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The Landscape of Brain Artery Network: Database Foundation, Graph Analysis, and Biomarker Application

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Abstract

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The cerebrovascular network plays a critical role in brain health, with its structural and functional characteristics linked to various neurological and cardiovascular conditions. Despite this importance, current approaches to cerebrovascular analysis face significant limitations: they often rely on isolated morphological features that inadequately capture complex network properties, utilize tools with limited 3D manipulation capabilities, lack large-scale harmonized datasets, and employ analytical methods not optimized for vascular networks’ graph-like nature. These limitations hinder our understanding of how cerebrovascular architecture relates to neurological health and disease.

This thesis establishes a comprehensive, reproducible framework for analyzing Brain Artery Networks (BANs) through graph-based approaches, integrating multimodal data to advance neurovascular health understanding across diverse populations. The framework consists of four major contributions. First, we created a harmonized, multi-site BAN dataset accompanied by demographic and clinical metadata, addressing data scarcity and heterogeneity through the development of VesselVoyager—an advanced 3D vessel annotation tool—and ComBat statistical harmonization. Second, we developed and improved advanced imaging sequences (iSNAP and CineMerge) that enable multi-contrast visualization and dynamic assessment of arterial pulsatility within a single acquisition, providing richer vascular characterization beyond static morphology. Third, we implemented specialized graph neu-

ral networks tailored for vascular analysis, including a novel hierarchical graph transformer with edge-aware structural encoding that captures the intrinsic hierarchical organization of arterial networks. Fourth, we identified and validated clinically relevant biomarkers through systematic ablation studies.

The impact of this work includes establishing a foundation for collaborative research through the Brain Artery Visualization & Analysis platform, enabling sophisticated quantitative analyses with lower barriers to entry. The long-term implications extend to precision medicine, where graph-derived vascular biomarkers may facilitate earlier disease detection, more accurate risk stratification, and personalized therapeutic monitoring in cerebrovascular diseases. Methodologically, our framework bridges imaging science and network theory, advancing analytical approaches that naturally represent the complex, interconnected nature of cerebrovascular systems.

While limitations exist in demographic representativeness, imaging resolution, and causal inference capabilities, this thesis represents a significant step toward decoding the rich information contained in brain arterial networks, with the ultimate goal of improving outcomes for individuals affected by cerebrovascular conditions worldwide.

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GLOSSARY

ACA: Anterior Cerebral Artery

ACOMA: Anterior Communicating Artery

ASL: Arterial Spin Labeling, a non-contrast MRI technique for measuring cerebral blood flow

AUC: Area Under the Curve

BAN: Brain Artery Network, the interconnected system of arterial blood vessels in the brain

BAVA: Brain Artery Visualization & Analysis

BMI: Body Mass Index

BOLD: Blood Oxygen Level Dependent

BRAVE: Brain and Vascular Health in the Elderly

CBF: Cerebral Blood Flow

CBV: Cerebral Blood Volume

CNR: Contrast-to-Noise Ratio

COMBAT: Combating Batch Effects, a statistical harmonization method

COW: Circle of Willis, the circular arterial structure at the base of the brain

CROP: Cardiovascular Risk of Older Population

CTA: CT Angiography

DBP: Diastolic Blood Pressure

DMRA: dynamic Magnetic Resonance Angiography

DSA: Digital Subtraction Angiography

DSC: Dynamic Susceptibility Contrast

ECG: Electrocardiogram

FOCI: Frequency Offset Corrected Inversion

FR: Framingham Risk

FRS: Framingham Risk Score

GA: Golden Angle

GAT: Graph Attention Network

GCN: Graph Convolutional Network

GM CBF: Gray Matter Cerebral Blood Flow

GNN: Graph Neural Network

GRE: Gradient Echo

GT: Graph Transformer

HDL: High-Density Lipoprotein

HGT: Hierarchical Graph Transformer

HS: Hyperbolic Secant

HT: Hypertension

ICA: Internal Carotid Artery

ICC: Intraclass Correlation Coefficient

ICAFE: intraCranial Artery Feature Extraction

ISNAP: improved Simultaneous Non-contrast Angiography and intraPlaque hemorrhage

KWIC: K-space Weighted Image Contrast

LDA: Linear Discriminant Analysis

LDL: Low-Density Lipoprotein

LN: Layer Normalization

MAE: Mean Absolute Error

MCA: Middle Cerebral Artery

MIP: Maximum Intensity Projection

MOCA: Montreal Cognitive Assessment

MPR: Multiplanar Reformation

MRA: Magnetic Resonance Angiography

MSDE: Motion-Sensitized Driven Equilibrium

MTT: Mean Transit Time

PC: Phase-Contrast

PCA: Posterior Cerebral Artery

PCOMA: Posterior Communicating Artery

PI: Pulsatility Index, a measure of the variability of blood velocity in a vessel

PPG: Peripheral Pulse Gating

SBP: Systolic Blood Pressure

SMRA: static Magnetic Resonance Angiography

SNAP: Simultaneous Non-contrast Angiography and intraPlaque hemorrhage

SNR: Signal-to-Noise Ratio

SPGR: Spoiled Gradient Echo

SVD: Small Vessel Disease

TC: Total Cholesterol

TMIP: temporal Maximum Intensity Projection

TOF: Time of Flight

TTP: Time-to-Peak

VA: Vertebral Artery

VISTA: Volume Isotropic Turbo spin echo Acquisition

VWI: Vessel Wall Imaging

WML: White Matter Lesion

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DEDICATION

to my dear family

Chapter 1

INTRODUCTION AND MOTIVATION

1.1 Motivation and Clinical Significance

The cerebrovascular network plays a critical role in maintaining brain health, with its structural, morphological, and topological characteristics directly linked to various health outcomes [58, 10]. The brain’s high metabolic demands require a stable and efficient vascular supply, making the integrity of the brain artery network essential for normal brain function. Alterations in brain artery morphology are associated with numerous conditions, from acute events like ischemic stroke and aneurysms to chronic diseases such as hypertension, diabetes, and vascular dementia [40, 83].

Magnetic Resonance Angiography (MRA), particularly Time of Flight (TOF) MRA and Simultaneous Non-contrast Angiography and intraPlaque hemorrhage (SNAP) imaging, enables detailed visualization of arterial structures [44]. These imaging modalities have revealed that subclinical conditions, such as hypertension and diabetes, subtly influence artery structure, contributing to long-term neurovascular impairments [40]. Even subtle changes in vessel structures often precede clinical symptoms, making early detection critical for intervention.

In recent years, the integration of advanced imaging techniques with computational methods has transformed vascular research. However, the quality, consistency, and diversity of available data significantly impact the effectiveness of analytical approaches. For meaningful insights into cerebrovascular health, several key components must be addressed:

First, advanced imaging sequences that provide quantitative and reliable vascular biomarkers are essential for comprehensive neurovascular assessment [19]. Traditional MRA sequences often capture only basic morphological features and may miss critical functional aspects of cerebrovascular health. Novel techniques that integrate hemodynamic information with structural details can provide multi-contrast visualization of intracranial vessels

within a single acquisition. These advanced imaging methods allow for the assessment of not just static vessel morphology but also dynamic properties such as arterial pulsatility—offering insights into vessel wall compliance and mechanical behavior [55]. By moving beyond conventional approaches, these techniques enable more robust quantitative metrics that can serve as reliable biomarkers for brain arterial networks in both research and clinical settings.

Second, tools for 3D vessel annotation and biomarker extraction are crucial for accurate analysis [10]. Conventional approaches for processing cerebrovascular image often rely on two-dimensional methodologies that inadequately represent the complex, convoluted nature of brain arteries. There is a critical need for interactive 3D annotation environments that enable direct tracing and labeling of vessel centerlines within a three-dimensional space. By facilitating more comprehensive and accurate vessel labeling, advanced 3D annotation tools can not only improve dataset quality for clinical assessment but also generate robust training data for advanced machine learning models.

Third, standardized criteria for dataset formation and management are crucial, particularly as datasets scale [25]. Currently, most datasets derive from isolated studies with distinct demographics, protocols, and clinical criteria, limiting the ability to perform robust cross-sectional analyses.

Fourth, scalable models tailored to brain arterial network analysis must be developed [13]. Graph Neural Networks (GNNs) show particular promise due to their ability to represent the network’s inherent connectivity while capturing high-dimensional relationships [72].

Finally, robust evaluation systems and benchmarks enable comparison of methods and tracking of progress in the field [54]. Open-source, publicly accessible datasets accelerate research by allowing researchers worldwide to test hypotheses and validate predictive models without needing to generate extensive datasets independently.

