%)	64 (68.8)	97 (85.1)	55 (84.6)	0.008*
Deep WMH, n (%)				
Absent	32 (34.4)	19 (16.7)	13 (20)	
Punctuate	46 (49.5)	71 (62.3)	34 (52.3)	0.022*
Confluent	15(16.1)	24 (21.1)	18 (27.7)	
PeriventricleWMH, n (%)				
Absent	47 (50.5)	30 (26.3)	13 (20.0)	
Thin	37 (39.8)	66 (57.9)	39 (60.0)	<0.001*
Extending	9 (9.7)	18 (15.8)	13 (20.0)	
Total WMH score, n (%)				
0 points	28 (30.1)	17 (14.9)	10 (15.4)	
1-2 points	50 (53.8)	68 (59.6)	34 (52.3)	0.019*
≥3 points	15 (16.1)	29 (25.4)	21 (32.3)	
EPVS presence, n (%)	93 (100.0)	114 (100.0)	65 (100.0)	
Basal ganglia EPVS number, n (%)				
≤10	52 (55.9)	61 (53.5)	27 (41.5)	
11-20	36 (38.7)	35 (30.7)	31 (47.7)	0.041*
≥21	5 (5.4)	18 (15.8)	7 (10.8)	
Centrum semiovale EPVS number, n (%)				
0	59 (63.4)	74 (64.9)	36 (55.4)	
≤10	24 (25.8)	30 (26.3)	24 (36.9)	0.541
11-20	14 (20.0)	17 (19.5)	22 (31.4)	
≥21	10 (10.8)	10 (8.8)	5 (7.7)	
CMBs presence, n (%)	17 (18.3)	27 (23.7)	11 (16.9)	0.472
CMBs number, n (%)				
0	75 (81.5)	88 (77.2)	54 (83.1)	
1	12 (13.0)	18(15.8)	5 (7.7)	0.541
≥2	5 (5.4)	8(7.0)	6 (9.2)	

Lacune presence, n (%)	21 (22.6)	28 (24.6)	23 (35.4)	0.166
Atrophy, n (%)				
Normal	34 (37.0)	20 (17.5)	11 (16.9)	<0.001*
Mild atrophy	46 (50.0)	64 (56.1)	29 (44.6)	
Moderate atrophy	12 (13.0)	26 (22.8)	25 (38.5)	
Severe atrophy	0 (0)	4 (3.5)	0 (0)	

Abbreviations: ICAS, intracranial atherosclerosis; Pre-ICAS group, subjects with plaque burden of ICAS <75%; Prog-ICAS group, subjects with higher plaque burden (≥75%) of ICAS; WMH, white matter hyperintensities; EPVS, enlarged perivascular space; CMBs, cerebral microbleeds. *: $p<0.05$.

3.3.3 Reliability of assessment

The inter-observer agreement of analyzing the presence, distribution, and grade of five imaging features of cSVD and ICAS was shown in **Table 3-4**. The inter-observer reliability was good for the evaluations.

Table 3-4 The inter-observer reliability of analyzing the presence, distribution, and grade of 5 cSVD imaging markers (WMHs, CMBs, lacune, brain atrophy, and ePVS) and the presence of ICAS in a total of 227 cases.

	Dr. Lai	**Yangyang**	**Inter-observer agreement Coefficient (95% CI)**
Presence of WMHs	207(91.2%)	199(87.6%)	0.81 (0.686-0.933)
Presence of periventricleWMHs	184(81%)	190(84%)	0.85 (0.771-0.928)
Presence of deep WMHs	193(85%)	177(78%)	0.79 (0.684-0.895)
WMHs grade			0.78 (0.699 – 0.857)
Mild	144 (63.4%)	132(58.1%)	
Mod	59(26%)	60(26.4%)	
Severe	4(2%)	7(3%)	
Presence of CMBs	45(20%)	56(24.6)	0.78 (0.682 - 0.878)

Presence of lacune	63(27.7%)	96(42.3%)	0.65 (0.552 - 0.748)
Presence of Global Cerebral Atrophy (GCA)	180(79.3%)	176(77.5)	0.81 (0.715-0.0.904)
Grade of GCA			0.73 (0.652 – 0.810)
Presence of ePVS	100%	100%	
Presence of ICAS (MCA, BA, VA); (n, %)	127(55.9)	123(54.2)	0.86 (0.793 - 0.926)

Abbreviations: CI, confidence interval; inter-rater agreement for binary disease diagnosis using Cohen's kappa and assessed ordinal disease severity consistency with weighted kappa

3.4 Discussion

Results of this study suggested that a greater number and higher burden of arteries involved by ICAS are found in individuals with higher incidence and greater severity of WMHs, BG-PVS, and brain atrophic grades. Evidence from prior research demonstrates that large artery disease and small vessel disease are structurally interrelated.[213] Despite differing in anatomical structures and physiological functions, both disorders are affected jointly by hemodynamic influence with sharing common risk factors, such as aging and hypertension.[87] Hence, the study of imaging subtypes of SVD in the context of large-arterial disease is important in the assessment of cerebrovascular disease.

In the evaluation of different atherosclerotic burdens of cerebral large arteries, results of the present study showed that higher grades of WMHs, BG-PVS, and brain atrophy were correlated with ICAS severity. In contrast, previous studies reported that intracranial large-artery atherosclerosis was not associated to ePVS and CMBs. [214, 215] This discrepancy can be explained by physiological mechanisms. In subjects with higher burden of ICAS, worsening hypoperfusion as stenosis progresses leads to an increase in centrum semiovale perivascular spaces which site in the white matter between the axon tracts. Meanwhile, the diameter of intracranial large arteries can decrease, affecting systemic hemodynamic pressures, which

increases in small vessels and reduces the efficiency of fluid clearance, potentially leading to a significant increase in the number of BG-PVS.[216] As a result, the effect of ICAS burden on the number of ePVS is substantial. Intracranial atherosclerotic burden is indicated as an all-encompassing semiquantitative gauge for assessing the overall extent of brain atherosclerosis.[217] Enlarged perivascular space, as a marker for various neurological conditions, may function in a 'glymphatic' role by facilitating cerebrospinal fluid flow and waste removal, thereby maintaining homeostasis.[218] This study shows that stiffening of the conduit cerebral large arteries may relate to higher ePVS load, therefore suggesting that ePVS may be markers of systemic arterial aging and its effect on pulsatile hemodynamics. Moreover, the burden of ICAS and its association with ePVS could accurately reflect cerebrovascular health, even in cases of asymptomatic atherosclerosis. Increasing awareness of the relationship between ICAS and ePVS can inform risk stratification, enabling healthcare providers to tailor management strategies, early intervention based on individual patient profiles. Consistent with the previous report demonstrated by Charidimou, the increased number of ePVS is independent risk factor of cerebrovascular atherosclerosis. [219] Similar findings were previously noted on the presence of lacune of subjects with intracranial carotid arterial calcification.[220] The possible explanation is severe intracranial atherosclerotic plaques may induce hypoperfusion through hemodynamic alterations, thereby impacting the formation and progression of lacunes associated with cerebral perfusion changes. [221] However, the association between ICAS and lacunes was not found in this study. The inconsistent finding may be related to the small sample size in the present study and the different types of subjects involved in these studies. Some studies indicated that lacunar infarcts, small subcortical infarctions, is recognized as one of the stroke subtypes[222], and can be caused by intracranial atherosclerosis.[223] Jeon, Kipyoung, *et al.* reported that the burden of ICAS and its association with lacunes has been found in patients with recurrent ischemic stroke.[224] The correlation has also been demonstrated by prior

epidemiological studies, with this relationship being more frequently observed in men and in African American patients with stroke or transient ischemic attack.[225] However, in this study, we investigated the association in the asymptomatic general population. In terms of CMBs, there was no association noted with the presence and severity of ICAS in the present study. Besides the relatively small sample size of the study, the main reason for the insignificant association may be because this study only recruited community stroke-free adults, thus CMB is not as apparent as patients with ischemic stroke in the previous study.[226] Similar to the present study, previous studies have investigated the relationship between ICAS and CMBs, suggesting the lack of a relationship between these two cerebral vascular conditions.[214, 227] To date, no consensus or sufficient evidence on the complex pathogenic mechanism of CMBs, whereas it is widely acknowledged as a risk factor for poor stroke outcomes.[228] Regarding the relationship between the grade of brain atrophy and the severity and prevalence of ICAS, a significant correlation was found in this study. Gradual loss of cerebral tissue in adulthood causes central nervous system atrophy. It can be a natural part of aging, but can also be accelerated by various factors, including pathology like atherosclerosis.[229, 230] Accumulated evidence has shown a significant positive correlation between the ICAS and global brain atrophy. Bos, D *et al.* investigated the relationship between ICAS and brain volume, revealing a significant correlation between ICAS and total brain volume.[231] Similarly, in a study conducted on the Japanese population, an association was found between carotid atherosclerosis and brain atrophy.[229] Another prior study also indicated that carotid intima-media thickness pattern was correlated with sulcal enlargement in brain. [232] In contrast, however, not all studies showed consistent results. Some researchers compared ICAS and cSVD findings and found no significant correlation with brain atrophy, particularly in cortical brain volume loss.[66, 198] These discrepancies may be explained by the different locations and severities of atherosclerosis which have varied impacts on brain atrophy patterns, and led to

different study results. Intracranial atherosclerosis and its association with brain atrophy are interactive and impacted by many risk factors. It is of clinical importance since it has been suggested that the extent and rate of progression of global and focal atrophy are associated with cognitive deterioration and conversion to dementia.[233] Therefore, further research is needed to investigate their relationships and the clinical value in predicting future cerebrovascular events.

WMHs is a common and important imaging feature for cerebral SVD. Consistent with a previous study [200], a higher prevalence of WMH was found in the large-artery-disease study group (79.4%) in the present study. WMHs commonly manifested simultaneously with other sub-cSVD markers like ePVS, CMBs, and are recognized as a risk factor of ischemic stroke. In the study results, an increasing number of arteries involved by ICAS with greater plaque burden was related to a higher prevalence and severity of WMHs. The association between intracranial atherosclerotic burden and WMHs may serve as a potential quantitative indicator of the burden on the brain's primary arteries and small vascular conditions, reflecting the cerebral vascular health status[217, 234]. However, the underlying mechanisms of ICAS and WMHs are complex, and their association remains unclear. Therefore, the present study aimed to explore the specific associations between different imaging characteristics of ICAS and various neuroimaging subtypes of cSVD, particularly on WMHs.

This study had limitations. First, the number of participants was relatively small. Second, the study population was restricted to Chinese adults, which may limit the generalisability of its findings. However, differs from prior studies that primarily focused on individuals over 80 years old, this study included both middle-aged and elderly adults. Third, this is a cross-sectional design that prevents determining the directional relationship between ICAS and cSVD. Although the progression of ICAS and cSVD was not tracked over time, the findings offer a valuable snapshot that enhances our understanding of their current burden and interplay.

Future prospective studies could be conducted to in-depth examine the temporal dynamics between these conditions. Consequently, the results may provide a more accurate reflection of the ageing population, encompassing a broader age range. The validity of the current findings is supported by the community-based design and the systematic approach for assessing the cSVD biomarkers, in addition to the use of validated semiquantitative methods to evaluate ICAS across different intracranial vascular beds using internationally recognised methods. Collectively, these factors constitute major strengths of the present study.

3.5 Conclusion

To summarize, the findings of this study indicate that the correlation between the presence and severity of ICAS and different imaging features of cSVD is not solely attributable to overlapping of risk factors but rather suggests a positive relationship between ICAS and cSVD. HRVW-MRI has the potential to elucidate diagnostic metrics and characteristics that reveal how ICAS affects distinct CSVD burdens, thereby enhancing clinical decision-making and risk stratification management.

Chapter 4. Study-2: Association of Intracranial Plaque Feature with The Severity of White Matter Hyperintensities in Middle-Aged and Older Community-Dwelling Adults

Chapter 4. Study-2

4.1 Background

Cerebral small vessel disease is the most common, progressive vascular disease with no optimal treatment till now. White matter hyperintensity is a radiographic biomarker for cerebral small vessel disease (cSVD), which is frequently observed in elderly people and plays a crucial role in the development of ischemic stroke and cognitive decline. [21, 136, 211, 235, 236] Previous studies demonstrated that the pathological progress of WMH is dynamic and complex. Many traditional risk factors such as aging[237], hypertension[238], and smoking, have been identified as significant contributors to WMH burden. [239] Recently, there has been growing evidence reporting that intracranial large artery atherosclerosis may be correlated with cSVD because they share some similar vascular risk factors.[200, 240] A recent meta-analysis of observational studies found that carotid atherosclerotic stenosis was correlated with the presence of WMHs. [192] Apart from atherosclerotic stenosis in the carotid artery, a positive association between the burden of WMHs and medial intracranial arterial calcification in patients with acute ischemic stroke was observed in a previous study. [235] Besides, researchers also revealed that a notable association was identified between intracranial atherosclerotic stenosis, intra-plaque enhancement, and greater burden of WMHs in patients with cerebral ischemic events. [217, 241] However, there is still a lack of evidence on the relationship between the severity of WMH and specific characteristics of intracranial atherosclerotic plaque in the healthy population. [217, 234, 242] Understanding the correlation between atherosclerotic patterns and the severity of WMHs would aid in early stratifying the future clinical risk of cerebrovascular events and support the development of individualized treatment strategies. Therefore, the aim of this study was to investigate the potential correlation between intracranial atherosclerotic imaging patterns and the severity of WMHs in middle-aged or older healthy adults by HR-MRI in a local community. I hypothesized that plaque-specific morphological features are correlated with WMH.

Chapter 4. Study-2

4.2 Methods and materials

4.2.1 Study subjects

In this Hong Kong community-based study, consecutive residents were recruited from November 2022 to December 2024. The inclusion and exclusion criteria were described in Chapter 3. The baseline information was collected by questionnaire, including age, gender, and other vascular risk factors (hypertension, diabetes mellitus, ischemic heart disease, current smoking and alcohol consumption) and any anti-vascular risk medication. The study followed the Declaration of Helsinki and was approved by the Institutional Review Board of the PolyU. All subjects provided informed written consent before the commencement of the study.

4.2.2 Assessment of plaque characteristics of intracranial arterial lesions

The participants and imaging and clinical data collected as described in Chapter 3 were used in this study. MRI images were independently analyzed by two observers (LH. L and YY. C) who have at least 3 years of experience in MRI image interpretation, and they were blinded to the clinical data of the participants. In the case of disagreement between the two observers, the images were reviewed by a third observer (JQ. L) who has more than ten years of neuroimaging experience, and consensus agreement was made among the three observers. The major intracranial artery segments were selected for the analysis, including bilateral M1 segment of middle cerebral arteries (MCAs), bilateral intracranial (V4) segment of vertebral arteries (VAs), and the basilar arteries (BAs). On 3D HR-VWI images, intracranial atherosclerotic lesions were evaluated on plaque vulnerability (lipid core, thinner fibrous cap, and a multitude of inflammatory cells)[243, 244], plaque remodeling[245], plaque burden, luminal stenosis[246], calcified deposit[247], intraplaque hemorrhage[248], and neovascularization.[54] For the atherosclerotic plaque measurements in MRI images, measurements were performed on the cross-sectional image slice with the maximum vessel wall thickness. The reference site for

measurements was chosen as the closest plaque-free cross section proximal to the plaque, or when no segment could be found proximally, the nearest plaque-free cross section distal to the plaque was selected. [208, 209] Both the outer wall and lumen were manually traced at both the lesion and reference site. The plaque area was calculated by subtracting the lumen area (LA lesion) from the outer wall area (OWA lesion) of the lesion. The degree of stenosis was assessed by using a previously described method: (1-LA lesion/LA reference) × 100%. [209] If tandem intracranial lesions were noted in both sites, the greater stenosis was chosen by measuring the percentage of stenosis. The remodeling index (RI) was calculated as OWA lesion/OWA reference. The remodeling patterns were classified as positive (RI >1.05), intermediate (0.95≤ RI ≤1.05), and negative (RI <0.95) remodeling.[249, 250] (**Figure 4-1**) The characteristics of plaque morphology on vessel-wall MRI were also evaluated. These characteristic findings were scored by specialized visual rating, including irregularity of plaque surface, eccentricity, and diffuse/focal plaque thickening pattern. Irregular morphology in transects is defined as the presence of disruptions or discontinuities in the plaque surface, while regular morphology is characterized by a smooth and uninterrupted inner wall. (**Figure 4-2** A represents an irregular surface & **Figure 4-2 B** represents a smooth surface). In accordance with a previous study, the distribution of the lesion was classified as eccentric if the maximal wall thickness exceeded twice the thinnest wall thickness at the site of maximal lumen narrowing, whilst it was categorized as concentric if the wall involvement was less than 50%.[43, 251] Intracranial lesions were categorized based on their involvement in the thickness scope along the trajectory of intracranial arteries. Lesions covering a longer trajectory (>0.5 cm) were considered to have a diffuse pattern (**Figure 4-3**), while lesions confined to a short region (<0.5 cm) or appearing as a dot were classified as having a focal pattern (**Figure 4-4**). Despite the fact that there is no standardized criteria for assessing the severity of intracranial arterial stenosis and the diameters of major intracranial arteries tend to be narrower and have more bnches than extracranial

arteries, in this study, the intracranial arterial stenosis was categorized into five groups: normal (i.e., no stenosis), < 25%, 25%-49%, ≥ 50% stenosis, and occlusion, based on the criteria of previous studies. [252-254]Vessels with stenotic degrees over 25% on HR-VWI were identified on the matched TOF-MRA. Participants were divided into two groups based on the degree of stenosis: those without ICAS or stenosis of less than 25% were Group 1, and those with intracranial artery stenosis of more than 25% were Group 2.