This thesis addresses these challenges by focusing on the brain arterial network as derived from MRA imaging. By developing comprehensive solutions across these domains, we aim to establish a foundation for understanding how cerebrovascular structures relate to neurovascular conditions.

1.2 *Limitations of Current Approaches*

Despite significant advances in vascular imaging and analysis, several critical limitations persist in brain artery network research.

Current analytical approaches often treat vascular features in isolation, overlooking the interconnected nature of arterial networks. Most studies rely on basic morphological features such as vessel length, diameter, and branch count, which inadequately represent the complex three-dimensional structure and connectivity patterns of the brain artery network [78]. These simplified approaches fail to capture spatial relationships between vessel segments and the hierarchical organization of the vascular tree, potentially missing important biomarkers associated with neurovascular health.

The tools available for processing and analyzing brain artery networks also present significant challenges. The existing software for extracting brain arterial networks, such as iCafe (intraCranial Artery Feature Extraction), involves time-consuming labeling processes and limited capability for direct 3D manipulation [10]. This makes it difficult to efficiently process large datasets or perform detailed analyses of complex vascular structures. The semi-automated nature of current tools introduces potential variability in feature extraction, complicating cross-study comparisons.

Perhaps most critically, there is a lack of large, comprehensive, and harmonized brain arterial network datasets. Existing datasets typically derive from isolated studies with distinct demographic profiles, imaging protocols, and clinical criteria [25]. This fragmentation limits the ability to perform robust cross-sectional analyses across diverse populations or to generalize findings across different neurovascular conditions. Additionally, variations in imaging acquisition parameters between studies can introduce technical biases that confound biological signals.

When attempting to connect brain arterial network characteristics with demographic factors and clinical information, researchers face significant methodological challenges. High-dimensional data from 3D vascular structures must be effectively reduced to meaningful features while preserving critical information. Current approaches that rely on extracted morphological features often discard valuable topological information about network con-

nectivity and organization [54].

The machine learning techniques traditionally applied to vascular analysis are often not optimized for the specific characteristics of brain arterial networks. Standard convolutional neural networks or statistical models may not adequately capture the graph-like nature of vascular structures [13], limiting their effectiveness for tasks like disease prediction or biomarker identification.

These limitations underscore the need for novel approaches that can better represent the complex nature of brain arterial networks, harmonize data across studies, and extract meaningful biomarkers that correlate with neurovascular health outcomes.

1.3 Thesis Aims

The overarching goal of this thesis is to establish a reproducible, scalable framework for analyzing brain artery networks as graph structures, integrating multimodal data to advance our understanding of neurovascular health across diverse populations. To achieve this goal, this thesis pursues the following aims:

Aim 1: Establish a Harmonized, Multimodal Dataset for Brain Artery Network Analysis. We will create a comprehensive, harmonized dataset of brain artery networks by integrating structural and morphological data from different MRA protocols with demographic and clinical metadata. This involves:

- Developing VesselVoyager, an advanced tool for 3D artery annotation that improves upon existing software by offering enhanced visualization, real-time 3D interaction, and more efficient processing.
- Constructing a brain artery dataset from magnetic resonance angiography (MRA) across multiple cohorts with distinct health profiles.
- Harmonizing data using the ComBat technique to address scanner- and protocol-induced variability [25], enabling meaningful cross-sectional comparisons.

- Validating reproducibility through scan-rescan assessments and sensitivity testing using longitudinal data.

Aim 2: Develop Advanced Imaging Sequences for Enhanced Vascular Characterization. To overcome limitations in current imaging techniques, we will:

- Develop the iSNAP sequence for improved artery characterization, combining the benefits of both TOF and SNAP imaging.
- Create the CineMerge sequence for capturing arterial pulsatility [55], providing dynamic information about vascular function.
- Compare these advanced sequences with traditional Time-of-Flight imaging to assess improvements in biomarker detection and reliability.

Aim 3: Develop Graph-based Analytical Pipelines for Predicting Neurovascular Health Outcomes. We will create specialized analytical frameworks that leverage the structural properties of brain artery networks through:

- Modeling brain arteries as graph structures with nodes representing bifurcations or endpoints and edges representing arterial segments [54].
- Developing a graph model for hemodynamic analysis in the Circle of Willis, capturing blood flow dynamics and directional information.
- Implementing Graph Neural Networks (GNNs) tailored for vascular analysis [13, 72] to extract high-dimensional features and identify patterns associated with neurovascular health.

Aim 4: Discover and Validate Clinical Biomarkers Derived from Brain Arterial Networks. Finally, we will:

- Conduct systematic feature importance studies to identify the most relevant aspects of brain arterial networks for various clinical outcomes.

- Analyze task-specific patterns related to conditions such as hypertension [40], cognitive impairment [83], and aging.

By addressing these aims, this thesis will establish not only valuable datasets and tools for the neurovascular research community but also novel analytical methods that can more effectively extract clinical insights from brain arterial networks. The ultimate goal is to advance our understanding of cerebrovascular health and disease, potentially informing early diagnostic approaches and personalized interventions.

1.4 Outline of Thesis

This thesis is organized into seven chapters that progressively build upon each other to develop a comprehensive framework for brain arterial network analysis.

Chapter 1 introduces the motivation and clinical significance of studying brain arterial networks, outlines the limitations of current approaches, and presents the specific aims of this research. This chapter establishes the importance of developing improved methods for analyzing cerebrovascular structures and their relationship to neurovascular health.

Chapter 2 provides essential background information and a review of related work. It begins by describing cerebrovascular structures and the imaging modalities used to visualize them, with particular attention to MRA techniques [44]. The chapter then explores graph-based models and their applications in biomedical research, current vascular imaging biomarkers, and identifies gaps in existing knowledge that this thesis aims to address.

Chapter 3 details the curation of a large-scale arterial network dataset, which forms the foundation for subsequent analyses. After introducing the general principles of dataset curation, this chapter describes the diverse data sources incorporated and their characteristics. It presents the development and implementation of VesselVoyager, an advanced tool for 3D vessel annotation, and discusses scanner effects encountered in large-scale multi-center dataset creation along with their solutions.

Chapter 4 explores advanced imaging sequences developed to enhance vascular characterization. It introduces the rationale for moving beyond traditional imaging approaches and details the development of the iSNAP sequence for improved artery characterization

and the CineMerge sequence for capturing arterial pulsatility. These novel sequences are compared with traditional TOF-MRA to demonstrate their advantages, followed by a discussion of limitations and implications for large-scale studies.

Chapter 5 presents graph-based approaches for arterial network analysis, the core methodological contribution of this thesis. After introducing graph-based models, it details a specialized graph model for hemodynamic analysis in the Circle of Willis and describes the implementation of GNNs for comprehensive vascular analysis. The chapter outlines training and validation strategies, evaluates performance through model comparisons, and discusses methodological considerations and limitations.

Chapter 6 focuses on clinical biomarker discovery from brain arterial networks. It begins by establishing the significance of biomarker discovery in neurovascular research and presents systematic ablation and feature importance studies.

Chapter 7 synthesizes the findings and contributions of the thesis through discussion and strategic integration. It summarizes the key contributions, explores their broader clinical and methodological implications, acknowledges limitations, and offers reflections on the research. The chapter concludes by identifying promising directions for future work in brain arterial network analysis and neurovascular health research.

Together, these chapters present a comprehensive approach to analyzing brain arterial networks, from dataset curation and advanced imaging to computational modeling and clinical applications. This structure reflects the interdisciplinary nature of the research, integrating techniques from medical imaging, computer vision, machine learning, and clinical neuroscience to advance our understanding of cerebrovascular health.

Chapter 2

BACKGROUND AND RELATED WORK

2.1 Cerebrovascular Structure and Imaging Modalities

The cerebral circulation comprises anterior and posterior systems that unite via the Circle of Willis (CoW), creating potential collateral pathways in case of vascular insufficiency. The anterior circulation originates from the internal carotid arteries (ICAs), which branch into the anterior cerebral arteries (ACAs) and middle cerebral arteries (MCAs). Posteriorly, the vertebral arteries converge to form the basilar artery, which bifurcates into the posterior cerebral arteries (PCAs). These vessels connect through communicating arteries at the base of the brain, classically forming a complete circle [32, 41].

Despite this canonical description, individual variations are common. The posterior communicating arteries, as well as segments of the ACAs or PCAs, may be hypoplastic or absent. Such configurations reduce collateral capacity and can elevate the risk of ischemic events. Although many variants remain clinically silent, they hold significance in neurosurgical planning and risk assessment, particularly when dealing with endovascular procedures or identifying aneurysm-prone sites.

2.1.1 Non-Contrast MRA

MRA allows for noninvasive vascular imaging without ionizing radiation or exogenous contrast. TOF-MRA, a typical bright-blood technique, highlights inflowing blood spins against a saturated background, yielding a high-signal vascular lumen [73, 23]. Although TOF-MRA provides reliable visualization of major intracranial arteries, small-vessel resolution and slow-flow states can pose challenges. In contrast, alternative modalities such as CT angiography (CTA) or digital subtraction angiography (DSA) may offer higher spatial resolution or dynamic flow assessment, but involve radiation exposure and, in the case of DSA, invasiveness.

2.1.2 *Bright-Blood vs. Black-Blood MR Angiography*

Bright-blood imaging. TOF-MRA exemplifies the bright-blood family of techniques. By repeatedly exciting stationary tissues within an imaging slab, background signal is saturated while fresh blood flowing from outside appears hyperintense. This mechanism makes TOF-MRA well-suited to depict patent arteries in the CoW and major branches with no need for contrast agents.

Black-blood imaging. Black-blood methods invert or null blood signal so that flowing blood appears dark, facilitating detailed vessel wall assessment. Simultaneous Non-contrast Angiography and intraPlaque hemorrhage (SNAP) is a well-known example, using an inversion recovery pulse to suppress moving blood while enhancing signals from hemorrhagic plaque [36]. The sequence provides comprehensive information about luminal caliber and plaque composition within one scan.

2.1.3 *iSNAP: Multi-Contrast Neurovascular Imaging*

As an evolution of SNAP, iSNAP integrates both bright-blood and black-blood contrasts in a single sequence [12]. By applying specialized inversion pulses and leveraging sophisticated reconstruction algorithms, iSNAP generates multiple image types—such as angiographic, vessel wall, and dynamic flow views—from a single acquisition. This unified approach holds promise for streamlining neurovascular workups, as clinicians can simultaneously evaluate arterial patency, plaque features, and flow patterns without multiple scans.

Summary: The arrangement of the cerebral vasculature, together with frequent anatomic variants, underscores the need for precise imaging techniques. Non-contrast TOF-MRA remains an indispensable tool for visualizing intracranial arteries safely, and black-blood sequences such as SNAP enhance vessel wall analysis by nulling luminal signal. Building on these technologies, iSNAP further consolidates bright-blood and black-blood information into a single exam, reflecting current trends toward more comprehensive and time-efficient neurovascular assessments.

2.2 Existing Arterial Network Datasets

Several open or partially restricted datasets provide human brain arterial imaging data, including TOF-MRA. These resources play pivotal roles in method development, validation, and reproducibility. This section categorizes relevant datasets into those offering primarily *raw* arterial scans and those furnishing *processed* data (e.g., vessel segmentations or annotations). Table 2.1 summarizes key attributes.

2.2.1 Raw Arterial Data Only

IXI Dataset [28]: The Internet Brain Segmentation Repository (IBSR) and IXI initiative provide a mix of MR data from multiple centers in London. A subset includes 600 three-dimensional TOF-MRA volumes for several hundred healthy adults. Demographic metadata (age, sex) are available, but no ground-truth vascular segmentation or explicit pathology labels are included. Studies often utilize IXI MRA for testing vessel tracking algorithms or establishing normative arterial morphometry. The multi-center acquisition, however, introduces scanner- and protocol-related variability.

NITRC MRA Atlas Dataset [33]: Hosted on the Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC), this collection contains high-resolution (~ 0.62 mm isotropic) TOF-MRA scans of 61 healthy subjects aged 19–64. It was initially used to create a vascular atlas, but mainly offers raw data without comprehensive vessel annotations. The focus on healthy volunteers and consistent 3T protocol make it suitable as a high-fidelity reference set for normal cerebrovascular structure.

2.2.2 Raw Data with Processed Outputs

UNC CASILab (Bullitt) Dataset [7]: A foundational resource of 109 healthy volunteers, each with 3D TOF-MRA and corresponding *manually curated* segmentations of the entire intracranial arterial tree. The published dataset includes centerline coordinates, vessel radii, and branch connectivity. Although its sample size is modest, the meticulous labeling has enabled decades of reproducible algorithm comparisons, particularly for arterial segmentation.

CHUV Lausanne Aneurysm TOF-MRA [15]: This open dataset (hosted on Open-Neuro) features 284 individuals, including 157 patients harboring intracranial aneurysms and 127 controls. High-resolution TOF-MRA volumes are available, accompanied by clinical annotations indicating aneurysm presence and approximate location. Such explicit disease labeling supports the training of computer-aided detection models and fosters research into aneurysm prevalence, morphology, and risk stratification.

RBWH Aneurysm MRA [14]: Collected at the Royal Brisbane and Women’s Hospital, this set contains 63 patient TOF-MRA scans (with 85 documented intracranial aneurysms). A unique facet is the inclusion of follow-up scans in some cases, enabling investigations of aneurysm growth or morphological changes over time. While smaller than the Lausanne dataset, its longitudinal dimension is valuable for temporal analyses.

ADAM Challenge Dataset [65]: Initiated for an aneurysm detection and segmentation competition, ADAM comprises 113 multi-center TOF-MRA studies: 93 with unruptured aneurysms and 20 healthy controls. Organizers supply ground-truth lesion masks, making it a benchmark for developing and comparing automated aneurysm segmentation algorithms. Although publicly accessible post-challenge, requests may be required for complete data packages.

COSTA Multi-center TOF-MRA [49]: A comprehensive collection comprising 423 TOF-MRA volumes acquired from eight different centers using MRI scanners from four distinct vendors at both 1.5T and 3.0T field strengths. The dataset features exceptional diversity in acquisition parameters, including various physical resolutions ranging from $0.20 \times 0.20 \times 0.40 \text{ mm}^3$ to $0.62 \times 0.62 \times 0.62 \text{ mm}^3$ and different matrix sizes. This heterogeneity makes COSTA particularly valuable for developing algorithms robust to variations in image quality and scanner characteristics. While the dataset provides expert-annotated vessel segmentation masks for major intracranial arteries, it lacks vessel-specific labeling, demographic information, and clinical data, which limits its utility for detailed vessel-type analysis or clinical correlation studies. The dataset includes previously described IXI subsets, ADAM, and NITRC (ICBM) collections, providing consistent ground truth segmentations across this diverse range of acquisition parameters.

Table 2.1: Representative Human TOF-MRA Datasets for Brain Arterial Imaging

Dataset	Subjects	Data Provided
IXI [28]	~600 (healthy)	Raw volumes only
NITRC [33]	61 (healthy)	Raw volumes only
UNC [7]	109 (healthy)	Raw + vessel trees
CHUV [15]	284 (aneurysm + control)	Raw + pathology labels
RBWH [14]	63 (aneurysm patients)	Raw + pathology labels, some follow-up
ADAM [65]	113 (aneurysm + control)	Raw + lesion masks (challenge)
COSTA [49]	423 (mixed)	Raw + vessel segmentations

2.2.3 Impact on Cerebrovascular Research

Access to these publicly shared or semi-open datasets has significantly advanced the field. *Raw-data-only* collections, such as IXI, enable normative studies of healthy arterial anatomy, albeit requiring in-house vessel extraction pipelines. In contrast, resources that *provide processed segmentations* (UNC CASILab, COSTA) or detailed lesion annotations (CHUV Lausanne, RBWH, ADAM) drastically reduce the labor of ground-truth labeling, accelerating the development of automated methods for arterial segmentation, aneurysm detection, and morphological analysis. The Lausanne dataset further highlight how disease-focused imaging, complete with demographic and clinical information, allows sophisticated clinical or biomechanical inferences.

Despite these benefits, several challenges persist. Many datasets remain modest in scale, and heterogeneous scanning protocols complicate cross-study comparisons. Large multi-center initiatives like COSTA partially address these issues by offering standardized annotations.

Summary: The proliferation of open-access arterial imaging datasets has facilitated rapid advances in vessel segmentation and arterial network analysis. Collections covering both *raw* TOF scans and *processed* labels or segmentations provide essential testbeds for reproducible research. While practical constraints (e.g., heterogeneous protocols, moderate sample sizes)

remain, these datasets collectively serve as a cornerstone for developing robust, data-driven approaches to studying the structural and pathological aspects of the cerebral vasculature.