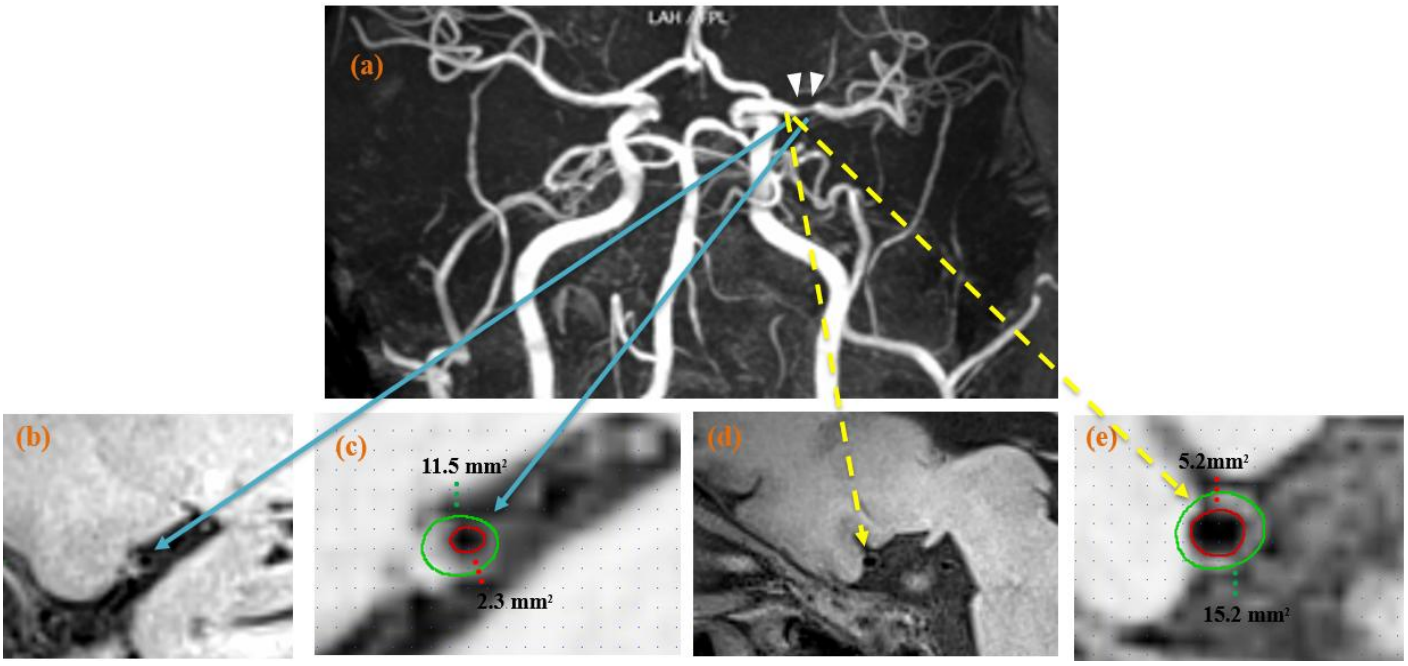


Figure 4-1 (a-e) Intracranial atherosclerotic plaque identified on the HR-MRI. Among these impinges, Fig. (a) shows the left MCA (M1) with significant luminal narrowing on MRA (white arrow). T1-weighted sagittal images, reconstructed from 3D high-resolution MRI acquisition, were utilized for lesion analysis (b, c) and reference site analysis (d, e). These images were orthogonal to the left M1 segment of the middle cerebral artery (MCA). The lesion locations were identified by arrows (blue solid line and arrows) on the MRA, while the reference site locations were indicated by arrowheads (yellow dotted lines and arrows). Contours were drawn to delineate the outer wall of the vessel (green) and lumen (red) of the nearest plaque-free or minimum lesion segment proximal to the lesion, which was selected as reference sites (d), and the cross section with the thickest plaque was selected as the maximum luminal narrowing (MLN) site (c). The reference vessel area was calculated as the luminal area at the proximal site due to vessel tapering. The remodeling index (RI) was computed as the vessel area at the MLN site divided by the reference vessel area 11.5/15.2 = 0.75, indicative of negative remodeling.

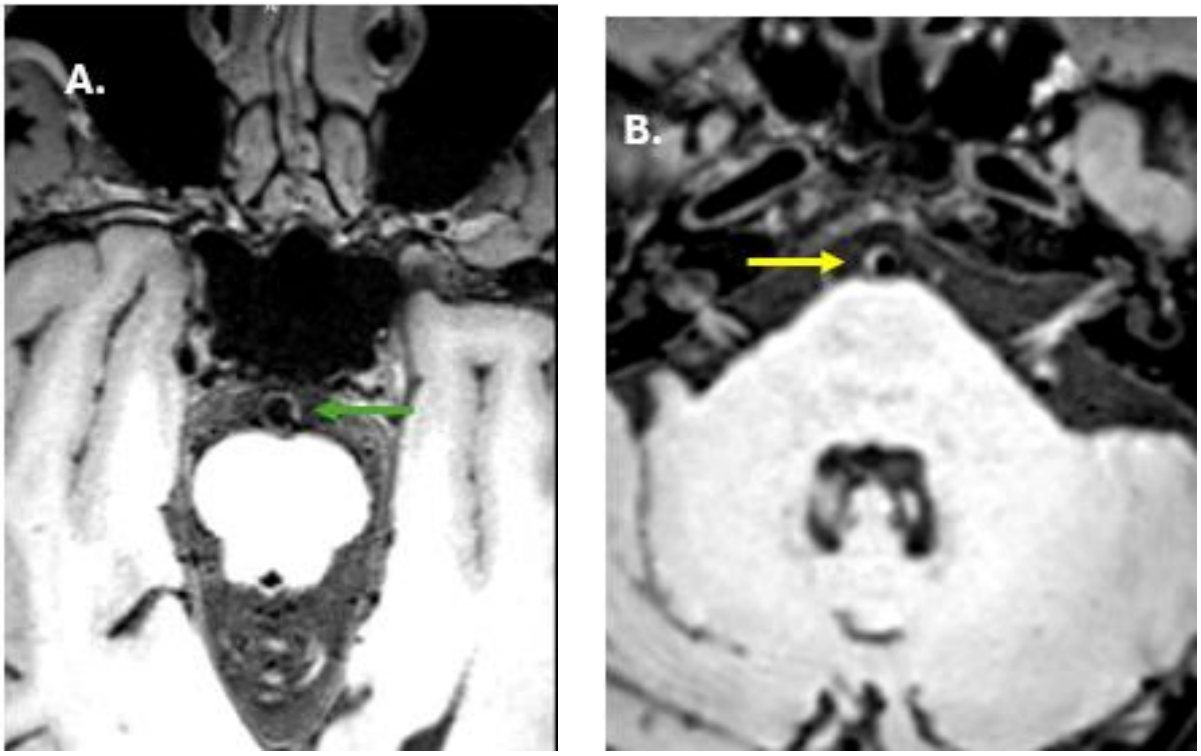


Figure 4-2 (A&B) Representative cases of intracranial atherosclerosis lesions. Figure 4-2. A 68-year-old man with hypertension for 5 years, this cross-section imaging shows an irregularity of plaque surface in BA (green arrow) on HR-VWI. Figure B. 74-year-old female without any cardiovascular disease. It shows a smooth surface of plaque in BA (yellow arrow) on HR-VWI.

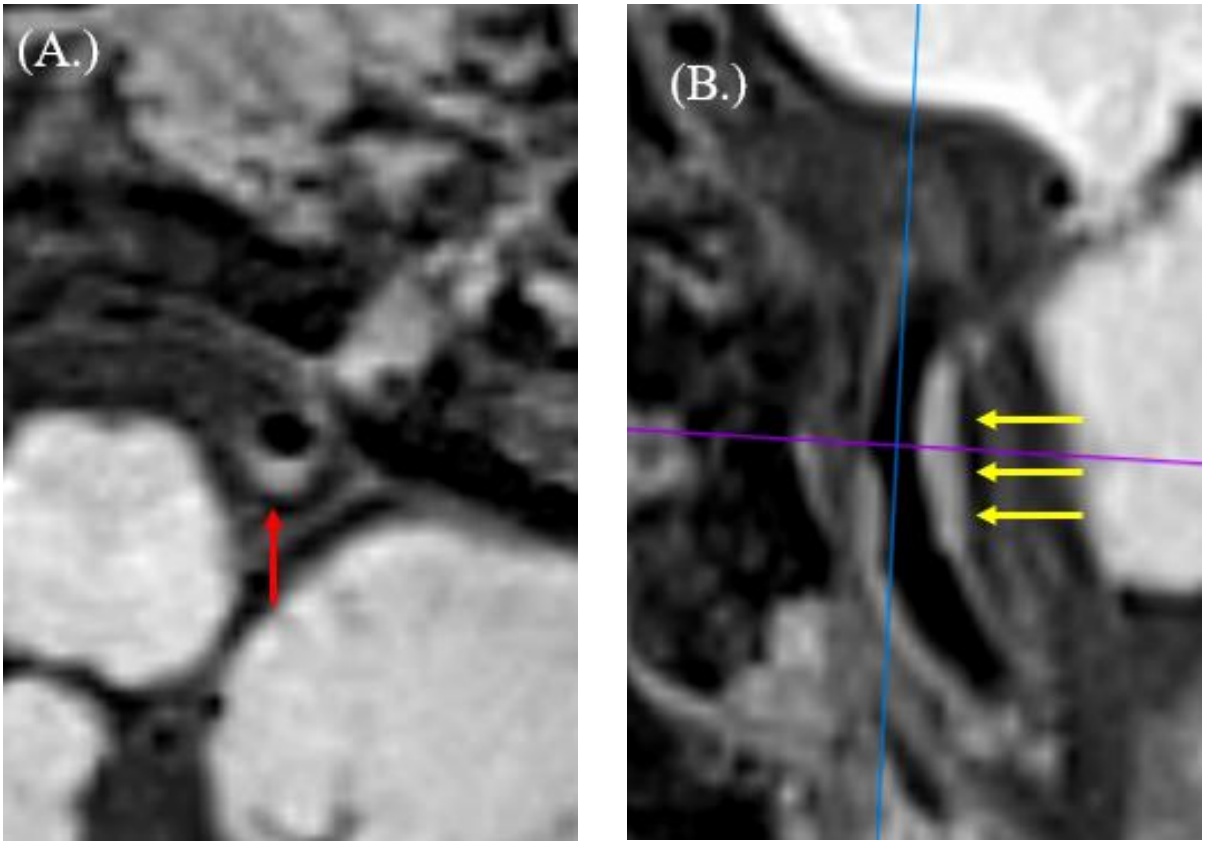


Figure 4-3 Diffuse and concentric pattern of plaque characteristics. A 73-year-old man without any cardiovascular disease. HR-VWI reveals mild stenosis of the left vertebral artery, as seen in the reconstructed cross-sectional view (A, red arrow) and axial view (B, yellow arrow). The images demonstrate a diffuse and concentric pattern of plaque in the vertebral artery.

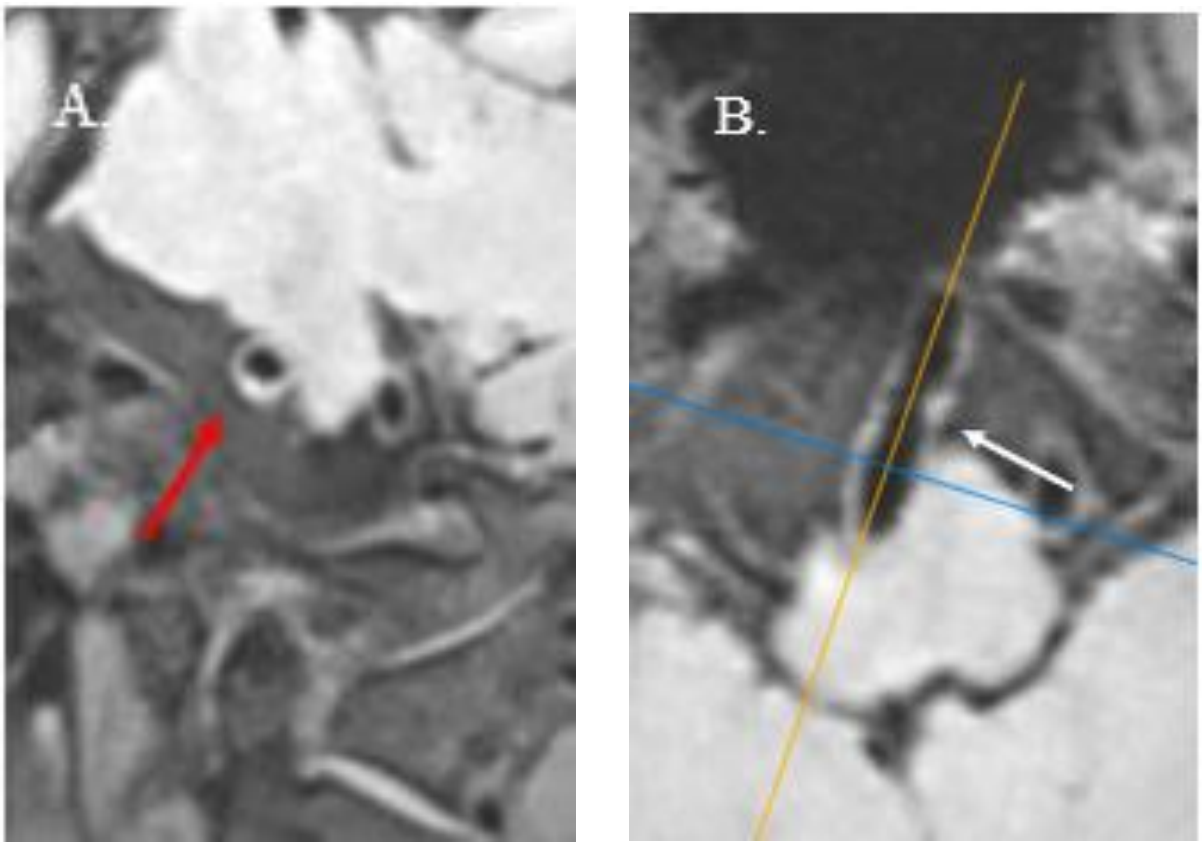


Figure 4-4 Focal pattern of plaque morphological characteristics. A 59-year-old female has had hypertension for three years. HR-VWI shows mild stenosis of the right vertebral artery, with a focal and concentric plaque pattern observed in both the reconstructed cross-sectional view (A, red arrow) and axial view (B, white arrow).