2.3 Graph-based Models in Vascular Research

Graph-based approaches have emerged as powerful tools for both *processing* vascular imaging data and *analyzing* the topological and structural characteristics of the vascular system. This section reviews representative high-impact works, with an emphasis on the cerebral vasculature but also drawing insights from related domains (e.g., retinal or tumor vasculature). We broadly divide the literature into two categories: *graph-based vascular processing* and *graph-based vascular analysis*. While the first category focuses on segmentation, centerline extraction, and anatomical labeling, the second category delves more deeply into topological patterns, morphological quantifications, and recent explorations using Graph Neural Networks (GNNs).

2.3.1 Graph-based Vascular Processing

Graph-centric methods have long been used for tasks such as vessel segmentation and centerline extraction. These methods typically treat voxel intensities and geometric cues as a graph, where edges capture local continuity or gradient-based costs. More recent studies incorporate deep learning, either by fusing graph insights with convolutional neural networks or by training GNNs directly on node-edge representations of the vasculature.

Segmentation and Centerline Extraction.

- **Tensor-Cut Graph Segmentation** [68]: Wang *et al.* proposed a graph-cut framework that embeds local tensor information to enhance vessel segmentation on CT angiography. By modeling each voxel with second-order tensors, the approach achieved accurate extraction of thin vessels (~ 1 mm radius), demonstrating higher overlap metrics compared to conventional cut-based methods.
- **Graph-Integrated Deep Segmentation** [60]: Shin *et al.* presented a CNN-GCN hybrid network where global vascular connectivity constraints are integrated into a

standard convolutional pipeline. Applied to retinal angiography and coronary X-ray angiography, the method reduced discontinuities in the final vessel masks, highlighting the benefit of graph awareness in segmentation.

- **DeepVesselNet** [63]: Tetteh *et al.* developed a 3D deep learning pipeline for *both* vessel segmentation and centerline extraction on TOF-MRA of the human brain (and micro-CT in animal models). Their specialized training strategies addressed class imbalance and improved continuity, resulting in robust vessel skeletons suited for subsequent topological analysis.

Anatomical Labeling of Vessel Trees. After extracting vessel masks or centerlines, labeling each segment by its anatomical designation remains nontrivial, especially under anatomical variation or pathologies.

- **GNN-Based Intracranial Artery Labeling** [9]: Using a dataset of 729 MR angiograms, Chen *et al.* constructed a node-edge graph for each vessel tree (bifurcations and branch segments as nodes/edges). A GNN then classified each segment into known artery types (e.g., ACA, MCA, PCA) with 97.5% node-level accuracy. This method was robust to CoW variants and offered a near-fully automated labeling workflow.
- **Deep Ensemble for Comprehensive Cerebral Labeling** [24]: Hong *et al.* developed an ensemble approach combining geometric preprocessing and multiple neural networks to label full cerebral arterial trees from TOF-MRA. By aligning vascular orientations and stacking segment-wise classifications, they reached 90–99% labeling accuracy across major vessels, including distal branches.

Graph-based methods in this domain thereby streamline the *entire* processing pipeline—from raw angiograms to detailed labeled vessel trees. The resulting node-edge representations lay a solid foundation for advanced structural or hemodynamic analyses.

2.3.2 Graph-based Vascular Analysis

Beyond processing, graph representations enable quantitative evaluations of vascular *topology, morphology, and function*. Early approaches utilized classical graph metrics (e.g., branching frequency, diameter distributions, connectivity), while recent works incorporate topological data analysis (TDA) and GNNs to reveal deeper insights.

Traditional Graph-theoretic and Topological Methods.

- **Cerebral Artery Morphometrics** [7]: In a foundational study, Bullitt *et al.* extracted arterial networks from MR angiograms of healthy adults, measuring vessel counts, lengths, radii, and tortuosities. Their analysis revealed region-specific statistical distributions in anterior *vs.* posterior circulations, providing baseline references for normal variability.
- **Persistent Homology in Brain Arterial Trees** [4]: Bendich *et al.* applied topological data analysis to the Bullitt dataset, characterizing loops and branches at varying scales. They uncovered stronger sex and age effects on vascular shape than conventional metrics had detected, illustrating the potential of TDA for capturing subtle topological variations.
- **Whole-Brain Microvascular Connectomics** [30]: Ji *et al.* constructed detailed microvascular graphs in mouse brains, showing that a largely uniform capillary topology allows for robust perfusion despite localized vessel pruning. Although performed in animal models, these insights demonstrate how analyzing global connectivity can inform vascular resilience in the cerebral cortex.

Such classical graph analyses have elucidated how vascular networks behave under normal and pathological conditions (e.g., tumor angiogenesis, microstroke simulations). They quantify geometric properties (e.g., length, radius, branching angles) or topological features (loops, connectivity) that may serve as biomarkers for disease.

Emergence of GNNs. The incorporation of GNNs has opened new frontiers in vascular analysis, enabling direct learning from graph-structured data:

- **Retinal GNN for Disease Prediction** [43]: Lux *et al.* modeled retinal vasculature as a heterogeneous graph (vessel segments, foveal zone) and employed GNNs to diagnose diabetic retinopathy. This yielded both improved predictive accuracy and greater interpretability, underscoring the potential for GNNs to learn clinically salient vessel patterns.
- **Aneurysm Rupture Risk via Graph Features** [51]: Niemann *et al.* constructed a semantic graph from intracranial aneurysm scans, integrating morphological attributes (e.g., curvature, torsion) within parent artery segments. Their model achieved 83% accuracy in classifying rupture status, highlighting how graph-based context can enhance clinical risk assessment.

Although GNN-based studies of *cerebral* vascular networks are relatively recent, initial results suggest that combining node-edge connectivity with deep feature extraction can reveal disease-specific patterns not captured by simpler descriptors. In the future, GNNs may facilitate advanced tasks such as predicting stroke risk, mapping collateral flow, and identifying microvascular abnormalities.

Summary: Graph-based models have become indispensable in vascular imaging research. At the *processing* level, graph algorithms (often combined with deep learning) streamline vessel segmentation, centerline extraction, and anatomical labeling. They convert volumetric angiograms into structured node-edge representations. At the *analysis* level, classical graph metrics and topological descriptors illuminate fundamental vascular architecture and disease-induced changes, whereas modern GNN frameworks provide a data-driven path to discovering predictive patterns in complex vascular networks. By treating the cerebral vasculature as a graph, these methods bridge the gap between raw imaging data and high-level inferences about cerebral blood supply and pathology.

2.4 *Current Vascular Imaging Biomarkers in MRI*

Despite the complexity of cerebrovascular function, MRI biomarkers for vascular assessment can be broadly considered in two interlinked domains: morphological biomarkers and functional biomarkers. In reality, structure and flow profoundly influence each other: distal artery patency, for instance, may reflect both the vessel’s morphological resilience and its hemodynamic environment [57]. This section highlights key biomarkers in each category, focusing on non-contrast MRI protocols where possible.

2.4.1 *Morphological Biomarkers*

Morphological biomarkers are derived from vessel geometry on bright-blood angiography, primarily using TOF-MRA or contrast-enhanced MRA techniques.

Vessel Geometry and Morphometrics

Definition & Relevance. Metrics such as vessel length, diameter, branch number, and tortuosity capture how the cerebral arteries adapt or deteriorate under different pathophysiological conditions [6]. Changes in distal artery patency, for instance, can reflect a cumulative effect of hemodynamic alterations and structural remodeling [7].

MRI Extraction. Geometric descriptors are typically derived from 3D angiographic data (e.g., TOF-MRA). Automated or semi-automated pipelines [24, 9] can skeletonize vessels and compute diameters or segment lengths. While such measurements historically focus on larger arteries, improved resolution can reveal smaller branches and thus more granular morphological changes.

Vessel Wall Properties

Definition & Relevance. Wall thickness, plaque distribution, and arterial wall pulsatility are increasingly recognized as markers for intracranial atherosclerosis and other vasculopathies [45]. Vessel walls that enhance post-contrast or demonstrate intraplaque hemorrhage on T1-weighted images suggest unstable, high-risk lesions.

MRI Extraction. Advanced *black-blood* sequences such as SNAP or MERGE null the lumen signal to highlight the arterial wall [36, 46]. By measuring wall thickness or enhancement, clinicians can differentiate atherosclerotic plaques from vasculitis. While these approaches offer high diagnostic value, they require extended scan times and careful parameter selection.

2.4.2 Functional Biomarkers

Flow functional biomarkers are mainly obtained from phase-contrast or spin-label techniques that encode hemodynamics.