4.2.3 Evaluation and grading of white matter hyperintensities

White matter changes were determined by visual rating, and they were defined as areas showing high signal intensities (≥5mm ill-defined hyperintensities) on both T2-weighted and FLAIR MRI sequences. According to the Standards for Reporting Vascular Changes on Neuroimaging [255], the severity of white matter hyperintensities (WMH) was assessed using the Fazekas et al. rating scale, which ranged from absent to severe. Grade 0 indicated the absence of deep or periventricleWMH. Grade 1 (mild WMH) refers to thin or rim-like lesions in the periventriclewhite matter or small punctate foci in the deep white matter. Grade 2 (moderate WMH) was characterized by thicker and smoother periventriclehalos with mild subcortical

lesions (convergence of deep WMH foci in subcortical regions). Grade 3 (severe WMH) represented confluent periventricleleukoaraiosis involving a large portion of the centrum semiovale and subcortical deep white matter. (**Fig.4-5**).[210] After grading WMH, we categorized the participants into two groups: group 1, those with either absent or mild lesions, and those with moderate or serious leukoaraiosis were group 2.

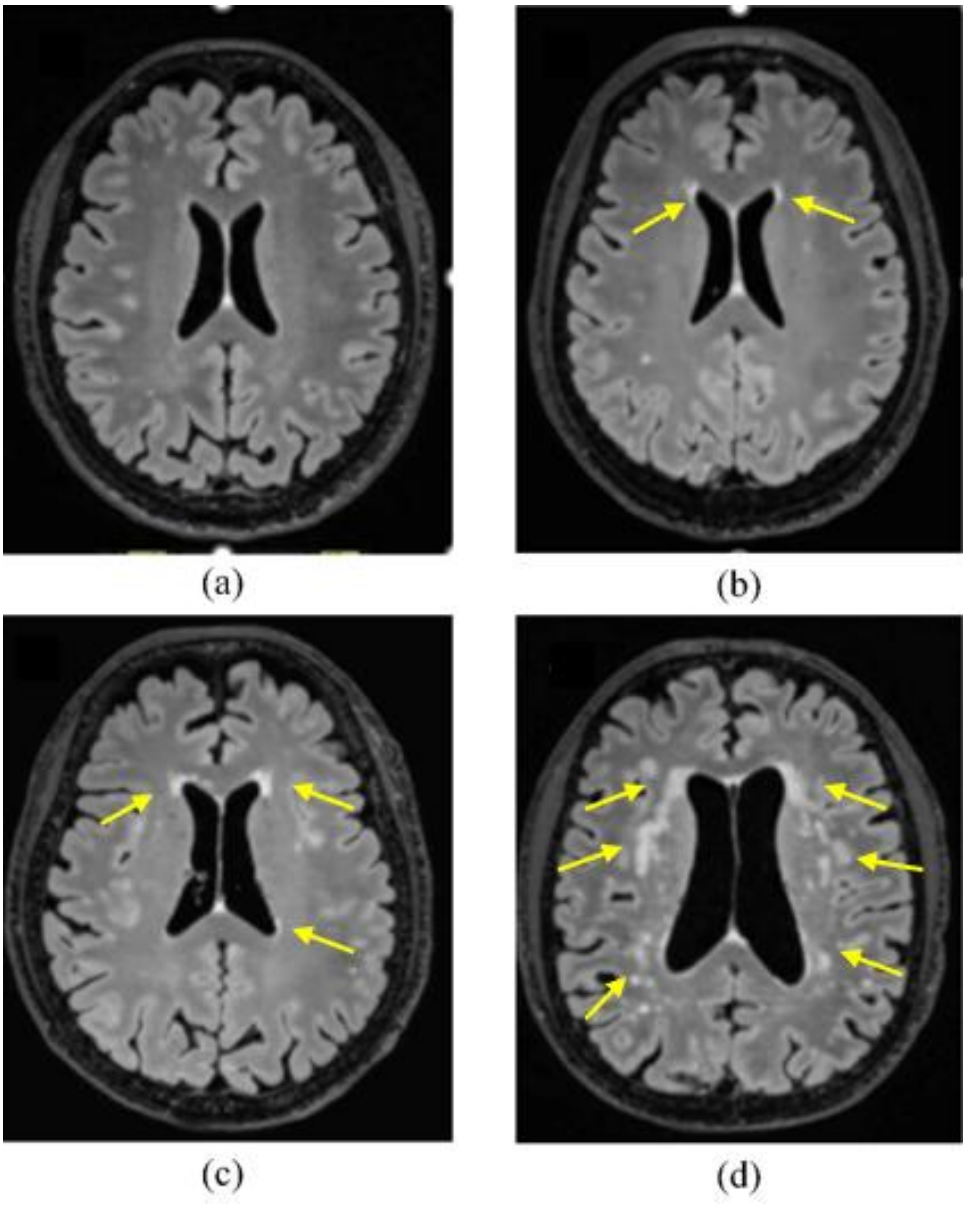


Figure 4-5 Representative cases of the different degrees of white matter lesions on FLAIR. (a) absent; (b) mild WMH; (c) moderate WMH; (d) severe WMH.

4.2.4 Statistical analysis

Statistical analysis was conducted using IBM SPSS version 27.0. Quantitative data were reported as means ± standard deviation (SD) for normally distributed variables or as median with interquartile range (IQR) for non-normally distributed variables. Categorical variables were presented as frequencies and percentages. An independent t-test and a Mann-Whitney U test were used to analyze continuous variables. Pearson's chi-square test and Fisher's exact test were employed to analyze categorical variables. The chi-square linear trend test was used to analyze the relationships of ordinal variables. Vascular risk factors with p-value <0.1 were considered confounding factors and subjected to collinearity diagnostics. The impact of confounding factors was examined by adjusting for them before and after analysis. Multiple binary logistic regression models were utilized to assess the associations between WMH burden and the presence of ICAS, degree of stenosis, and plaque morphological features, respectively. The inter-rater reliability was assessed by Cohen's kappa analysis. A two-sided *p*-value <0.05 was considered statistically significant.

4.3. Results

4.3.1 Baseline characteristics

From November 2022 to Dec. 2024, of the 284 subjects initially recruited for the study, 12 were excluded because of poor imaging quality (n=2), incomplete scan (n=3), and refusal to participate (n=7). Of the remaining 272 subjects (aged from 45 to 84) included in this study, 118(43.4%) were men, and 67(24.6%) had moderate to severe WMHs. In addition, there were 80 (29.4%), 33 (12.1%), and 104 (38.2%) subjects having hypertension, diabetes, and hyperlipidemia, respectively. Among the 272 subjects, 14 (5.2%) subjects were current smokers, and 20 (7.4%) subjects had alcohol consumption. There were 84(30.9%), 13 (4.8%), and 31

(11.4%) subjects taking statins, antiplatelet, and anticoagulant drugs, respectively. There were significant differences in the subjects' age (p=0.035), systolic blood pressure (p=0.001), diastolic blood pressure (p=0.042), and body mass index (p=0.006) between subjects with intracranial large artery stenosis <25% and those with the stenosis ≥25%. Specifically, the group of individuals with a greater degree of luminal stenosis were older, tended to have higher blood pressure, and more likely to have vascular risk factors, including hypertension, hyperlipidemia, and a higher body mass index (BMI) (all p <0.05). **Table 4-1** illustrates the demographic features and vascular risk factors of the subjects included in the study.

In total, WMH was found in 216 (79.4%) subjects, among whom 150 (55.1%) subjects had mild WMH, 62 (22.8%) were categorized as moderate WMH, and 5 (1.8%) were identified to have severe WMH. Depending on site and pathogenesis, periventricleWMH was observed in 182 (66.9%) cases, while 208 (76.5%) cases showed deep WMH. Furthermore, a positive correlation was found between the degree of intracranial atherosclerotic stenosis and the severity of WMH (p=0.035). Subjects with higher degrees of stenosis exhibited a greater severity of WMH in both the deep and periventriclewhite matter regions, and were more likely to present with higher total WMH scores, compared to those with mild or absence of WMH (p= 0.003). **Table 4-1** compares the baseline and WMH characteristics in subjects with different degrees of intracranial artery luminal stenosis.

Table 4-1 Demographic and clinical characteristics based on HR-MRI measured intracranial artery luminal stenosis grading.

Characteristics	Total (n=272)	Luminal stenosis < 25% (n = 161)	Luminal stenosis ≥ 25% (n = 111)	*p*-value
Demographics				
Age, y, mean ± SD	63.4±6.8	62.6 ± 6.5	64.4 ±7.1	**0.035**
Sex, male, n (%)	118 (43.4)	65 (40.4)	53 (47.7)	0.228

SBP, mmHg, mean ± SD	129.9 ± 17.1	127.19 ± 17.0	133.9± 16.5	**0.001**
DBP, mmHg, mean ± SD	79.9 ± 10.5	78.8 ± 10.8	81.4 ± 9.8	**0.042**
Body mass index ≥25 kg/m^2, n (%)	84 (32.0)	33 (25)	40 (42.1)	**0.006**
Medical comorbidities, n (%)				
Hypertension	80(29.5)	36(22.4)	44(39.6)	**0.002**
Diabetes mellitus	33(12.2)	19(11.8)	14(12.6)	0.840
Coronary artery disease	17(6.3)	10(6.2)	7(6.3)	0.975
Hyperlipidemia	104(38.4)	49(30.4)	55(49.5)	**0.001**
Medications, n (%)				
Statins	84(30.9)	38(28.8)	41(43.2)	**0.025**
Antiplatelet	13(4.8)	5(3.8)	8(8.4)	0.138
Anticoagulant	31(11.4)	17(12.9)	8(8.4)	0.290
Habits, n (%)				
Current Smoker	14(5.2)	10(6.2)	4(3.6)	0.339
Alcohol Drinking	20(7.4)	13(8.1)	7(6.3)	0.583
The Severity of WMH				**0.035**
Nil	55 (20.2)	40(24.8)	15(13.5)	
Mild	150 (55.1)	87(54.0)	63 (56.8)	
Moderate	62 (22.8)	33(20.5)	29(26.1)	
Severe	5 (1.8)	1(0.6)	4(3.6)	
WMH classification				0.105
Nil to mild WMH	205(75.4)	127 (78.9)	78(70.3)	
Moderate to severe	67(24.6)	34(21.1)	33(29.7)	
The Distribution of WMH, n (%)				
Deep WMH	208(76.5)	114(70.8)	94(84.7)	**0.008**
PeriventricleWMH	182 (66.9)	97(60.2)	85(76.6)	**0.005**
Total WMH score, median (min, max)	2 (0, 6)	2 (0, 3)	2 (1, 6)	**0.003**

Abbreviation: SBP indicates systolic blood pressure; DBP, diastolic blood pressure; WMH, white matter hyperintensity; SD, standard deviation.

4.3.2 Compared baseline clinical characteristics of subjects in different WMH degrees

Table 4-2 shows the comparison of demographic characteristics in subjects with different degrees of white matter hyperintensities. Compared to the subjects with nil to mild WMHs, those with moderate-to-severe WMHs were older (66.7 ± 7.5 years old vs. 62.3 ± 6.2 years old, p <0.001) and had significantly greater systolic blood pressure (134.0 ± 14.4 vs. 128.6 ± 17.7, p =0.024). The prevalence of vascular risk factors, including hypertension (47.8% vs. 23.4%, p <0.001), diabetes (19.4% vs. 9.8, p=0.036), ischemic heart disease (11.9% vs. 4.4%, p=0.039), and hyperlipidemia (52.2% vs. 33.7%, p=0.007) was significantly higher in subjects with severe WMH burden. Additionally, the use of anticoagulant drugs was more frequent in individuals with moderate-to-severe WMH (p=0.048). No significant differences were found in other clinical characteristics between the two groups. (all p >0.05)

Table 4-2 The comparisons of clinical characteristics between participants with and without moderate to severe WMH.

Characteristics	Total (n=272)	Adults without mod to severe WMH (n = 205)	Adults with mod to severe WMH (n =67)	*p*-value
Demographics				
Age, y, mean ± SD	63.4±6.8	62.3± 6.2	66.7 ± 7.5	**<0.001**
Sex, male, n (%)	118 (43.4)	84(41.0)	34(50.7)	0.161
SBP, mmHg, mean ± SD	129.9 ± 17.1	128.6 ± 17.7	134.0 ± 14.4	**0.024**
DBP, mmHg, mean ± SD	79.9 ± 10.5	79.5 ± 10.7	81.1 ± 9.8	0.275
Body mass index ≥25 kg/m^2, n (%)	87 (32.0)	63(30.7)	24(35.8)	0.438
Medical comorbidities, n (%)				
Hypertension	80(29.5)	48(23.4)	32(47.8)	**< 0.001**
Diabetes mellitus	33(12.2)	20(9.8)	13(19.4)	**0.036**
Coronary artery disease	17(6.3)	9(4.4)	8(11.9)	**0.039**
Hyperlipidemia	104(38.2)	69(33.7)	35(52.2)	**0.007**

Medications, n (%)				
Statins	84(30.9)	58(28.3)	26(39.4)	0.090
Antiplatelet	13(4.8)	8(3.9)	5(7.6)	0.316
Anticoagulant	31(11.4)	19(9.3)	12(18.2)	**0.048**
Habits, n (%)				
Current Smoker	14(5.2)	10(4.9)	4(6.0)	0.752
Alcohol Drinking	20(7.4)	15(7.3)	5(7.5)	0.968

4.3.3 Comparisons of The Distribution and Characteristics of Atherosclerotic Plaque between the Subjects with or Without Moderate to Severe WMHS

The results of the comparison of atherosclerotic plaque imaging features between these two WMH groups are presented in **Table 4-3**. Among 272 subjects, 152 (55.9%) subjects exhibited intracranial atherosclerotic stenosis. Of whom, the majority of the cases should be <25% stenosis with 154 subjects (56.6%), 95 (34.9%) displayed stenosis within the range of 25% to 49%, and only 23 (8.5%) subjects were identified with stenosis >50%. On HR-MRI, a total of 209 (15.4%, 209/1360) lesions were identified, including 105 lesions in MCAs, 68 lesions in VAs, and 36 lesions in BAs. Participants with moderate-to-severe WMH were more prone to be involved with ICAS (67.2% vs. 52.2%, p=0.032). Additionally, A positive correlation was found between WMH severity and both plaque burden and luminal stenosis, as indicated in **Figure 4-6** & **Figure 4-7**. Individuals with a greater WMH burden are presented with higher plaque burden (p=0.004) and more severe intracranial luminal stenosis (p=0.012).

Of these lesions, 110 (40.4%) were diffuse, 119 (43.8%) were eccentric, 65 (23.9%) had an irregular surface, and 94 (34.6%) had a positive remodeling index. Moreover, the differences were observed in terms of the severity of white matter hyperintensity and specific plaque characteristics, such as diffuse or eccentric thickening patterns. As presented in **Table 4-3**, subjects with a higher burden of WMH were more likely to exhibit diffuse thickening (46.3%

vs. 38.5%, *p*=0.032) and an eccentric plaque pattern (55.2% vs. 40.0%, *p*=0.029) compared to those without moderate-to-severe WMH.

Table 4-3 The comparison of atherosclerotic plaque characteristics between participants with and without moderate-to-severe WMHs.