Velocity, Flow Rate, and Pulsatility

Definition & Relevance. Blood flow velocity, volumetric flow rate, and pulsatility index (PI) are foundational measures of cerebral hemodynamics. Elevated PI in major intracranial arteries has been correlated with microvascular damage, leukoaraiosis, and increased risk of small vessel disease (SVD) [48]. Conversely, reduced flow in the middle cerebral artery can be an indicator of upstream stenosis or insufficient collateral flow [5].

MRI Extraction. Non-contrast *4D Flow MRI*, an extension of phase-contrast MRI, quantifies velocity fields throughout a volume over the cardiac cycle [74, 47]. It allows retrospective analysis of large artery segment for flow waveform, volumetric rates, and derived indices like wall shear stress. Alternatively, single-slice or 2D phase-contrast sequences can assess flow in specific vessels with shorter scan times, albeit with limited spatial coverage. In addition, 4D Flow acquisitions remain relatively lengthy and demand specialized post-processing.

Transit Times and Perfusion Indices

Definition & Relevance. Transit time biomarkers (e.g., arterial arrival time) and perfusion metrics such as cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT) characterize blood delivery to the tissue. Prolonged transit or reduced CBF often signals underlying arterial stenosis or collateral insufficiency [39]. These measures

are critical in stroke imaging and chronic ischemia assessments.

MRI Extraction. *Arterial spin labeling (ASL)* exploits labeled inflowing spins as an endogenous tracer, enabling entirely non-contrast evaluation of tissue perfusion and arterial arrival times [1]. Time-resolved ASL techniques can produce dynamic angiograms (4D MRA), which illustrate labeled blood transit in cerebral vessels over multiple delay times. *Dynamic susceptibility contrast (DSC)* perfusion MRI similarly provides CBF and MTT maps by analyzing gadolinium bolus transit but requires contrast injection [22].

2.4.3 Comparison of Biomarker Categories

In combination, both biomarker classes furnish a more complete picture of cerebrovascular health. While TOF-MRA’s practical balance of speed, resolution, and simplicity ensures its continued clinical dominance, advanced biomarkers offer unprecedented insights despite requiring longer acquisition times, specialized expertise, and occasionally contrast agents.

2.5 Vascular Imaging Biomarkers and Their Clinical Associations

Modern cerebrovascular MRI permits the extraction of two broad classes of quantitative biomarkers:

1. **Morphological biomarkers**, derived from vessel geometry on bright-blood angiography (e.g. TOF-MRA or contrast-enhanced MRA). These include segment length, mean or maximal diameter, branch count, and tortuosity.
2. **Functional biomarkers**, obtained from phase-contrast or spin-label techniques that encode haemodynamics, such as time-resolved flow velocity, PI, and tissue perfusion.

Here, we summarise the evidence linking each class of biomarker to three key outcomes: (i) aging, (ii) cognitive function, and (iii) common vascular risk factors such as hypertension.

2.5.1 Morphological Biomarkers

Aging

Large cross-sectional cohorts have shown a clear age-related increase in intracranial vessel tortuosity and segment length, together with progressive dilation of major conductance arteries (e.g. basilar and internal carotid) [7]. In a high-resolution TOF-MRA study of 356 community adults, odds of marked carotid tortuosity were $\approx$ 5-fold higher in the oldest tertile than in the youngest [64].

Cognitive function

Elevated blood pressure in late life has differing effects on brain structure and cognitive function depending on midlife hypertension history [50]. For instance, individuals without midlife hypertension showed a stronger link between higher late-life BP and white matter lesions, whereas lower diastolic BP in those with midlife hypertension was associated with smaller brain volumes and poorer memory. Meanwhile, arterial pulsatility drives glymphatic clearance of neurotoxic solutes, suggesting that disruptions in normal vascular pulsations may facilitate harmful protein accumulations [27]. Finally, cerebral blood flow declines 0.3–0.5% annually in healthy aging, accelerating to 2–5% in Alzheimer’s disease, underscoring its role in pathological brain changes [20].

Hypertension and other risk factors

Lifetime hypertension exacerbates both arterial dilatation and tortuosity, reflecting chronic wall remodelling and loss of elastin [7, 64]. Conversely, patients on consistent antihypertensive therapy exhibit significantly lower tortuosity indices than untreated counterparts [64]. Type-2 diabetes and smoking show weaker but still measurable associations with larger intracranial diameters and branch rarefaction [42].

2.5.2 Functional Biomarkers

Aging

Phase-contrast and 4D-flow MRI consistently demonstrate that arterial PI and central flow waveform amplitude rise with age, mirroring systemic arterial stiffening [27]. ASL studies report a gradual $\sim 0.3\text{--}0.5\%$ /year decline in whole-brain perfusion in otherwise healthy adults [20].

Cognitive function

Elevated intracranial pulsatility and reduced cerebral blood flow both predict declines in memory and executive performance, likely through microvascular damage, impaired waste clearance, and diminished nutrient delivery to the brain. The study demonstrated that normal pulsations are crucial for glymphatic drainage and clearance of neurotoxic metabolites [27], while Graff et al. [20] linked heightened pulsatility index and lower regional perfusion to poorer cognition. Echoing these findings, another study [50] showed that each standard deviation decrease in baseline cerebral blood flow conferred a 31% higher risk of future dementia, underscoring the pivotal role of vascular health in maintaining cognitive function.

Hypertension and other risk factors

Chronic hypertension intensifies the pulsatile nature of blood flow in the brain and diminishes the brain's ability to maintain adequate blood supply (perfusion reserve) by causing damage to the small penetrating arteries. Research indicates that older adults with a history of hypertension who exhibit the highest pulsatility index (PI) also experience the most rapid decline over time in processing speed and the integrity of their white matter [50].

Morphological vs. Functional Biomarkers

Morphological metrics benefit from *stable, widely available* bright-blood acquisitions (TOF-MRA) and therefore exist in large, multi-centre datasets. Functional biomarkers, by contrast, rely on specialised 4D-flow, phase-contrast, or ASL sequences that are still predominantly research-oriented; sample sizes remain modest and protocols heterogeneous. Never-

theless, functional metrics provide complementary pathophysiological insight—arterial stiffness, distal perfusion, neurovascular coupling—that cannot be inferred from vessel geometry alone.

Chapter 3

LARGE-SCALE ARTERIAL NETWORK DATASET CURATION

3.1 Introduction to Dataset Curation

The complex architecture of Brain Artery Networks (BANs) is critical for maintaining brain function, and alterations in these networks are implicated in aging, hypertension, and diverse neurological diseases [40]. Despite this importance, a significant gap hinders the advancement of neurovascular research: the lack of large-scale, publicly accessible BAN datasets that are diverse, deeply phenotyped with both vascular and clinical information, and rigorously harmonized across different acquisition sources. This scarcity limits the development and validation of robust computational models, such as Graph Neural Networks (GNNs), needed to unravel the complex links between vascular structure and brain health outcomes.

Foundational pipelines for processing Magnetic Resonance Angiography (MRA) data and extracting quantitative vascular features have been established, with notable contributions like the iCafe toolkit providing methods for automated tracing and analysis [10]. However, challenges related to dataset scale, population diversity, annotation efficiency for complex vasculatures, cross-scanner data consistency, and unified data accessibility persisted. This thesis directly confronts these challenges. This chapter details the comprehensive effort undertaken to curate a large-scale BAN dataset, specifically designed to bridge the existing gap and enable next-generation neurovascular analysis. The core contributions described herein encompass: (1) the strategic integration of multi-source data, (2) the development and validation of an enhanced annotation tool, VesselVoyager, (3) the creation of an accessible web-based platform, for data visualization and dissemination, and (4) the application of robust statistical harmonization techniques to ensure feature integrity.

The creation process began with aggregating MRA datasets from several pertinent studies [11, 40]. The resulting cohort primarily consists of middle-to-late aged individuals (55 years and older) of East Asian descent, representing a spectrum from community-dwelling

individuals without overt severe cardiovascular diseases. To handle the intricate task of feature extraction across this large dataset, we developed and employed VesselVoyager, a 3D interactive annotation platform demonstrated to be significantly more efficient, particularly for distal vessels, compared to previous slice-by-slice approaches iCafe. To maximize the utility and reach of this curated resource, we developed the Brain Artery Visualization & Analysis (BAVA) platform, providing interactive tools for data filtering, 3D visualization, and facilitating data access for the research community via linked repositories. Finally, addressing the critical issue of data heterogeneity inherent in multi-site studies, we implemented the ComBat harmonization algorithm [16] to statistically adjust for scanner-induced variations in key vascular morphological features.