	Total (n=272)	**Adults without mod to severe WMH (n = 205)**	**Adults with mod to severe WMH (n =67)**	***p*-value**
The presence of ICAS, n (%)	152 (55.9)	107 (52.2)	45 (67.2)	**0.032**
ICAS in MCA n (%)	105 (38.6)	70 (34.1)	35 (52.2)	**0.008**
ICAS in VA, n (%)	68 (25.0)	46 (22.4)	22 32.8)	0.088
ICAS in BA, n (%)	36 (13.2)	21 (10.2)	15 (22.4)	**0.011**
The degree of stenosis, n (%)				0.072
< 25%	154 (56.6)	121 (59.0)	33(49.3)	
25-49%	95 (34.9)	71 (34.6)	24 (35.8)	
≥ 50%	23 (8.5)	13 (6.3)	10 (14.9)	
Irregular surface (n, %)	65 (23.9)	46 (22.4)	19 (28.4)	0.110
Diffuse lesion (n, %)	110(40.4)	79 (38.5)	31 (46.3)	**0.032**
Eccentric lesion (n, %)	119(43.8)	82(40.0)	37 (55.2)	**0.029**
Positive remodeling index (n, %)	94(34.6)	64(31.2)	30(44.8)	**0.087**

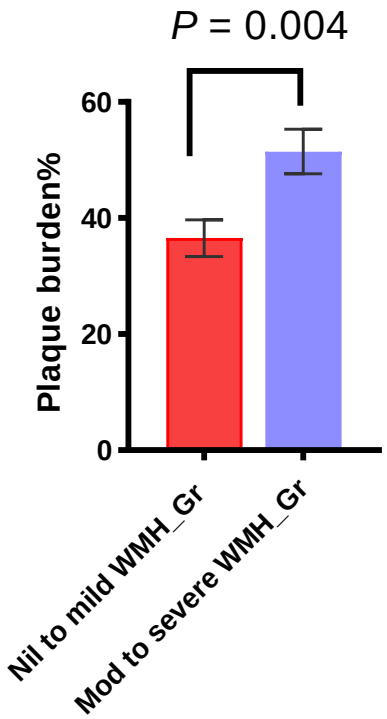


Figure 4-6 Comparison of WMH severity in subjects with different grades of plaque burden.

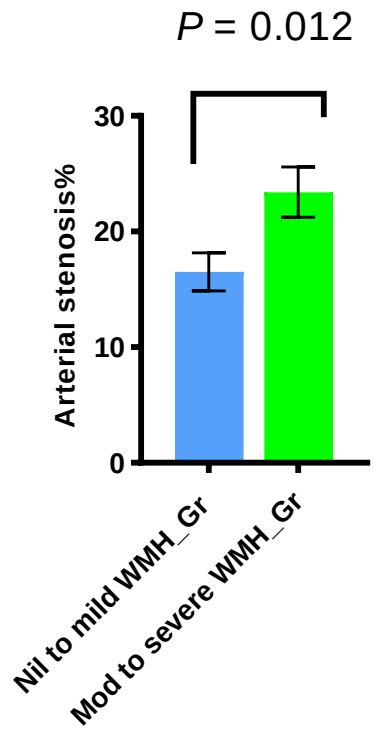


Figure 4-7 Comparison of WMH severity in subjects with different luminal stenosis.

4.3.4 Associations between characteristics of ICAS and severity of WMH

Univariate logistic regression analysis showed that the luminal stenosis, diffuse plaque, and eccentric thickening pattern were correlated with moderate-to-severe WMH (all p <0.05). (**Table 4-4**.). After further adjusting for confounders, eccentricity (OR, 1.47; 95% CI,1.04 -2.10; p= 0.036) was independently associated with moderate-to-severe WMH. Luminal stenosis and diffuse plaque thickening were not significantly associated with moderate-to-severe WMH. (all p > 0.05)

Table 4-4 The association between the severity of WMH and the imaging features of ICAS.

	The severity of WMH Odds ratio (95%CI)	*p*-value
Characteristics		
Stenosis degree (%)	1.52 (1.01 – 2.30)	**0.046**
Plaque burden (%)	1.01 (1.00– 1.02)	**0.055**
Irregular surface	0.74 (0.54 – 1.01)	**0.060**
Diffuse thickening pattern	1.41 (1.01– 1.96)	**0.041**
Eccentric lesion	1.59 (1.13 – 2.22)	**0.007**
Model-1 Adjusted for confounding factors (age, sex)		
Stenosis degree (%)	1.36 (0.88 – 2.11)	0.163
Plaque burden (%)	1.01 (0.99 – 1.01)	0.195
Irregular surface	0.81 (0.58 – 1.13)	0.213
Diffuse thickening pattern	0.72 (0.40 – 1.29)	0.269
Eccentric lesion	1.51 (1.06 – 2.12)	**0.020**
Model-2 Adjusted for confounding factors (age, sex, hypertension, hyperlipidemia)		
Stenosis degree (%)	1.28 (0.82 – 2.02)	0.281
Plaque burden (%)	1.01 (0.99 – 1.01)	0.259

Irregular surface	0.87 (0.62 – 1.22)	0.418
Diffuse thickening pattern	1.19 (0.83 – 1.71)	0.334
Eccentric lesion	1.47 (1.04 – 2.10)	**0.036**

OR, Odds ration; 95% CI, 95% confidence interval.

4.3.5 Reliability assessment

The inter-reader agreement was assessed by randomly selecting 227 subjects. The interobserver agreements of reviewing the MRI imaging characteristics of ICAS were good. The Cohen's kappa of ICAS presence was 0.86 (95% CI, 0.793 - 0.926, p <0.001). Kappa of plaque eccentricity was 0.77 (95% CI, 0.692 - 0.847, p <0.001), plaque irregularity was 0.82 (95% CI, 0.727 – 0.912, p <0.001), and diffuse thickening was 0.71(95% CI, 0.631 – 0.797, p <0.001). Cohen's kappa of WMH presence was 0.81 (95% CI, 0.686-0.933, p <0.001). Kappa of classifying WMH severity was 0.78 (95% CI, 0.699 – 0.857, p <0.001). **Table 4-5**

Table 4-5 The inter-observer reliability of analyzing the presence of intracranial atherosclerosis (ICAS) with other plaque imaging features and WMH severity.

	Dr. Lai	**Yangyang**	**Inter-observer agreement Coefficient (95% CI)**
Presence of ICAS (MCA, BA, VA); (n, %)	127(55.9)	123(54.2)	0.86 (0.793 - 0.926)
Plaque eccentricity; (n, %)	102(45%)	86(37.9%)	0.77 (0.692 - 0.847)
Plaque irregular surface; (n, %)	51(22.5)	45(20.0%)	0.82 (0.727 – 0.912)
Plaque diffuse thickening (n, %)	94(41.4%)	78(34.4%)	0.71(0.631 – 0.797)
Presence of WMHs	207(91.2%)	199(87.6%)	0.81 (0.686-0.933)
WMHs grade			0.78 (0.699 – 0.857)
Mild	144 (63.4%)	132(58.1%)	
Mod	59(26%)	60(26.4%)	
Severe	4(2%)	7(3%)	

4.4. Discussion

The present study explored the potential relationship between atherosclerotic characteristics of intracranial major arteries and the severity of WMHs in asymptomatic individuals. In the study, we found that subjects with moderate-to-severe WMHs were more likely to be involved with ICAS, and have morphological MRI imaging features representing the presence of intracranial arterial plaque, when compared to those without moderate-to-severe WMHs. The study also identified the prevalence of intracranial arteries (including MCAs, BAs, and VAs) involved by ICAS, and provided strong evidence that the severity of stenotic vessel (>25% luminal stenosis), plaque burden, and plaque-specific imaging features were correlated with the burden of WMH in the general elderly. Multivariate logistic regression analysis showed that an eccentric lesion was independently associated with moderate-to-severe WMH. These findings supplement the commonly recognized plaque vulnerability based on histopathologic markers, including intracranial plaque hemorrhage, large lipid core, and thin fibrous cap, suggesting a comprehensive imaging protocol should be provided to assess the intracranial plaque vulnerability.

In the study, subjects with greater intracranial artery luminal stenosis had significantly higher Fazekas scores than those without greater intracranial artery luminal stenosis, which was in line with previous studies. [217, 256] In another study focusing on carotid plaque, individuals with carotid atherosclerotic stenosis had a significantly higher Fazekas score for WMHs in comparison to those without carotid atherosclerotic stenosis. [257] The findings of a study conducted by JH Park et al. demonstrated that the WMH score significantly increased with the multiplicity of intracranial atherosclerotic stenosis. [236] Therefore, these results suggest that a greater degree of intracranial and extracranial artery luminal stenosis is associated with more severe white matter changes. In the present study, results showed that 152 (55.9%) subjects

exhibited multiple sites of intracranial stenotic-artery lesions, which appeared to be associated with a higher likelihood of hypoperfusion. This hypothetical concept was derived from the findings of cerebral hemodynamics and MCA obstruction reported by Ogasawara *et al*. [258] Consistent with previous research, the degree of atherosclerotic stenosis, a significant predictor of ischemic stroke, may independently contribute to the pathogenesis of cerebrovascular small vessel disease (cSVD), and this relationship can be attributed to hypoperfusion and inflammatory processes.[234, 259] Another presumed mechanism underlines the association between ICAS stenosis and the development of WMH might exist as microembolization of intra-arterial stenotic lesions. In addition, vascular resistance could be a contributor to the burden of WMHs. Previous studies demonstrated that arterial stiffness induced by atherosclerosis can disrupt perfusion in small blood vessels, leading to ischemic injury and the subsequent aggressive promotion of WMH formation. [260] However, the present study could not find an independent association between intracranial arterial stenosis and moderate-to-severe WMHs. I speculate a possible reason for the lack of relationship between both brain vessel diseases in asymptomatic individuals is the presence of compensatory mechanisms such as vascular remodeling and collateral circulation. These mechanisms may mitigate the impact of stenosis on the development of WMH.

The frequency of asymptomatic ICAS in this community population is higher than that reported in other previous studies. [80, 261, 262] This discrepancy may be caused by the various age groups, definitions, and imaging modalities used to detect ICAS. [42, 262, 263] Wong *et al*. reported a 6.9% prevalence of ICAS among individuals aged ≥ 40 years who lived in a rural region of China. [264] In a large autopsy study, it was reported that over 90% of specimens for subjects aged from 70 to 90 years had revealed different degrees of ICAS. [265] To our knowledge, age is an independent risk factor for cerebral large and small vessel diseases. The higher prevalence of ICAS in the present study is probably due to the subjects in the present study were older

(63.38 ± 6.79). Moreover, different medical imaging methodologies could potentially account for the discrepancy of study findings, including arterial assessment by transcranial Doppler (TCD) versus arterial vessel wall imaging. In China, as noted by earlier investigations using TCD and MRA, the asymptomatic rate of ICAS ranged from 7.6% to 13.2%, which is considerably lower than that found in the present study. [40, 266, 267] This is because the present study used HR-MRI to evaluate five major intracranial arteries through vessel wall imaging techniques, which allow better detection of pathological changes in smaller intracranial vessel segments. Reasonably, due to the use of advanced imaging techniques, the prevalence of ICAS in asymptomatic individuals detected in the present study could be more accurate when compared to previous studies. In the past, studies usually focused on stroke or post-stroke patients, but few studies have reported various degrees of asymptomatic intracranial atherosclerotic disease (ICAD) in the community-cohort. Currently, with the aid of HR-MRI examination, our groundbreaking research is the first to reveal the specific prevalence of ICAS in stroke-free adults, which benefits controlling risk factors in people with asymptomatic ICAS to prevent stroke onset, potentially outweighing post-stroke intervention and rehabilitation.

The results of our study revealed that intracranial plaque morphologic features might be effective indicators for the severity of WMHs. The multivariate logistic regression analysis showed that the eccentricity of plaque was a predictive factor for a greater burden of WMH. More severe WMH was frequently found in individuals with atherosclerotic eccentric lesions, and there was a significant correlation. This observation can be explained by the hypothesis that the eccentricity of the plaque may act as a predisposing factor aggravating WMH by increasing tensile pressure on the wall of the intracranial arteries. In line with the findings of the present study, a clinical study by Ohara T *et al*. found that the eccentric plaque is deemed as a potential biomarker for ipsilateral cerebrovascular events.[268] Another study also reported that individuals with asymptomatic ICAS lesions were more likely to present in eccentricity of

plaque, which was consistent with the current study's results. [43, 269] Based on previous histopathologic evidence, a higher incidence of brain ischemia was frequently involved by the eccentricity of plaque.[43, 268] Considering the plaque is usually wildly involved in intracranial vascular beds, and the eccentricity of plaque may remodel the vascular dimensions, these vascular changes could directly impact the distribution of cerebral blood flow and the hemodynamics of the artery.[268, 270] This alteration in vascular geometry may lead to increased vascular resistance and compromise the blood flow in multiple medullary arteries, ultimately exacerbating hypoperfusion in the white matter region.[43, 270, 271] However, some investigators presented contrasting findings regarding the association between eccentric plaque and cerebrovascular disease. [43, 270, 271] Such inconsistency might be caused by different study populations and designs. In the past, intracranial atherosclerosis has received less attention compared to extracranial atherosclerosis, such as carotid or aortic stiffness, particularly in stratifying stroke-free elderly populations. This oversight may be attributed to variations in evaluation techniques and the challenges associated with observing cerebral arteries and their latent status using conventional diagnostic imaging modalities.[91] Besides the traditional vascular risk factors such as age, hypertension, diabetes, hypercholesterolemia, and smoking[67, 88-90], the Rotterdam Study has reported that intima-media thickness (IMT) of the common carotid artery (CCA), carotid plaque burden, and stenosis measured by ultrasonography are associated with WMH.[272] Recently, Heng et al. demonstrated that different patterns of intracranial arterial calcification identified by CT are also associated with the burden of WMH classified by the eight-score criterion in stroke patients.[235] Moreover, a study involving a Korean population indicated that the presence of ICAS was independently associated with WMH severity.[234] Another study with asymptomatic adults also demonstrated that ICAS was associated with larger WMH volume.[273]

In the study, there was no significant association between intracranial arterial stenosis and

moderate-to-severe WMHs. Despite the fact that atherosclerosis-induced arterial stenosis may influence the perfusion in small blood vessels and result in ischemic reactivity to the regions of white matter tracts[260], the insignificant association might be attributed to compensatory mechanisms such as collateral circulation.[274, 275] These mechanisms could potentially mitigate the impact on the development of WMHs. Furthermore, there was no significant association between plaque with irregular, diffuse thickening patterns and moderate-to-severe WMHs. The insignificant finding may be due to the small sample size and a homogeneous ethnic cohort of the present study. This regional homogeneity could potentially result in distinct findings when examining the correlation between WMH and ICAS. To mitigate such bias and comprehensively investigate the associations between ICAS and WMHs, future research with a larger sample size and has a diverse population from multiple ethnic regions is suggested. Results of the present study contribute additional value to the understanding of WMHs from multiple perspectives. The study results identified eccentricity as an imaging marker for ICAS, and this imaging marker is closely associated with the development of leukoaraiosis. As such, these study findings provide a foundation for future investigation aiming to explore the clinical benefits of evaluating intracranial vessel-wall with MRI, monitoring patients with ICAS, and assessing patients' treatment response and prognosis. Moreover, cerebral white matter lesions are commonly observed in the elderly population without any apparent neurological signs and symptoms. Even though the mechanism leading to this association remains unclear, these risk factors potentially contribute to the development of cSVD, causing irregular cerebral blood flow, endothelial dysfunction, and inflammation, which disrupt the blood-brain barrier and lead to demyelination and gliosis, and fibrinoid necrosis in the region of the white matter. A growing body of evidence reported that WMHs are closely associated with intima-media thickness as well as the number of carotid plaques. [234, 235, 272] Therefore, early detection of the eccentric ICAS pattern could help to inform primary prevention strategies, serve as a potential risk factor

for timely intervention in atherosclerosis-induced ischemia and hypoperfusion cascades leading to the development of WMH, along with targeted lifestyle modifications and personalized management plans. These findings highlight the substantial impact of ICAS patterns on the progression of leukoaraiosis, and this is the first time in the existing clinical literature to address a notable gap regarding the role of ICAS to WMH in a community-based cohort.

This community-based dwelling study investigated the possible correlation between intracranial large artery disease and cerebral small vessel disease. There are limitations in this study. First, due to the limited time for data collection, the sample size of the study was small. The small sample size also impacted on the limited number of individuals with >50% stenotic vessel, and those with severe degree of WMH, which potentially affect the effectiveness of data analyses such as multiple regression analysis. To address this limitation, I adopted a merged group and cutoff of 25% stenosis rate comparison approach to mitigate the impact of grouping bias in the analysis. Additionally, it is important to note that the subjects in this cohort were predominantly recruited from Asia, which may introduce regional variations in the prevalence of ICAS and WMH burden. This regional homogeneity could potentially result in distinct findings when examining the correlation between WMH and ICAS. While the study did not specifically examine a cohort comprised of stroke patients, the primary focus of the study was to explore the potential association between ICAS and WMH in a general population. These findings have significant clinical relevance and provide valuable insights into the relationship between these two conditions. Lastly, we did not investigate the associations between ICAS and other neuroimaging subtypes of cSVD, such as lacunar infarcts, microbleeds, enlarged perivascular spaces, and cerebral atrophy, as well as not address attention to the cognitive decline. In addition to identifying the impact of ICAS and other neuroimaging markers of cerebral small vessel disease, future studies to explore the association between brain and heart diseases to uncover novel biomarkers of brain-cardiac function for early identification and risk

stratification are suggested.

4.5. Conclusions

Intracranial large-arterial atherosclerotic plaque characteristics are correlated with the severity of WMHs in MRI. Intracranial atherosclerotic lesions with eccentric patterns in MRI may be significantly associated with higher burden of WMHs, which extends beyond mere co-existence due to shared risk factors, suggesting the presence of a dose-effect relationship between plaque eccentricity and moderate-to-severe WMHs. To the best of our knowledge, this is the first study to comprehensively evaluate plaque imaging features by HR-MRI and explore the association between eccentricity of plaque and progressively greater WMH burden in healthy subjects, highlighting the clinical significance of understanding these relationships for improved clinical decision-making.

Chapter 5. Study-3: Correlation between Cardiovascular Dysfunction from ECG dispersion Mapping and Intracranial Atherosclerosis Identified by HR-MRI in Community Cohort Study

Chapter 5. Study-3

5.1 Background

The presence of ICAS has been recognized as an important predictor to guide clinical risk stratification of stroke patients.[35, 276] Based on the result of imaging examinations and other clinical data such as age, hypertension, and diabetes, *etc.* of previous studies, Asians have a much higher incidence of ICAS in stroke-free individuals, ranging from 3.5% to 45%[277-279] than Caucasians (a prevalence of 8%). [280] Recently, a growing body of research has focused on the question of under-appreciated risk factors as markers for early detection of ICAS. Autonomic nervous system (ANS) dysfunction, recently recommended as a novel risk factor, has been associated with an increased risk of cerebrovascular diseases. [281] The main proposed mechanisms involve the modulatory effects of ANS on cerebral circulatory autoregulation and blood pressure regulation.[282-284]

Heart rate variability (HRV) is an ingenious metric of ANS function, and is routinely detected by an electrocardiogram (ECG) to monitor the balance of the sympathetic-vagal nervous system. [285] Recently, some studies have demonstrated that reduced HRV can be used as a biomarker for stratifying multiple cardiovascular risk factors and is related to cerebrovascular disease.[285-288] As stated by Mäkikallio AM *et al*., decreased HRV is strongly associated with cardiovascular mortality in the elderly post-stroke survivors.[289] Another study has proven that reduced night-time HRV is associated with increased risk of incident ischemic stroke. [290] Even though previous studies have reported that lower HRV is correlated to a higher risk of cerebrovascular disease, no studies have investigated the correlation between daytime HRV and intracranial atherosclerosis as well as plaque imaging features in the healthy/sub-healthy population.

Therefore, in this study, I hypothesized that short-term daytime HRV and other metrics identified by ECG could serve as early risk predictors of intracranial atherosclerotic lesions.

Chapter 5. Study-3

The aim of the current study was to explore the potential relationships between cardiovascular dysfunction measured by 3-minute ECG monitoring and the presence of ICAS identified by HR-MRI. These evaluations could help the understanding on how these surrogates of cardiac dysfunction reflect the presence of ICAS and associate with the structural features of subclinical or asymptomatic plaques.

5.2 Materials and methods

5.2.1 Subjects and Baseline Characteristics

This observational study, approved by the Institutional Review Board of the Hong Kong Polytechnic University, was conducted in November 2022. A total of 284 consecutive adults aged 45 and older were recruited from the Hong Kong community, all of whom are part of the same group of subjects detailed in Chapter 3. All the subjects provided informed consent prior to participation and the eligibility criteria are also outlined in that Chapter.

5.2.2 Cardiac Function Assessment

Electrocardiographic recordings were acquired using 3-minute ECG dispersion mapping (ECG-DM) monitoring (HeartVue system, KARDi2/4-B, Medical Computer Systems Ltd, Russia). **Fig. 5-1** ECG-DM is used to assess the myocardial micro-alternation index (MMI), which serves as an ischemic indicator to reflect myocardial abnormalities at a metabolic level. [291] ECG-DM, therefore, is not a diagnostic test but a nonspecific indicator of myocardial health. The parameters such as heart rate (bmp), time (SDNN, RMSSD, pNN50 %, SDSD, ms) and frequency domain (power HF, power LF, LF/HF) heart rate variability, myocardial micro-alteration index(MMI, %), stress index(%), atrium and ventriclehypoxia status, and regulatory system functional status assessment(RISA), *etc.*, were automatically recorded by the 3-minute ECG-DM and analyzed by HealthExpress package system. **Fig. 5-2** This procedure is non-

invasive, and a series of cardiac data is automatically recorded when subjects are seated calmly with standard ECG limb leads in place.[292] These parameters can be derived from 3-minute continuous ECG recordings including HRV, MMI, atriums deviation, ventricles deviation, heart rate. In the current study, HRV measurement is defined as intervals SDNN, which characterizes overall HRV and is categorized into tertile for HRV analysis. Moreover, three parameters of frequency domain were also analyzed, including high frequency power (HF, Hz), low frequency power (LF, Hz), and low:high frequency power ratio (LF/HF). The overall myocardial micro-alteration index (MMI), expressed as a percentage, is represented by the micro-alterations from all nine groups (G1-G9) in the dispersion mapping, and the mean MMI value was selected and recorded. [293] **Figure 5-1 (a&b)**

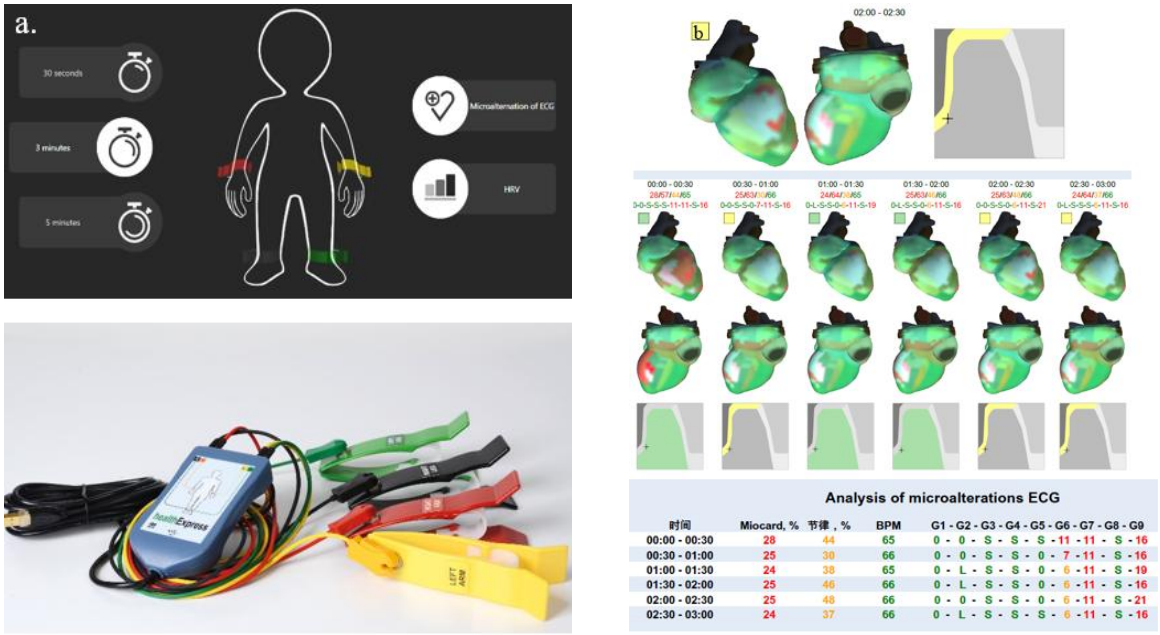
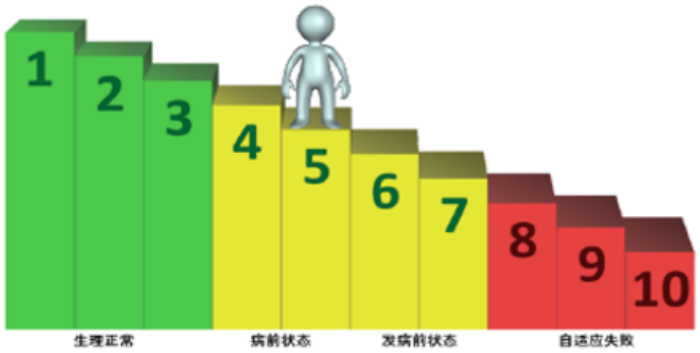
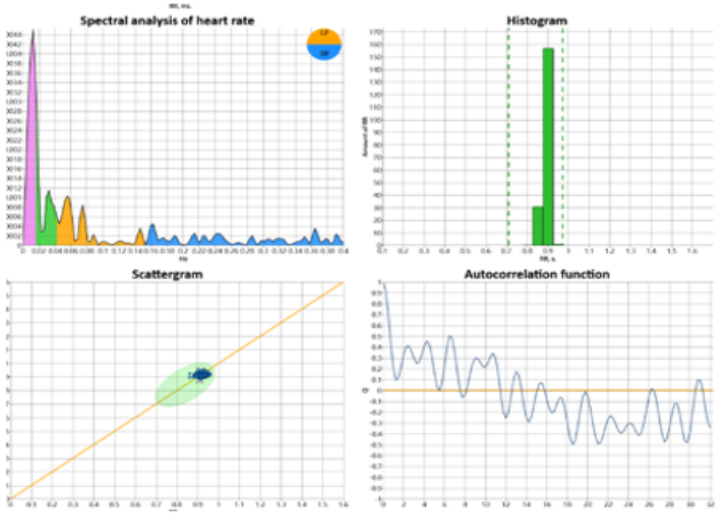


Figure 5-1 (a&b) shows the ECG-DM device and images of myocardial microalterations, illustrating how the parameters of myocardial variability were generated. (a.) (a) shows the ECG-DM device with four colored electrode clips connected to the limbs. A series of cardiac function parameters is automatically generated through a 3-minute analysis by the ECG-DM software during a resting state. b) depicts a gradated color-coded image of different segments of the atrium and ventriclemyocardium, with green indicating a healthy state and red representing ischemic and hypoxic changes. For instance, the subject's myocardial

microalteration index (MMI) is 25%, with localized ischemic and hypoxic changes visible in the left and right ventriclelateral walls (red areas) on the myocardial distribution map in (b).





IRSA	5	0 - 3	Power Total (TP), ms²	130.89
BPM	65.5	61.8 - 85	Power HF, ms²	29.17
Mx, ms	954	-	Power LF, ms²	30.05
Mn, ms	880.4	-	Power VLF, ms²	29.89
MxDMn, ms	73.6	64 - 152	Power ULF, ms²	41.78
MxRMn	1.1	-	Power HF,%	32.7
pNN50, %	0.5	-	Power LF,%	33.7
RMSSD, ms	20.8	-	Power VLF, ms²	29.89
SDNN, ms	15.2	11.2 - 28.6	LF/HF	1
CV, %	1.7	1.6 - 3.5	IC	2.1
Mo, ms	925	-	AVNN, ms	916.4
AMo, %	83.1	51.5 - 100	SDE, ms	1.1
Stress index (SI)	610.1	175 - 1185	SDSD, ms	20.8

Figure 5-2 is the report of HRV analysis for one case. It includes the regulatory system functional status assessment, the spectral analysis of HRV images, and a table presenting a series of parameters related to HRV that reflect the balance of autonomic nervous function at the end of the report.

5.2.3 Evaluation on Intracranial Arterial Plaque Characteristics

Intracranial arterial plaque imaging features were assessed using HR-MRI, focusing on the major large arteries: MCAs, VAs, and BAs. Morphological characteristics assessment of the plaques, including focal/diffuse distribution, irregular/smooth surfaces, eccentric/concentric patterns, positive/negative remodelling, and luminal stenosis, are detailed in Chapter 4. MRI images were independently analyzed by two observers (YY. C and LH. L) who have at least 3 years of experience in MRI image interpretation, and they were all blind to the clinical data of the participants. In the case of disagreement between the two observers, the images were reviewed by a third observer (JQ. L), who has more than ten years of neuroimaging experience, and consensus agreement was made among the three observers. For the atherosclerotic plaque measurements in MRI images, measurements were performed on the cross-sectional image slice with the maximum vessel wall thickness.

5.2.4 Statistical Analysis

IBM SPSS (27.0, SPSS, Inc.) was performed for statistical analysis. Continuous variables were reported as means ± standard deviation (SD) or as medians and interquartile range (IQR) for normally or non-normally distributed data. Normality test was assessed using the Shapiro-Wilk test. Categorical variables were presented as numbers and percentages (%). Appropriate tests such as Fisher's exact test, Pearson's chi-square test, or Mann-Whitney U test were employed to assess differences among independent groups. The inter-rater reliability of ICAS measurement was assessed by Cohen’s kappa analysis, are detailed in Chapters 2 &3.

Independent T-test was used for comparisons of age, blood pressure, luminal stenosis, plaque burden, MMI, and heart rate (bpm). Fisher's exact test, Pearson's chi-square test, or Mann-Whitney U test were used for comparisons of other risk factors between different ICAS and heart rate deviation groups. SDNN was divided into tertile groups to compare vascular risk

factors and plaque characteristics by using the Kruskal-Wallis H test. Factors with a *p*-value less than 0.05 were considered as confounding factors. Univariate and multivariate logistic regression models were utilized to determine the independent association between cardiac function and the presence of ICAS with other plaque morphological features. A two-sided p-value of less than 0.05 was considered statistically significant.

5.3 Results

5.3.1 Demographic and Clinical Characteristics

A total of 227 participants from the community were included in the study, and their demographic and clinical characteristics are shown in **Table 5-1**. The mean age of the participants was 63.4 ± 6.8 years old, and their mean BMI was 23.7 ± 3.3 kg/m^2. Among them, 118 participants (43.4%) were male. Participants with ICAS tended to be older (64.1± 6.8 years old vs. 62.4 ±6.7, p=0.041), had significantly greater systolic blood pressure (132.7 ± 16.3 vs. 126.4 ± 17.5, p<0.003), diastolic blood pressure (81.5 ± 10.1 vs. 77.8 ± 10.7, p=0.005), and higher prevalence of BMI>25 kg/m^2 (39.5% vs. 22.5%, p=0.003), compared to the non-ICAS group. There were more participants with ICAS suffering from hypertension (38.8% vs. 17.5%, p<0.001) and hyperlipidemia (47.4% vs. 26.7%, p<0.001), when compared to those without ICAS.

Table 5-1 Demographic and clinical characteristics of subjects with or without ICAS (MCAs, BAs, VAs).