The outcome of these integrated efforts is a unique, large-scale, harmonized BAN dataset. It combines detailed graph-based representations of cerebrovascular networks—rich in morphological and topological features—with extensive clinical and demographic metadata. Made accessible through the BAVA platform and public archives, this resource is poised to significantly lower the barrier for sophisticated quantitative analyses, foster reproducible research, and accelerate discoveries in cerebrovascular structure, function, and its relation to brain health and disease across the lifespan.

3.2 Data Sources and Characteristics

The curated dataset integrates data from three cohorts with distinct demographic and clinical characteristics:

1. The Brain and Vascular Health in the Elderly (BRAVE) study, which included 167 older males (≥ 55 years) with essential hypertension but without clinically overt neurological, cardio- or cerebrovascular disease [40].
2. The Cardiovascular Risk of Older Population (CROP) study, comprising 113 community-dwelling older adults (age 56-85 years, mean 71.6 ± 5.9 years) without recent cardiovascular symptoms [11].
3. An unpublished cohort from the Catholic University of Korea that included patients

diagnosed with 122 Alzheimer’s disease dementia and amnestic mild cognitive impairment between March 2017 and November 2020 (Korean Dementia Study).

Table 3.1 summarizes the key demographic and clinical characteristics of the integrated dataset.

Table 3.1: Demographic and Clinical Characteristics of Integrated BAN Dataset

Characteristic	BRAVE (n=167)	CROP (n=113)	Korean Dementia (n=122)
Age (years)	64.9±7.2	71.6±5.9	73.2±6.8
Male sex (%)	100	45.4	41.8
Hypertension (%)	100	49.4	59.2
Diabetes (%)	20.1	18.5	25.5
Hyperlipidemia (%)	–	64.8	62.2

All participants underwent 3D time-of-flight (TOF) magnetic resonance angiography (MRA) with standardized imaging parameters. The typical MRA parameters included: TR/TE = 25/3.5 ms, flip angle = 20°, in-plane resolution = 0.35-0.5 mm, and slice thickness = 0.7-1.4 mm. Images were acquired on 1.5 T and 3.0T scanners from major vendors (Philips, GE, Siemens, and Hitachi).

Artery centerlines were extracted using intraCranial Artery Feature Extraction (iCafe) [10] to create the BAN dataset, which enables comprehensive quantification of vascular features. As illustrated in Figure 3.1, the dataset includes: (a) demographic and clinical data with detailed risk factors; (b) raw and processed imaging data in multiple formats; (c) benchmark tasks for risk prediction; and (d) visualization of global and local vasculature patterns.

For each subject, a rich set of vascular features was extracted, including:

1. Morphometry features: number of branches, total artery length, average diameter, artery volume, tortuosity, and bifurcation angles.

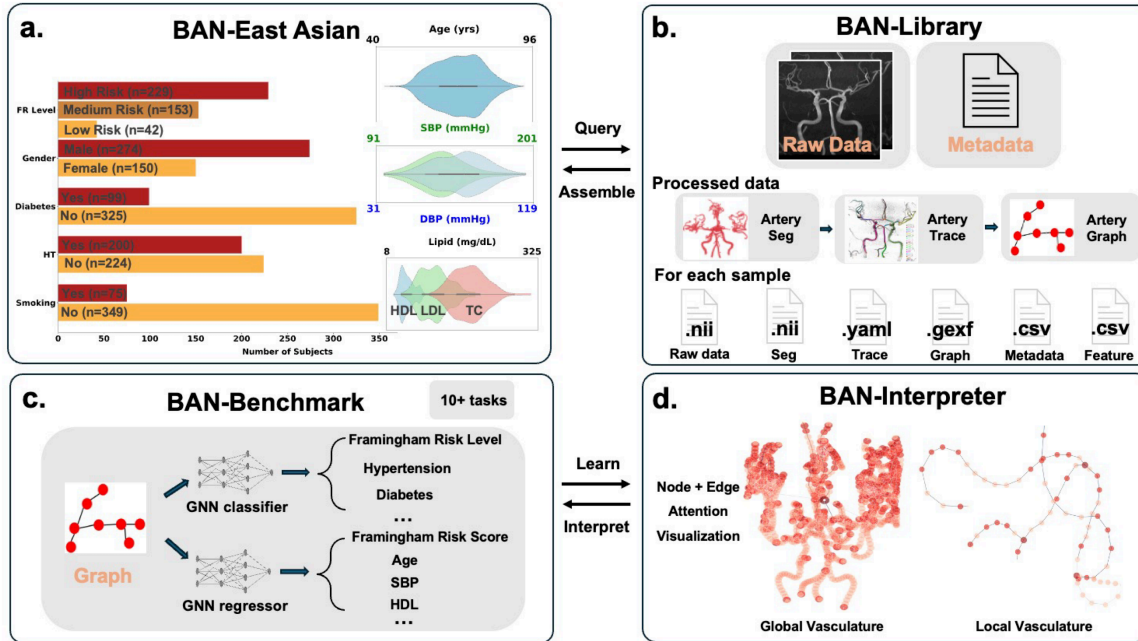


Figure 3.1: Overview of the BAN dataset and benchmark. (a) BAN-Overview: Demographic and clinical characteristics of the dataset, including Framingham Risk Score (FRS), gender, diabetes, hypertension (HT), smoking status, and distributions of age, blood pressure (SBP, DBP), and lipid levels (HDL, LDL, TC). (b) BAN-Library: A database containing raw MRA images, artery segmentation, traced artery centerlines, and graph representations, with corresponding metadata and extracted features. (c) BAN-Benchmark: A suite of GNN models for predictive tasks. (d) BAN-Interpreter: Visualization of node- and edge-level attention from attention-based GNN, enabling interpretation of global and local vascular structures that contribute to cardiovascular risk assessment.

2. Topological features: vessel hierarchy, connectivity patterns, and branching order.

3. Flow-related features: normalized signal intensity in TOF MRA.

The dataset captures the complete cerebral arterial tree, including the anterior cerebral arteries (ACA), middle cerebral arteries (MCA), posterior cerebral arteries (PCA), and their branches. These were further categorized into proximal segments (A1, M1, P1) and distal segments (A2+, M2+, P2+) to enable region-specific analyses.

3.3 VesselVoyager Development and Implementation

VesselVoyager is an interactive 3D platform for annotating, visualizing, and quantifying intracranial arteries from MR angiography (MRA). Its design addresses limitations of conventional 3D vessel-tracing methods by providing real-time volumetric rendering, local signal enhancement, and automated morphometric computations. This section is divided into two parts: (1) *Technical Description and Capabilities*, and (2) *Validation and Reproducibility Studies*.

3.3.1 Technical Description and Capabilities

Motivation. Existing tools such as iCafe [10] and 3D Slicer [56] typically rely on slice-by-slice approaches for vessel annotation, which can be time-consuming and prone to missing small or tortuous arteries. Although iCafe has several 3D annotation functions (merge, cut, connect, etc.), it cannot create a separate trace directly in 3D. To overcome these challenges, we developed VesselVoyager with the following goals:

- **Introduce Direct 3D Centerline Annotation:** To address the core limitation of existing tools by enabling users to define and create vessel centerlines directly and intuitively within a real-time 3D volumetric rendering of the MRA data.
- **Boost Annotation Efficiency and Accuracy:** Significantly reduce annotation time and improve the accurate capture of the complete vascular tree, especially challenging distal, tortuous, or low-contrast segments.

Design Principles. VesselVoyager leverages the inherently high-contrast signal of time-of-flight (TOF) MRA to build a real-time maximum intensity projection (MIP) for 3D navigation and annotation (Fig. 3.2). An *arcball* camera model allows users to orbit, zoom, and pan around the cerebrovascular tree. Key features include:

- **3D Camera System:** Integrates vessel signal detection to position centerline points directly in three-dimensional space.

- **Local Enhancement:** Selectively boosts intensities of faint vessel segments, mitigating misclassification issues from partial-volume or low flow.
- **Cross-sectional Verification:** A side panel automatically displays orthogonal slices for each selected centerline point, confirming lumen-center alignment.
- **Flexible Labeling and Editing:** Users can split or merge centerlines, mark bifurcations, and assign vessel-type labels (e.g., ACA, MCA) or custom designations.
- **Graph-Based Network Analysis:** Transforms annotated centerlines into a mathematical graph structure, enabling advanced topological analysis of the cerebrovascular network through metrics like centrality and vessel-specific connectivity patterns.

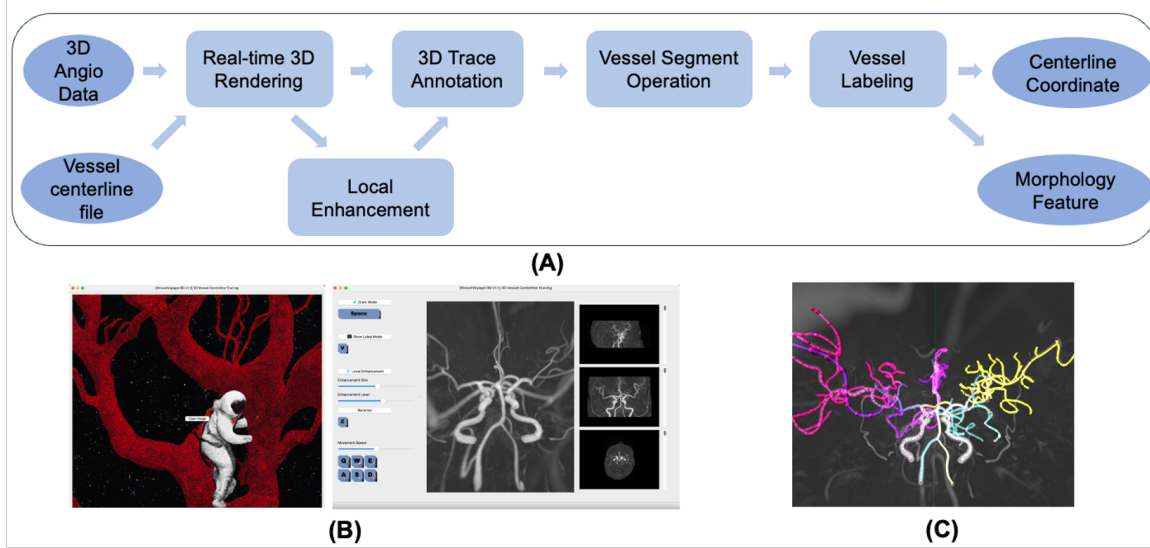


Figure 3.2: Conceptual diagram of VesselVoyager’s workflow. (A) Processing pipeline after TOF-MRA dataset was loaded into the VesselVoyager. (B) Interactive annotation of centerlines. (C) Automatic morphometric analysis.

Data Import/Export and Feature Computation. The platform accepts 3D volumes in DICOM or NIFTI formats and can optionally load existing centerline files (e.g., .yaml,

.swc). After user refinements, morphometric features are computed and written to a .csv file. In line with iCafe [10], VesselVoyager quantifies the arterial length, branch number, and tortuosity of the BAN.

Graph Representation and Analysis. VesselVoyager converts centerline annotations into a standardized graph format (.gexf), enabling network analysis of the cerebrovascular system. The conversion process involves:

- **Node Generation:** Each centerline point becomes a network node with attributes including 3D coordinates, vessel radius, and vessel type.
- **Bifurcation Detection:** Points where multiple vessel types converge are automatically identified as bifurcation nodes.
- **Edge Assignment:** Adjacent points are connected with edges that inherit vessel type information.
- **Centrality Metrics:** The resulting graph calculates key network properties including eigenvector, betweenness, and closeness centrality, quantifying each vessel segment’s importance in the overall network.

This graph-based approach facilitates advanced visualization through interactive 3D plots where edges are color-coded by vessel type and nodes are sized by their network importance. The implementation leverages NetworkX for graph construction and Plotly for creating interactive visualizations that allow researchers to explore the vascular network topology through rotation, zooming, and hovering for detailed information.

3.3.2 Validation and Reproducibility Studies

Comparative Morphological Analysis. We assessed VesselVoyager’s performance on iCafe in a cohort of eight TOF MRA scans. Major intracranial vessels (ACAs, MCAs, PCAs, etc.) were traced in both software packages by an experienced rater. Table 3.2 illustrates key metrics (length, number of branches, tortuosity), along with mean differences

Table 3.2: Comparison of VesselVoyager (VV) and iCafe on 8 Sample TOF-MRA Datasets

Metric	Mean $\pm$ SD		Mean Diff. (95% CI)	Agreement		
	VV	iCafe		SDw	CVw	ICC (95% CI)
Length (cm)	153 $\pm$ 16	149 $\pm$ 20	4	10	7%	0.90 (0.82–0.96)
Branches (count)	68 $\pm$ 11	64 $\pm$ 17	4	8	9%	0.87 (0.75–0.93)
Tortuosity	1.64 $\pm$ 0.26	1.58 $\pm$ 0.32	0.06	0.1	5%	0.86 (0.76–0.92)

Table 3.3: Feature Comparison: VesselVoyager, iCafe, and 3D Slicer

Feature	VesselVoyager	iCafe	3D Slicer
Real-time 3D annotation	Yes	No	Partial
Local enhancement (faint vessels)	Yes	No	No
Comprehensive metric suite	Yes	Yes	Limited
Cross-sectional validation	Yes	No	Partial
Label vessel anomalies	Yes	No	No
Multi-platform availability	Yes (Win/Mac/Linux)	Windows only	Yes
Typical annotation time	<20 min	30–60 min	>30 min

and intraclass correlation coefficients (ICCs). Results showed strong agreement ($ICC \geq 0.85$) while VesselVoyager achieved faster annotation times, particularly for distal or faint vessels due to its 3D local enhancement feature.

Software Feature Comparison. Table 3.3 contrasts VesselVoyager with iCafe and 3D Slicer. VesselVoyager stands out for real-time 3D navigation, local enhancement, and integrated morphological analyses, while iCafe employs a more slice-based user interface, and 3D Slicer lacks specialized vessel-labelling functionalities.

Overall, these validation and reproducibility tests support VesselVoyager’s accuracy and efficiency, particularly in tracing distal arteries and handling complex pathologies. The software thus represents a promising step forward in neurovascular imaging and analysis.

3.4 Brain Artery Visualization & Analysis Platform (BAVA)

The Brain Artery Visualization & Analysis (BAVA) platform¹ was developed to provide an accessible, comprehensive resource for the neurovascular research community, focusing specifically on brain artery network visualization, exploration, and analysis [81]. This web-based platform serves as a central repository for the harmonized brain artery network datasets while offering powerful tools for interactive exploration and community-driven research.

3.4.1 Platform Architecture and Development

BAVA implements a modern web application architecture combining a FastAPI backend with a Streamlit frontend to ensure both performance and accessibility. This design choice eliminates the need for complex software installations, allowing researchers to access the platform through standard web browsers. The system architecture prioritizes: **Scalability**: The platform is designed to accommodate the growing dataset as new contributions are integrated; **Responsiveness**: Interactive visualization components deliver real-time feedback despite the complexity of 3D artery network data; **Accessibility**: Web-based implementation ensures cross-platform compatibility without specialized hardware requirements.

The platform uses a SQLite database (`subjects_all.db`) to store both the demographic and clinical data and BAN graph data, with FastAPI endpoints facilitating data retrieval and manipulation.

3.4.2 Interactive Data Exploration and Visualization

BAVA facilitates exploration of the curated brain artery network dataset through an integrated interface combining interactive visualization and powerful data filtering. At its core is a 3D visualization engine that renders BANs as navigable graphs, critical for understanding complex spatial relationships (Fig. 3.4). This interface allows users to dynamically navigate (zoom, rotate, pan) the color-coded artery networks to examine structures of interest.

¹<https://github.com/BrainArteryNetwork/BAVA>

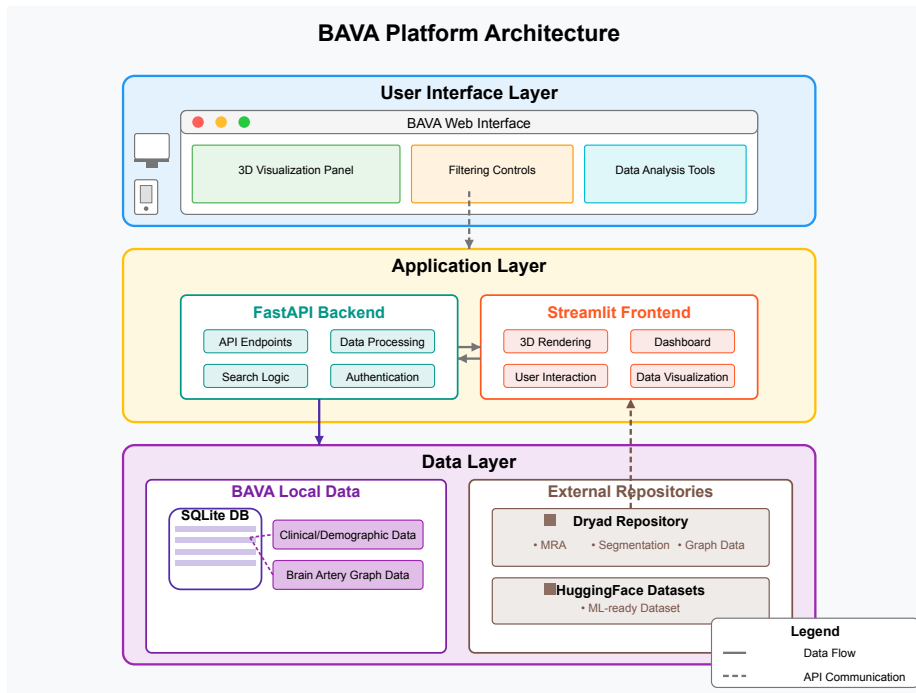


Figure 3.3: BAVA Platform Architecture. A three-tier architecture illustrating the Brain Artery Visualization & Analysis platform. The User Interface Layer (top) shows the web interface with visualization, filtering, and analysis components. The Application Layer (middle) depicts the FastAPI backend and Streamlit frontend that handle data processing and user interactions. The Data Layer (bottom) displays the local SQLite database storing clinical/demographic data and brain artery graph structures for visualization, alongside connections to external repositories (Dryad) which host the complete multimodal dataset including raw MRA, segmentation, and machine learning-ready formats.