Characteristics	Total (n=272)	Adults without ICAS (n = 120)	Adults with ICAS (n = 152)	*p*-Value
Demographics				
Age, y, (mean ± SD)	63.4 ± 6.8	62.4 ± 6.7	64.1 ± 6.8	**0.041**
Sex, male, n (%)	118 (43.4)	46 (38.3)	72 (47.4)	0.135

SBP, mmHg, (mean ± SD)	129.9 ± 17.1	126.4 ± 17.5	132.7 ± 16.3	**0.003**
DBP, mmHg, (mean ± SD)	79.9 ± 10.5	77.8 ± 10.7	81.5 ± 10.1	**0.005**
Body mass index ≥25 kg/m^2, n (%)	87 (32.0)	27 (22.5)	60 (39.5)	**0.003**
Medical comorbidities, n (%)				
Hypertension	80 (29.5)	21 (17.5)	59 (38.8)	**<0.001**
Diabetes mellitus	33 (12.2)	13 (10.8)	20 (13.2)	0.560
Coronary artery disease	17 (6.3)	4 (3.3)	13 (8.6)	0.077
Hyperlipidemia	104 (38.2)	32 (26.7)	72 (47.4)	**<0.001**
Medications, n (%)				
Statins	84 (30.9)	25 (21.0)	59 (38.8)	**0.002**
Antiplatelet	13 (4.8)	4 (3.4)	9 (5.9)	0.328
Anticoagulant	31 (11.4)	11 (9.2)	20 (13.2)	0.315
Habits, n (%)				
Current Smoker	14 (5.1)	5 (4.2)	9 (5.9)	0.516
Alcohol Drinking	20 (7.4)	9 (7.5)	11 (7.2)	0.934

Abbreviation: SBP indicates systolic blood pressure; DBP, diastolic blood pressure; WMH, white matter hyperintensity; SD, standard deviation.

5.3.2 Comparisons of Characteristics of Electrocardiogram Between Adults with and without ICAS

The comparison of cardiac function characteristics between participants with and without ICAS is included in **Table 5-2**. Among the 272 subjects, 57 (37.7%) of cases showed abnormal electrical activity waveforms, with the mean heart rate being 72.2 ± 10.4 bmp. Subjects with ICAS were more likely to present atrium micro-ischemic alteration (69.7% vs. 57.5%, p =0.03) compared to those without ICAS. There is significant difference in the SDNN between subjects with and without ICAS. (39.5% vs 28.3%, p = 0.040).

Table 5-2 The comparison of ECG characteristics between the participants with and without ICAS.

Characteristics	Total (n=272)	Adults without ICAS (n = 120)	Adults with ICAS (n = 152)	*p*-value
Electrocardiogram				
Abnormal, n (%)	102 (37.5)	45(37.5)	57(37.7)	0.967
Heart rate, bmp	72.2 ± 10.4	71.9 ± 11.2	72.4 ± 9.8	0.740
ECG dispersion mapping				
MMI, mean ± sd	19.1 ± 8.6	19.8 ± 10.4	18.4 ± 6.9	0.193
Atrium deviation, n (%)	**175 (64.3)**	**69 (57.5)**	**106 (69.7)**	**0.030**
Ventricles deviation, n (%)	235 (86.3)	103(85.8)	132(86.8)	0.703
Heart rate variability				
Power HF, ms^2 median (IQR)	154.9(67.4, 319.8)	161.5(75.0, 317.8)	154.6(64.2, 320.6)	0.345
Power LF, ms^2 median (IQR)	100.5(47.0, 235.2)	96.3(52.7, 194.8)	107.7(43.7, 270.3)	0.326
LF/ HF ration <1, n (%)	168 (61.7)	71(59.2)	97(63.8)	0.393
SDNN, abnormal, n (%)	94 (34.5)	34 (28.3)	60 (39.5)	0.040

5.3.3 Comparison of Plaque Imaging Features and Baseline Clinical Characteristics among Different Heart Rate Variability Groups

The comparison of atherosclerotic plaque characteristics and baseline demographic variables among different HRV groups is shown in **Tables 5-3 & 5-4**. Among the 272 subjects, 94 individuals (34.5%) with ICAS showed a greater propensity for heart rate deviation. Of these subjects, the majority presented with ICAS in the MCAs (41.5%), followed by those in VAs (35.1%), while only 22.3% had ICAS in BAs. Subjects with heart rate deviation had a higher prevalence of irregular plaque surfaces (40.4% vs. 20.3%, p=0.026), diffuse ICAS patterns (55.3% vs. 32.2%, p = 0.047), and more eccentric lesions (55.3% vs. 32.2%, p=0.038),

compared to those without deviations.

Table 5-3 The comparison of different patterns of ICAS between the participants with and without HRV deviation.

Characteristics	Total (n=272)	Adults with HRV deviation (n = 94)	Adults without HRV deviation (n = 177)	*p*-value
The presence of ICAS, n (%)	151 (55.5)	60 (63.8)	91 (51.4)	0.050
ICAS in MCA, n (%)	104 (38.2)	39 (41.5)	65 (36.7)	0.443
ICAS in VA, n (%)	67 (24.6)	33(35.1)	34(19.2)	0.004
ICAS in BA, n (%)	36 (13.2)	21(22.3)	15 (8.5)	0.345
Plaque morphological features				
Irregular surface, n (%)	64 (23.5)	38 (40.4)	36 (20.3)	0.026
Diffuse lesion, n (%)	109 (40.1)	52 (55.3)	57 (32.2)	0.047
Eccentric lesion, n (%)	119 (43.7)	52(55.3)	67(37.8)	0.038
Positive remodelling, n (%)	94 (34.6)	37 (39.4)	57(32.2)	0.239

Table 5-4 shows the comparison of the different clinical characteristics and ICAS imaging features among participants in different SDNN-time domain groups. Totally, subjects with the lowest SDNN values were older (65.0 ± 5.9 years old vs. 63.3 ± 6.6 years old vs. 62.0 ± 7.4 years old, p=0.010). Participants with lowest and moderate SDNN values are more likely to have a history of hypertension than those with highest SDNN value (34.4% vs. 35.2% vs. 18.7%, p = 0.026), compared with the moderate and highest SDNN groups. Moreover, participants with the lowest SDNN value were more prone to be involved by ICAS (55.5% vs. 48.3% vs. 49.4%, p=0.032) compared to participants in the other SDNN groups. However, comparative analyses revealed no statistically significant differences in plaque characteristics among the three HRV tertile groups (all p>0.05).

Table 5-4 The comparison of characteristics of subjects among different SDNN-time domains.

Characteristics	Group 1 0 ~20.75 ms (n = 90)	Group 2 20.76 ~29.64 ms (n = 91)	Group 3 ≥ 29.641 ms (n = 91)	*p*-value
Demographics				
Age, y, mean ± SD	65.0±5.9	63.3± 6.6	62.0 ±7.4[ac]	**0.010**
Sex, male, n (%)	40(44.4)	38(41.8)	40(43.9)	0.915
SBP, mmHg, (mean ± SD)	128.8 ± 17.7	131.5 ± 16.9	128.9± 16.4	0.487
DBP, mmHg, (mean ± SD)	79.1± 9.4	80.9 ± 11.1	79.3 ± 10.7	0.432
Body mass index ≥25 kg/m^2, n (%)	26(28.9)	31 (34.1)	30(32.9)	0.723
Medical comorbidities, n (%)				
Hypertension	31(34.4)	32(35.2) [bc]	17(18.7) [ac]	**0.026**
Diabetes mellitus	14(15.6)	11(12.1)	8(8.8)	0.392
Coronary artery disease	7(7.8)	5(5.5)	5(5.5)	0.771
Hyperlipidemia	36(40.0)	33(36.3)	35(38.5)	0.868
The presence of ICAS, n (%)	50 (55.5)	44 (48.3) [ab]	45 (49.4) [ac]	**0.032**
Plaque burden%, mean ± SD	47.4 ± 3.7	38.5 ± 3.8	44.8 ±3.9	0.243
Luminal stenosis, mean ± SD	23.0 ± 19.8	17.1 ± 19.9	17.4 ± 20.1	0.121
Plaque characteristics				
Irregular surface, n (%)	21 (23.3)	22 (24.2)	21 (23.3)	0.933
Diffuse lesion, n (%)	35 (38.9)	38(41.8)	36 (39.5)	0.757
Eccentric lesion, n (%)	40 (44.4)	38 (41.8)	41 (45.1)	0.869
Positive remodeling, n (%)	33 (36.7)	28 (30.8)	33 (36.2)	0.629

ac, Group 1 vs. Group 3, $p<0.05$; ab, Group 1 vs. Group 2, $p<0.05$; bc, Group 2 vs. Group 3, $p<0.05$

5.3.4 Association between Heart Rate Deviation and the Presence of ICAS

Univariate logistic regression analysis showed that atriums hypoxia (OR, 0.031; 95% CI, 1.05 – 2.87; *p*=0.031) and lower SDNN (an important quantitative global marker of HRV, OR, 1.40; 95% CI, 1.01 – 1.94; *p*= 0.044) were closely associated with the presence of ICAS (**Table 5-5**.). After covariate adjustment for age, gender, and hypertension, BMI, hyperlipidemia, lower SDNN (OR, 1.55; 95%CI,1.10-2.18; *p*=0.012) and atriums hypoxia (OR, 1.85; 95%CI,1.10-3.14; *p*=0.022) were found to be independent predictors for ICAS incidence in the participants.

Table 5-5 Multiple logistic regression models on the correlation between HRV and the presence of ICAS.

	Intracranial large artery lesion, Odds ratio (95%CI)	***p*-value**
Characteristics		
SDNN deviation	1.40 (1.01 – 1.94)	**0.044**
Atriums hypoxia	1.74(1.05 – 2.87)	**0.031**
Model-1 Adjusted for confounding factors (age, WMH burden)		
SDNN deviation	1.57 (1.12 – 2.21)	**0.009**
Atrium hypoxia	1.72(1.03 – 2.85)	**0.038**
Model-2 Adjusted for confounding factors (age, WMH burden, gender, hypertension, BMI, hyperlipidemia)		
SDNN deviation	1.55 (1.10 – 2.18)	**0.012**
Atrium hypoxia	1.85 (1.10 – 3.14)	**0.022**

OR, Odds ration; 95% CI, 95% confidence interval

5.4 Discussion

This study shows, for the first time, the relationship between cardiac dysfunction and

intracranial atherosclerosis in a community-based population. We found that time-domain HRV deviation and oxygenation disorder in the atria may serve as independent risk factors for ICAS occurrence. These results were consistent across most, but not all, of the time domain HRV measures. The study findings provide the first evidence suggesting that heart rate variability (HRV) may serve as a valuable indicator of cardiac dysfunction, particularly for early screening of higher risk in adults with asymptomatic intracranial atherosclerosis. These results shed light on further investigations to understand the underlying pathophysiological mechanisms associated with this relationship, which may not be fully attributable to traditional vascular risk pathways.

HRV is a cardiovascular metric which describes a series of automatic calculations for psychophysiological responses between consecutive heartbeats.[25, 180] A lower HRV is proven to be associated with either increased parasympathetic activity or decreased sympathetic activity, and is correlated with multiple vascular events and an elevated risk of all-cause mortality. [185, 290] However, the results of previous studies focused on the association of HRV in cerebrovascular diseases are contradictory.[31, 254, 288, 294-296] In the Multi-Ethnic Study of Atherosclerosis, Whelton *et al*. indicated that a higher nocturnal resting heart rate is associated with increased carotid and aortic arterial stiffness.[297] On the contrary, previous studies reported that low HRV may be an early indicator of declining health[28] and precedes mortality post-myocardial infarction.[298] In the Atherosclerosis Risk in Communities Study(ARIC), Fyfe-Johnson AL,*et al*., demonstrated that lower HRV was associated with a higher risk of incident stroke among middle-aged adults with prevalent diabetes.[31] In line with previous reports, the present community-based study found that reduced daytime HRV is significantly associated with an increased risk of pro-atherogenic effects. Although the pathogenesis remains unclear, I propose several possible explanations for the relationship between ANS imbalance and ICAS. Firstly, low HRV often indicates dysfunction in the autonomic nervous system

(ANS), leading to an imbalance between sympathetic and vagal activity. This imbalance can cause brain environment homeostasis, trigger inflammation, and disrupt endothelial cell function. The process of ICAS is dynamic, can be seen as a struggle between vascular auto-repair and injury, where persistent inflammation fosters a predominance of aggressive mechanisms and a derangement of vascular reparative capacity, thereby contributing to the development of ICAS.[299] Secondly, the relationship between HRV and ICAS may be influenced by other vascular risk factors such as hypertension. Hypertension is an important covariate in the association between HRV and cerebral vascular events due to its link to circulatory autoregulation and cerebral blood perfusion.[283, 300] Low HRV may trigger fast pressure changes in the cerebral vasculature, leading to unregulated vascular homeostasis, and impacts on vascular health and subsequent stroke risk.[301] Sympathetic overactivity caused by ANS dysfunction was correlated with hypertension due to restricted vasodilation, resulting in elevated ambulatory blood pressure and reduced blood flow, thereby increasing the risk of ICAS.[302] Additionally, consistent with previous reports[290, 303, 304] in the current study, hypertension was one of the covariates in the models to investigate any potential confounding effects of hypertension on the relationship between HRV and ICAS. Lastly, evidence suggests that endothelial cells play an important role in regulating vascular homeostasis,[305] and endothelial dysfunction is an early marker for atherosclerosis.[306] Suppressed heart rate suggests impaired autonomic balance, induces inflammation, and disrupts endothelial homeostasis, promoting the production of vasoconstrictors (e.g., endothelin and angiotensin II), which activate macrophages and vascular smooth muscle cells, ultimately contributing to plaque formation in intracranial atherosclerosis. [305, 307]

In addition, the present study found an independent association between atrium hypoxia and ICAS occurrence; however, the primary mechanisms are intricate and interconnected. The explanation for this finding remains unclear, and the possible causes may include myocardial

metabolic disturbances, hemodynamic changes due to cerebral vascular remodeling and arterial stiffness, and oxidative stress effects. Metabolic disturbances in the heart can elevate reactive oxygen species (ROS) and impair antioxidant defenses, thereby inducing oxidative stress that disrupts endothelial function. This leads to endothelial dysfunction and the release of endothelin-1 (ET-1), a potent vasoconstrictor released by endothelial cells. ET-1 may significantly augment the hemodynamic significance of coronary stenoses, thereby exacerbating myocardial ischemia.[308] Furthermore, the previous study suggested that structural remodeling of vascular dimensions affects cerebral blood flow distribution, and the altered flow pattern can trigger inflammation and exacerbate endothelial dysfunction, facilitating the progression of ICAS. [309] The ischemia and inflammation of blood vessels restrict vasodilation, resulting in chronic hypoperfusion of cerebral and cardiovascular structures, and impaired blood pressure regulation, which consequently leads to endothelial dysfunction and promotes increased arterial stiffness along with atherosclerotic plaque formation.[305, 307]

In the study, I used the 3-minute HRV monitoring to assess the association between HRV and different MRI imaging features of atherosclerotic plaques, aiming to identify high-risk patients for timely clinical management and treatment. Eccentric thickening lesion was commonly used as a criterion for identifying ICAS and is associated with ischemic events. [268, 269, 310] The present study, however, found that there was no association between intracranial atherosclerotic plaque imaging features and HRV. This result may also be limited by the small sample size and a homogeneous population of the present study. Further investigations are warranted to HRV and expand the sample size for a more in-depth exploration of the risk stratification between atherosclerotic plaque imaging features and HRV, and include patients with cerebral ischemic events.

This study has some limitations. Besides the relatively small sample size, it lacks an

understanding of cSVD mechanisms, such as collateral circulation, which may mitigate the impact of damage to cortical or subcortical structures and the neural pathways that regulate the cardiovascular autonomic system. Besides, the study did not have long-term ECG recordings of the participants to comprehensively investigate the correlation between frequency domain measures (HF, LF, and LF/HF) and ICAS. which restricts the applicability of power spectral analysis to accurately capture LF and HF components.[191] Finally, this study is an observational study conducted at a single center, which may introduce selection bias. Future studies to investigate the relationship between MRI imaging markers of small vessel disease in the context of ICAS and cardiac dysfunction are suggested for a better understanding cerebrovascular and cardiovascular diseases.

5.5. Conclusion

This study found that reduced HRV and atrium metabolic ischemic impairment may be valuable predictors for early identification of higher-risk subjects who develop ICAS. These pathogeneses can be attributed to ANS dysfunction, endothelial cell dysfunction, and unregulated vascular homeostasis. These findings may substantially improve clinical risk management and guide the prevention strategies for cerebrovascular events. Further prospective evidence is needed to validate the causal relationships and underlying mechanisms between HRV and cSVD

Chapter 6. Study-4: Implication of Electrocardiographic Features on White Matter Hyperintensity and Cerebral Microbleeds: A Heart–Brain Microvascular MRI study

Chapter 6. Study-4

6.1 Background

Atherosclerosis, the leading cause of cardiovascular disease (CVD), is known as a systemic disease that commonly involves both intracranial and extracranial arteries.[38, 311] According to the literature, atherosclerosis is one of the most common causes of stroke worldwide[312], with higher prevalence in Asian populations than in Whites.[313] The brain-heart axis (BHA), as a syndromes rather than isolated diseases affecting the brain and heart, is involved in a series of physiological functions. There is a growing interest in understanding the association between major large-arterial atherosclerosis and cardiovascular disease.[314, 315] However, limited studies have investigated the relationship between cerebral small vessel disease(cSVD) and cardiac dysfunction. Prior studies has reported cSVD frequently coexists with intracranial atherosclerosis (ICAS) [23, 80] and is associated with a higher risk of stroke recurrence [81, 82] as well as less favorable stroke outcomes. [83] In fact, the underlying mechanisms of cerbral microcirculation and autonomic nervous regulation are complex, it has been hypothesized that cSVD and cardiac function are closely interrelated due to the similarities in vascular anatomy and the distribution of conduit arteries between the brain and heart, which provide organ perfusion through microcirculation. On MRI, MRI-defined brain microbleeds and white matter hyperintensities (WMHs) are imaging markers for intracerebral vascular lesions, and are commonly found in the older general population.[260] Till now, limited studies have investigated the relationship between lower HRV with the development of WMHs.[296, 316] HRV is a cardiovascular metric detected by electrocardiography, and is commonly used for detecting and monitoring various subclinical and clinical cardiovascular diseases.[317] Yamaguchi, Y., et al reported that HRV was increased in patients with severe white matter changes[318], whereas some other studies did not find an association between HRV and subclinical cerebrovascular disease.[296] By contrast, there is scant information on the association of ECG parameters with cerebral microbleeds(CMBs) in healthy middle-aged and

older adults. Much of the enduring interest in CMBs relates to their high prevalence in the context of adverse cerebrovascular events and permanent disability and in healthy individuals.[319] In the past, research literature overwhelmingly emphasized the future hemorrhagic risk associated with CMBs[319], but there is a lack of rapid and effective examination for clinicians to early identify 'silent' CMBs for risk stratification. Given the absence of investigation in this area, we provide the latest research findings and personal expertise suggestions where possible, hoping to offer at least a direction to other clinicians and support the development of individualized treatment strategies. Both WMHs and CMBs are important neuroimaging markers of cerebral small vessel disease. Individuals with WMH and/or CMB on MRI will commonly have various neurological conditions, including small vessel disease, dementia, and intracerebral hemorrhage [320-322], and these neuroimaging markers are also associated with other pathologies such as recurrent ischemic stroke, hypertension, and chronic kidney disease.[323] Despite a spectrum of traditional vascular risk factors and blood-based biomarkers for WMHs and CMBs identified by previous studies, there are still controversies and a lack of knowledge regarding the biological processes underlying the development of these two neuroimaging signatures of cSVD. [90, 97, 324, 325] Therefore, identifying novel biomarkers for a better understanding of both typical neuroimaging markers of cSVD may provide a strong foundation for advances in knowledge and clinical management.[326, 327]

It is hypothesized that if ECG parameters can be used as predictors of an increased risk of WMHs or CMBs, these parameters can be used to assess asymptomatic brain small vessel disease in elderly patients for effective and early detection and intervention of cerebrovascular diseases. Therefore, this study investigated the association of various ECG parameters with the presence and severity of WMHs and CMBs, aiming to identify potential ECG-related risk factors for cSVD disorders, particularly in the general elderly population.

Chapter 6. Study-4

6.2 Methods and Materials

6.2.1 Subjects

This cross-sectional study was conducted in November 2022 and approved by the Institutional Review Board of the Hong Kong Polytechnic University. A total of 284 consecutive adults aged 45 and older were recruited from the Hong Kong community, all of whom are part of the same group of subjects detailed in Chapter 3. All the subjects provided informed consent before participation, and the eligibility criteria are also outlined in that Chapter.

6.2.2 Imaging Data Collection and Assessment on WMHs and CMBs

WMHs and CMBs were examined by a 3.0-T MRI scanner (Siemens Medical Systems, XR Numarism, Germany) with a 64-channel head coil. MRI images were reviewed on OsiriX DICOM Viewer (Geneva, Switzerland) and independently analyzed by two observers (LH. L. and YY. C.), who were both blind to the clinical data of the participants. WMH was demonstrated on FLAIR and T2-weighted imaging as patchy hyperintense areas. [328] The severity of WMH was scored according to the Fazekas scale[119], from absent to severe. Individuals with mild WMHs were those with a total score of ≤2 in the MRI examination (including PV-WMH and D-WMH scores, as described in Chapters 2&3), moderate WMHs were defined as a total of 3-4 points, and severe WMHs were total of 5-6 scores.[97, 98] For the CMB assessment, CMBs were detected on the blood-sensitive MRI sequences, and they appeared as small, dot-like hypointense haemosiderin foci in the images.[133] According to previous studies[329, 330], CMBs are classified based on the total number and hemispheric location in the brain, with a focus on 2-10 mm rounded areas of very low signal intensity on SWI sequence as described in Chapters 2 and 4.

6.2.3 Cardiac Function Assessment

Electrocardiographic data were acquired by 3-minute ECG dispersion mapping (ECG-DM) monitoring (HeartVue system, KARDi2/4-B, Medical Computer Systems Ltd, Russia). The HealthExpress package system was used to analyze ECG parameters, including time-domain and frequency-domain HRV, MMI (reflecting the myocardial micro-hypoxia index), atrium and ventricledeviation, and heart rate (bpm), as described in Chapter 5. As for MMI assessment, the mean MMI percentage from all nine groups (G1-G9) was recorded and categorized into the four groups: Group I - normal (mean MMI=0-14%), Group II - mild abnormality (mean MMI=15-18%), Group III - moderate abnormality (mean MMI=19-23%), and Group IV - severe myocardial hypoxia (mean MMI≥24%).[293]

6.2.4 Statistical Analysis

Data analysis was conducted using IBM SPSS (27.0, SPSS, Inc.). Continuous variables were described as means ± standard deviation (SD), while non-continuous data were reported as medians and 2.5–97.5 percentiles. Categorical variables were presented as numbers and percentages (%). Pearson's chi-square test was used to test differences in ECG characteristics in the different WMHs degrees and CMBs severity. In order to test the association between the presence, severity of CMB, WMH, and ECG features, the correlation coefficients and regression analysis were performed. A p-value < 0.05 was regarded as indicating statistical significance, and all correlation values were calculated using a two-tailed significance level.

6.3 Results

6.3.1 Comparisons of Characteristics of Electrocardiogram between Adults with and without Moderate to Severe WMHs

A total of 272 adults (mean age, 63.8±6.8; male, n= 118) were consecutively recruited.

Of these subjects, 24.6% were classified as having moderate to severe white matter hyperintensities (WMHs): 62 individuals (22.8%) with moderate WMHs and 5 individuals (1.8%) with severe WMHs. The remaining 75.3% showed normal or mild WMHs, including 55 individuals (20.2%) classified as normal and 150 (55.1%) with mild WMHs. Subjects with moderate and severe WMHs were more likely to present atrium (76.1% vs. 60.5%, p=0.023) and ventricledeviations (88.1% vs. 69.3%, p=0.003). Depending on the rate of frequency-domain (LF/HF) of overall heart rate variation and time-domain (SDNN), no significant difference was found in subjects with or without moderate to severe WMH, as shown in **Table 6-1.**

Table 6-1 The comparison of ECG characteristics between the participants with and without moderate to severe WMH.

Characteristics	Total (n=272)	Adults with mod to severe WMH (n = 67)	Adults without mod to severe WMH (n =205)	*p*-value
Electrocardiogram				
Abnormal, n (%)	102(37.6)	27(40.3)	75 (36.5)	0.604
Heart rate, bmp	72.2 ± 10.4	72.4 ± 10.3	72.1 ± 10.5	0.847
ECG dispersion mapping				
MMI, mean ± sd	19.1 ± 8.6	19.6 ± 9.6	18.9 ± 8.3	0.572
Atriums deviation, n (%)	175 (64.3)	51 (76.1)	124(60.5)	0.023
Ventricles deviation, n (%)	201 (73.9)	59(88.1)	142(69.3)	0.003
Heart rate variability				
LF/ HF ration <1, n (%)	168(61.7)	38(56.7)	168(81.9)	0.305
SDNN, abnormal, n (%)	94(34.5)	25(37.3)	69(33.6)	0.239

6.3.2 Comparisons of Characteristics of Electrocardiogram between Adults with and without CMBs

Based on qualitative and quantitative MRI assessments, the prevalence, distribution, and number of CMBs were analyzed in relation to myocardial instability changes as defined by daytime electrocardiographic monitoring. Among the 272 subjects in the study, 55(20.2%) subjects were identified as having CMBs on MRI images. Subjects characterized by the presence of CMBs were more likely to present a higher index of myocardial metabolic impairment (22.3 ±10.2 vs. 17.6 ± 7.5; p= 0.043), and a lower change in time-domain (SDNN) of HRV (12.7% vs. 40.1%, p< 0.001). **Table 6-2**

Table 6-2 The comparison of ECG characteristics between the participants with and without CMBs.

Characteristics	Total (n=272)	Adults with CMBs (n = 55)	Adults without CMBs (n =217)	*p*-value
Electrocardiogram				
Abnormal, n (%)	102(37.5)	23(41.8)	79 (36.4)	0.474
Heart rate, bmp	72.2 ± 10.4	71.6 ± 8.2	72.5 ± 10.9	0.400
ECG dispersion mapping				
MMI, mean ± sd	19.5 ± 9.2	22.3 ± 10.2	17.6 ± 7.5	0.043
Atrium deviation, n (%)	175 (64.3)	35 (63.6)	140 (64.5)	0.870
Ventricle deviation, n (%)	201(73.8)	42(76.3)	159(73.2)	0.677
Heart rate variability				
LF/ HF ration <1, n (%)	168(61.7)	40(72.7)	128(58.9)	0.066
SDNN, abnormal, n (%)	94(34.5)	7(12.7)	87(40.1)	<0.001

Table 6-3 shows a comparison of the presence, number, and distribution of cerebral microbleed (CMB) characteristics between subjects with and without myocardium micro-alteration index (MMI). A total of 75 individuals (27.5%) were observed to have subtle changes in myocardial function. subjects were more likely to present CMBs (30.7% vs. 16.2%, p = 0.008) and with more than one bleeding focus(p<0.05), compared to those without MMI. Based on the severity of myocardial micro-alteration index (MMI) groups, the greater the severity of myocardial micro-ischemic change, the higher the number of cerebral CMBs observed. **Table. 6-4**

Table 6-3 The comparison of CMBs characteristics between the participants with and without myocardium micro-alteration index.

Characteristics	Total (n=272)	Adults with MMI change (n =75)	Adults without significant MMI change (n = 197)	*p*-Value
Presence CMBs				0.008
Yes, n (%)	55(20.2)	23(30.7)	32(16.2)	
CMBs number, n (%)				0.029
1	33(12.1)	15(20.0)	18(9.1)	
≥2	16(5.9)	8(10.6)	8(4.1)	
Sides of CMBs, n (%)				0.055
right	22(8.1)	6(8.0)	16(8.1)	
left	18(6.6)	10(13.3)	8(4.1)	
bilateral	11(4.0)	3(4.0)	8(4.1)	

MMI, Myocardium micro- alteration; CMBs, cerebral microbleeds

Table 6-4 Correlations between the severity of myocardium micro-alteration index (MMI) and the cerebral microbleeds features.

	Subjects with different severity of MMI				*p*-Value
	Normal (n=30)	Grade I (n=167)	Grade II (n=39)	Grade III (n=35)	
CMBs presence, n (%)	2 (6.6)	31 (18.6)	9 (23.1)	13(37.1)	0.018
CMBs number, n (%)					0.010
1	2 (6.6)	17 (10.2)	6 (15.4)	8(22.9)[bc]	
≥2	0 (0)	13 (7.8)	3 (7.7)	4 (11.4)[bc]	
Sides of CMBs, n (%)					0.153
right	1(3.3)	16(9.6)	1(2.6)	4(11.4)	
left	1(3.3)	7(4.2)	5(12.8)	5(14.3)	
bilateral	0(0)	8(4.8)	2(5.1)	1(2.9)	

b,Group I; c, Group II, d, Group III; $p<0.05$

6.3.3 The Association between Cardiac Instability Variation and Cerebral Small Vessel Disease (WMHs and CMBs)

Multivariable logistic regression analysis was performed to investigate the association of myocardial instability in WMH severity and the presence of CMB. After adjusting for confounding factors (age, gender, and hypertension), multiple binary logistic regression models suggested that both atrium (OR 2.1, 95% CI 1.07 – 4.21, $p = 0.007$) and ventricledeviation (OR 3.1, 95% CI 1.37 – 7.29, $p = 0.038$) were independently and significantly associated with higher level of WMHs **(Table 6-5**). Meanwhile, for the association between cardiac function and the presence of CMBs, HRV (time-domain SDNN, OR 0.56, 95% CI 0.35 – 0.91, p=0.019) and myocardial micro-alteration index, which indicates myocardial micro-ischemic impairment (OR 1.69, 95% CI 1.18 – 2.41, $p = 0.004$), were predictive risk factors for CMBs occurrence (**Table 6-6**).

Table 6-5 Multiple logistic regression models on the correlation between WMHs and cardiac dysfunction.

	The severity of WMHs Odds ratio (95%CI)	*p*-Value
Characteristics		
Ventricle deviation	3.2 (1.45 – 7.14)	0.004
Atrium deviation	2.09 (1.08 – 4.01)	0.027
Model-1 Adjusted for confounding factors (age, gender)		
Ventricle deviation	3.3 (1.44 – 7.50)	0.005
Atrium deviation	2.0 (1.02 – 3.92)	0.042
Model-2 Adjusted for confounding factors (age, gender, hypertension, diabetes)		
Ventricle deviation	3.1 (1.37 – 7.29)	0.007
Atrium deviation	2.1 (1.07 – 4.21)	0.030

OR, Odds ratio; 95% CI, 95% confidence interval.

Table 6-6 Multiple logistic regression models on the correlation between cardiac dysfunction and CMBs.

	The presence of CMBs Odds ratio (95%CI)	*p*-Value
Characteristics		
MMI change	1.70 (1.21 – 2.39)	0.002
HRV(SDNN)	0.56 (0.35 – 0.91)	0.018
Model-1 Adjusted for confounding factors (age)		
MMI change	1.68(1.180 – 2.38)	0.003
HRV(SDNN)	0.558 (0.346 – 0.900)	0.017
Model-2 Adjusted for confounding factors (age, gender, hypertension)		
MMI change	1.69 (1.18 – 2.41)	0.004
HRV(SDNN)	0.56 (0.35– 0.91)	0.019

OR, Odds ratio; 95% CI, 95% confidence interval.

6.4 Discussion

The findings of this study indicated that daytime HR deviation and myocardium micro-alteration index are independent risk factors of the presence of CMBs, independent of traditional cardiovascular risk factors, in the middle-aged and elderly community population. In addition, myocardial hypoxia index in both atrium and ventriclechambers showed a significant association with higher burden of WMHs but not with HR variability.

Previous evidence from epidemiological studies showed that tachycardia is associated with the aggressive development of mortality and morbidity of cardiovascular events. [331, 332] Contrary to the current study's finding, previous research indicated that night-time heart rate is a better predictor of total mortality and cardiovascular risk when compared to other heart rate

statuses, such as daytime or resting heart rate. [333, 334] As stated by Johansen *et al.* [334], heart rate at night was an independent predictor of cardiovascular events after adjustment for other vascular risk factors in middle-aged adults with no apparent heart disease. However, the association between HR variability and cerebral SVD (WMHs and CMBs) remains unclear and conflicting. Yamaguchi, Y., *et al*[318] showed that patients with severe white matter changes tended to have higher HRV, whereas another study did not find an association between HRV and subclinical cerebrovascular disease.[296]

MRI-defined WMHs and CMBs play important roles in typical neuroimaging phenotypes of cSVD, and these imaging features are commonly observed in asymptomatic elderly adults in the community. Although WMHs and CMBs are not the primary culprits of strokes presenting with overt clinical symptoms, they should not be regarded as entirely benign and silent, as there is a close association between them and subtle neurological symptoms, increased risk of cerebral attacks, and even death. [129, 335-337] In this study, I found independent associations of cardiac dysfunction (daytime HR variability and myocardial microdysfunction) with the presence of CMBs and severity of WMHs. Notably, abnormal SDNN showed a more substantial relationship with the presence of CMBs than WMHs. The underlying mechanisms of these associations are not clear, but I propose several potential explanations. First, impaired arterial compliance and distensibility in individuals with dysrhythmic heart rates can lead to increased blood pressure fluctuations, resulting in elevated stress on cerebral blood vessels.[302] The increased stress on blood vessels and hemodynamic instability contribute to the development of microbleeds.[338] Second, the findings of the present study were different from those of previous studies. Previous studies has supported that only the lower nighttime SDNN was correlated with higher burden of WMHs and cSVD.[187, 339, 340] However, in the present study, no significant relationship was observed between daytime SDNN and WMHs in the elderly population. This discrepancy in the findings may be attributed to different research

methodologies. One possibility explained by Ben-Dov lZ., *et al*. is that dysregulation of HR at night can persistently overdrive the sympathetic tone, and better reflect mechanical stress on the arterial wall than daytime HRV. [341] Moreover, different factors could impact heart rate stability, such as mental stress, physical activity, and emotion.[342] Tian, Y., *et al.* demonstrated that the balance of ANS function may be affected by unstable HRV during wakefulness, resulting from mental or various physical activity triggers.[343] On the other hand, dysregulation of time-domain HRV (SDNN) was found to be associated with the presence of CMBs. To the best of our knowledge, this present study is the first to find the adverse relationship between HRV and CMBs. Till now, no prior evidence has supported the association between either in clinical research or in radiological analysis. Although CMBs are not the primary culprit of stroke presenting with overt clinical symptoms, they should not be regarded as entirely benign and silent, as there is a close association between CMBs and subtle neurological symptoms, increased risk of cerebral attacks, and even death. [129, 335] The potential mechanisms linking CMBs and autonomic nervous system dysfunction remain unclear, but we propose that the brain-heart axis interacts closely due to a complex series of cascading responses.[343] Moreover, the development of CMBs is caused by endothelial dysfunction, disruption of the blood-brain barrier, and eventual fatigue and rupture of elastic fibers [344, 345], which are influenced by autonomic nervous system regulation and reflected in HRV parameters such as SDNN. Abnormalities in SDNN indicate an imbalance in sympathetic and parasympathetic control, leading to hemodynamic instability and increased pulsatility in cerebral arterioles, which in turn increases the risk of microangiopathy and subsequent microbleeds. [296, 346] In contrast, white matter lesions are primarily associated with chronic ischemic processes, inflammation, and metabolic dysregulation, and in daytime, HR is less stable than at night, primarily due to emotional or physical activities. Therefore, it can be explained that WMHs may not quickly respond to autonomic fluctuations as CMBs. Hence, this may explain the significant

association between HRV and CMB (a kind of cerebral microangiopathy) that was found in the present study.

For myocardial metabolic dysfunction, the findings of the present study are consistent with previous studies investigating oxygen metabolic status in the presence and burden of WMHs and CMBs. Previous studies have found that oxymetabolic stress is a better predictor of WMH burden. [347] Chronic ischemic hypoxia alters the microstructural integrity of normal white matter and predicts the expansion of white matter lesions, leading to reduced hypoperfusion. [348] In the current study, ECG-recorded hypoxic-ischemia was found in atrium and ventriclemyocardium as an independent risk factor for WMH burden. The variations in myocardium hypoxia or micro-ischaemic impairment contribute to the development of brain intersected fiber tracts and collateral vessels, which develop with distinct mechanisms from large arterial atherosclerosis.[349-351] Indeed, we found that more severe myocardial hypoxia was significantly associated with a greater burden of WMHs, indicating that individuals with higher levels of hypoxic-ischemic stress may be at increased risk of developing WMHs. This may, in part, explain that cardiac myocardium hypoxia can reduce cardiac output, resulting in decreased cerebral blood flow and low perfusion, specifically localized in the white matter fields. This condition indicates episodic imbalance between oxygen demand and supply, resulting in intermittent reduced microvascular blood volume, microstructural alterations, and concomitant capillary dysfunction, contributing to hypoxic tissue injury.[352]

In addition, the present study found that MMI could be a risk predictor of cerebral microbleeds, because the study finding showed that a higher myocardial variability index was associated with a greater burden of CMB. Although multiple etiologies may contribute to the development of CMB, they are primarily observed with cerebral amyloid angiopathy and chronic hypertension. [353] In fact, the pathological mechanism of CMBs is complex and still debated. However, the current study provides evidence to demonstrate a novel cardiac

biomarker that could indicate the presence of CMBs. Previous studies found that patients with critical illness conditions, such as high-altitude exposure and acute respiratory distress syndrome, are more likely to experience cerebral microbleeds in the juxtacortical white matter. [354, 355] This similarity between high-altitude exposure microbleeds and acute respiratory distress syndrome-associated microbleeds suggests that they may have a common pathogenesis. A possible explanation for these critical illness-associated CMBs is hypoxemia, which may induce chemical or hydrostatic disruptions of the blood-brain barrier, potentially contributing to the extravasation of erythrocytes. [356] In the present study, the 75 subjects presented with MMI changes did not have a history of such critical illness, and 32.5% of them had different levels of CMB. Since the precise pathological mechanism related to CMBs and myocardial variability index remains unclear, further studies investigating this pathological mechanism are needed to verify this finding.

This study has limitations. First, the sample size of the study was small, and the study data, including the MRI data, were collected from a single center. Although the role of WMHs and CMBs on cardiac dysfunction is different in the elderly, the specific pathogenesis for the association between cerebrovascular abnormality and cardiac dysfunction was not investigated in this study. Second, the myocardium metabolic regulation and electrical conduction of the subjects were examined using a 3-minute ECG only during the daytime, and this may not comprehensively assess the cardiac function due to the absence of heart rate variability recordings at night. Third, this study only investigated the association of WMHs and CMBs with changes in cardiac function, lacking exploration of the relationships between other subtypes of cSVD, such as EPVs, lacunes, brain atrophy, and cardiac dysfunction. Further studies to investigate the association between different subtypes of cSVD and cardiac function are suggested.

6.5 Conclusion

The results of our study demonstrate a dose-response association between cardiac function (time-domain HRV and myocardial deviation) and the presence and burden of cSVD markers (WMHs and CMBs) that extends beyond conventional risk factors. This suggests a possible role for ANS regulation and myocardial micro-metabolic impairment, indicating that HRV and oxygenation intervention may serve as novel therapeutic targets for the development of cSVD in the future.

Chapter 7. Summary and Future Research

Chapter 7. Summary and Future Research

7.1 Conclusions

Intracranial atherosclerosis and cerebral small vessel disease are common in the aging population and are highly associated with various cerebrovascular events, such as strokes and dementia. [13, 357] Thus, assessment of both cerebral large and small vessel diseases to achieve optimal brain health is crucial for public health and a significant challenge to the healthcare burden. Cardiovascular diseases are the foremost cause of mortality and disability worldwide.[358] Brain-heart system is interdependent on the maintenance of brain and bodily health and linked through shared risk factors.[200, 241] Previous studies demonstrated that people with various cardiac conditions may have covert brain microstructural changes and cognitive impairment.[359] By addressing cardiovascular health earlier in life, it may be possible to reduce the risk of stroke and delay the onset or progression of cognitive impairment later. However, there is a lack of information about the association between intracranial vascular diseases and cardiac function. Therefore, in this PhD study, I investigated the potential associations within the brain-heart system to understand how cardiac dysfunction (cardiac micro-ischemic metabolic change and autonomic dysfunction), as identified by 3D-ECG, to predict intracranial vascular changes in order to reduce the use of MRI, which is costly, less readily available, and contraindicated to some patients.

Moreover, in this PhD study, I explored the relationship between intracranial atherosclerosis and cerebral small vessel disease in the aspects of imaging morphological features of intracranial atherosclerotic plaque, the presence and severity of WMHs, and CMBs. In Chapter 3, I investigated HR-MRI imaging morphological characteristics of intracranial large-arterial atherosclerosis and assessed the associations between the imaging features of cSVD phenotypes. This multimodal imaging-based study is consistent with prior research and has proven that the association between the presence and severity of ICAS and different

imaging phenotypes of cVSD extends beyond the co-existence due to shared risk factors, suggesting the presence of a positive relationship between ICAS and cSVD. Considering the intraplaque imaging morphological features differently may reflect different clinical manifestations, I further investigated the association of different imaging morphological features of ICAS with the presence and severity of WMHs, and this study is presented in Chapter 4. The results of the study demonstrated that the subtle changes (increment or decrement) in intracranial atherosclerotic features, such as plaque load, positive/negative remodeling, degree of luminal stenosis, eccentricity, and other morphology (ICAS severity) may parallelly influence the burden of WMHs. The study results also showed that plaque eccentricity derived from HRVW-MRI could predict the structural features of subclinical or asymptomatic plaques, and was significantly associated with moderate to severe WMHs burden.

In Chapters 5 and 6, I explored the association of intracranial large-arterial atherosclerosis and small vessel disease with cardiac metabolic capability, and autonomic dysfunction, emphasized on the HRV and MMI. In this study, the cardiac metabolic capability of the subjects was assessed by directly visualizing oxygen levels through 3D-ECG dispersion mapping, utilizing different color-coded distributions of cardiac regions to evaluate the degree of myocardial micro-ischemic impairment. Autonomic nervous system function control to the heart was evaluated by time and frequency-domain heart rate variability (SDNN, HF, LF, and LF/HF ratio), as derived from 3D-ECG dispersion mapping. In Chapter 5, I found reduced HRV and atrium metabolic ischemic impairment may be valuable predictors for early identification of higher risk subjects who develop ICAS. These manifestations can be attributed to ANS dysfunction, endothelial cell dysfunction, and blood hypoperfusion. The results of Chapter 6 revealed that daytime HR deviation and myocardium micro-alteration index are independent risk factors of the presence of CMBs, and myocardial hypoxia index in both atrium

and ventricle chambers showed significant association with higher burden of WMHs but not with HR variability. These findings might suggest that individuals with ICAS and cSVD may have deteriorated hemodynamics in the brain, which could induce an imbalance in the sympathetic-vagal nervous system caused by cerebral irregularities of the autonomic nervous system and, consequently, impaired HR fluctuations with myocardial metabolic capability, therefore leading to neurologic dysfunction. To the best of my knowledge, this is the first community study to evaluate plaque imaging features by using HR-MRI and explore the association between two cerebral diseases and cardiac function. The study findings may help guide future clinical management of the silent cerebrovascular diseases and screening of cerebral and cardiovascular diseases in the general population.

7.2 Future Research

7.2.1 The Impact of Intracranial Vascular Involvement on Cognitive Decline

Cerebral small vessel disease is a chronic microvascular disease and has been suggested to be associated with neurological disorders, including dementia, emotional disorders, and cognitive impairment. [360] Microvascular damage in the brain can manifest as WMHs, CMBs, and lacunes, which may finally lead to cognitive impairment and dementia. [211, 361] However, there is a lack of information regarding the association between cognitive decline and cardiac dysfunction in patients with ischemic stroke. This PhD study was conducted on a community-based cohort and evaluated the associations of cerebral small vessel disease, ICAS, and cardiac dysfunction. Further investigation of the potential impact of ICAS imaging features on cognitive function in patients with cerebrovascular events is suggested.

7.2.2 The Impact of Clinical Potential of ECG-DM in Early Detection and Autonomic Assessment

This study is an observational study conducted at the HK community sample. However, robust recruitment strategies of random selection of Chinese participants from different communities in Hong Kong minimized potential selection bias. Moreover, Clinical information on vascular risk factors, including hypertension and diabetes mellitus, was derived from standardized self-reported questionnaires rather than laboratory verification. While this method may introduce recall bias, it enables efficient, cost-effective data collection in community-based cohorts. Self-reported health information from questionnaires has been widely used in epidemiological research and can provide reasonable estimates of vascular risk profiles when combined with the standardized questionnaire and trained interviewer. Additionally, compared with conventional HRV analyses, ECG-DM (3-minute recording) features a shorter collection time and simpler data processing. However, this novel short-term ECG-DM technology is highly sensitive, such that even minor signal abnormalities can markedly influence the resulting indicators used for comprehensive physiological analysis. The selection of an appropriate heart rate data collection method should consider the specific research design or clinical background. For evaluations of long-term dynamic autonomic function and malignant ventricular arrhythmias following myocardial infarction, conventional long-term HRV analysis is preferred, whereas for analyzing data over shorter durations to provide early warning of potential instantaneous myocardial hypoxic metabolic injury and autonomic function disorder, the short-term method is generally sufficient. Lastly, we did not include antihypertensive and other cardiovascular medications in the confounder analysis due to the relatively small sample size and the limited number of participants receiving such treatments. Nevertheless, potential residual confounding related to medication use cannot be completely excluded.

ECG dispersion mapping is a state-of-the-art developmental technique that enables

noninvasive assessment of myocardial pathology and contributes to pre-nosological diagnosis[171]. In the present study, 3-minute ECG-DM was employed as a novel approach for the early detection of ischemic myocardial metabolic impairment and autonomic dysfunction associated with brain vascular health. Compared with direct ‘‘beat-to-beat’’ long-duration measurement of ECG micro-alternations, this method is much more sensitive and permits assessment under resting conditions. Notably, the 3-minute acquisition aligns with short-term HRV consensus: although a 5-minute resting segment is the conventional standard, methodological studies support reliable estimation of time-domain indices from 2–5-minute recordings under resting conditions[285, 362]. To the best of our knowledge, the 3-minute ECG-dispersion mapping (ECG-DM) protocol has been validated primarily in human studies to date—across community-based and clinical cohorts—focusing on autonomic function and myocardial metabolic assessment. Systematic experimental validation in animal models is still lacking. In the future, rigorous, controlled animal studies are warranted to elucidate the electrophysiological mechanisms and to establish the biological correlates of 3-minute ECG-DM parameters under diverse physiological and pathological conditions. Although other techniques may outperform ECG-DM in diagnosing cardiac disease, potential asymptomatic disturbances in the autonomic regulatory balance of the brain–heart axis and transient hypoxia-related metabolic impairment of the myocardium are more likely driven by rapid changes in cerebral hemodynamics and tissue oxygenation than by disease severity per se. Distinct from many diagnostic modalities and clinical judgment, the 3-minute ECG-DM protocol provides an objective, comprehensive, and highly efficient assessment, is inexpensive to perform, and requires no specialized expertise for interpretation.

Finally, this study is an observational study conducted at a single center, which may introduce selection bias. Further prospective studies with large sample sizes in multiple centers are suggested to validate the clinical application of 3-minute HRV monitoring in identifying

ICAS and other cSVD markers.

7.3 Summary

Intracranial atherosclerosis and cerebral small vessel disease, as major causes of ischemic stroke and increased risk of recurrent stroke, have gained increased attention from diagnosis to treatment. In this thesis, we primarily focus on the correlations between ICAS and cSVD imaging features and cardiac function. We investigated the differences between large artery atherosclerosis and small vessel disease in their associations with myocardial micro-ischemic metabolic function using advanced ECG-DM monitoring and multimodal imaging-based community studies. Future studies should conduct more comprehensive investigations about the effect of ICAS characteristics on the pathophysiology of cognitive and renal function. Multi-centre collaborative research will enable a better understanding of ICAS-related cerebrovascular disorders and benefit individualized screening for more sub-healthy adults.

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