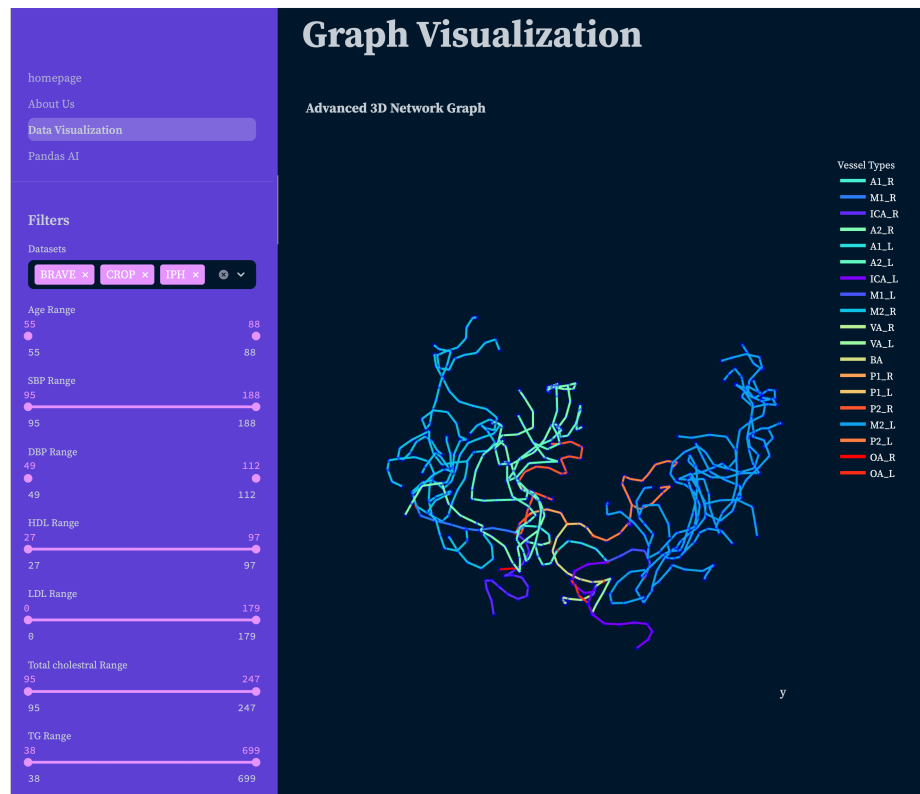


Figure 3.4: BAVA’s 3D visualization interface showing a color-coded brain artery network with interactive controls. The right panel displays the interactive 3D visualization of the BAN with color-coded vessel types. The left panel contains comprehensive filtering controls allowing researchers to refine datasets based on cohort and clinical parameters.

Complementing the visualization, BAVA implements comprehensive filtering capabilities. Researchers can refine the dataset for targeted analysis by querying across multiple dimensions, including demographic parameters (e.g., age, sex) and clinical information (e.g., hypertension status, cognitive scores). This combination of interactive visualization and multi-dimensional filtering supports both exploratory research and hypothesis-driven investigation, enabling users to visually identify patterns and analyze specific subgroups within the diverse dataset.

3.4.3 Data Access and Distribution

To maximize accessibility and support different research workflows, the brain artery network dataset is hosted through multiple complementary platforms:

1. **BAVA web interface:** Primary access point with interactive visualization and analysis tools
2. **Dryad repository:** Permanent archival storage with DOI assignment for citation in academic publications [81]

BAVA itself provides comprehensive visualization tools for all derived data, including 3D graph structures, statistical analyses, and demographic correlations. However, for larger data components such as raw MRA data and multi-label segmentation data, users are directed to the Dryad repositories, which host:

- Raw MRA data
- Multi-label artery segmentation data [10, 9]
- Brain arterial network graph data
- Clinical and demographic structured data

This multi-platform distribution strategy ensures both long-term preservation and compatibility with evolving computational methodologies. Each distribution channel provides appropriate metadata and documentation to support proper dataset utilization.

By combining interactive visualization, powerful filtering capabilities, and multi-platform distribution, BAVA establishes a foundation for collaborative research into brain artery networks and their relationship to neurovascular health.

The complete dataset is made available through multiple distribution channels to support diverse research needs and computational workflows. While BAVA provides interactive visualization and analysis of derived metrics, the full dataset—including raw imaging data,

segmentations, and graph structures—is archived on Dryad [81] for long-term preservation. The comprehensive data organization, file formats, and access protocols are detailed in Appendix A.

3.5 Data Harmonization

3.5.1 Introduction to Scanner Effects in Brain Arterial Networks

In multi-site neuroimaging studies, non-biological variation introduced by differences in MRI scanners and acquisition protocols presents a significant challenge for reliable analysis. These non-biological sources of variability, termed "scanner effects" by Fortin et al. [16], can impede the detection of imaging features associated with clinical covariates of interest and potentially lead to spurious findings. In the context of BANs, such scanner effects are particularly concerning as they may mask subtle vascular changes associated with aging or disease.

For our multi-site dataset of brain arterial networks, we observed notable scanner-dependent variations in key morphological features despite standardization efforts during image acquisition. Vessel morphological features such as tortuosity, radius, length, and branch number exhibited systematic differences between acquisition sites that may not be attributed to biological factors alone. These observations align with findings from previous multi-site neuroimaging studies [61, 16], underscoring the need for robust harmonization methods to ensure that downstream analyses reflect true biological variation rather than technical artifacts.

3.5.2 Nature of Scanner Effects in Arterial Features

Scanner effects in BAN features manifest in two principal ways:

1. **Location effects:** Systematic shifts in the mean values of vascular features across different scanners
2. **Scale effects:** Differences in the variability (variance) of measurements across scanners

Figure 3.5 illustrates these effects in our dataset, showing both shifts in mean values and differences in variance for vessel tortuosity and branch count measurements across different acquisition sites. In particular, we observed that higher field strength scanners (3T) generally yielded higher vessel count and branch detection compared to lower field strength (1.5T) systems, consistent with findings from previous studies on intracranial vasculature [11].

As shown in Figure 3.5, the Philips_Achieva_3T scanner consistently detected significantly more arterial branches compared to other scanners ($p \leq 1e-5$), with mean distal branch numbers approximately twice as high as those from the Siemens_Avanto_1.5T scanner. These differences persisted even after accounting for relevant demographic and clinical factors such as age and gender, which showed significant variation across sites ($p \leq 0.001$), with the Siemens_Avanto_1.5T cohort being older on average.

3.5.3 ComBat Harmonization Model

To address these scanner effects, we implemented the ComBat (Combating Batch Effects) harmonization approach developed by Johnson et al. [31] and adapted for neuroimaging by Fortin et al. [16]. While originally developed for genomics data, ComBat has demonstrated excellent performance for harmonizing neuroimaging features [16], including cortical thickness measurements across multiple sites.

For each morphological feature v (e.g., vessel length, branch number, tortuosity) observed in subject i at imaging site j , ComBat models the measurement Y_{ijv} as:

$$Y_{ijv} = \alpha_v + X_{ij}^T \beta_v + \gamma_{jv} + \delta_{jv} \epsilon_{ijv} \quad (3.1)$$

Where:

- α_v represents the global mean of feature v across all sites
- X_{ij} represents biological covariates (e.g., age, sex) for subject i at site j
- β_v is the vector of regression coefficients for biological covariates

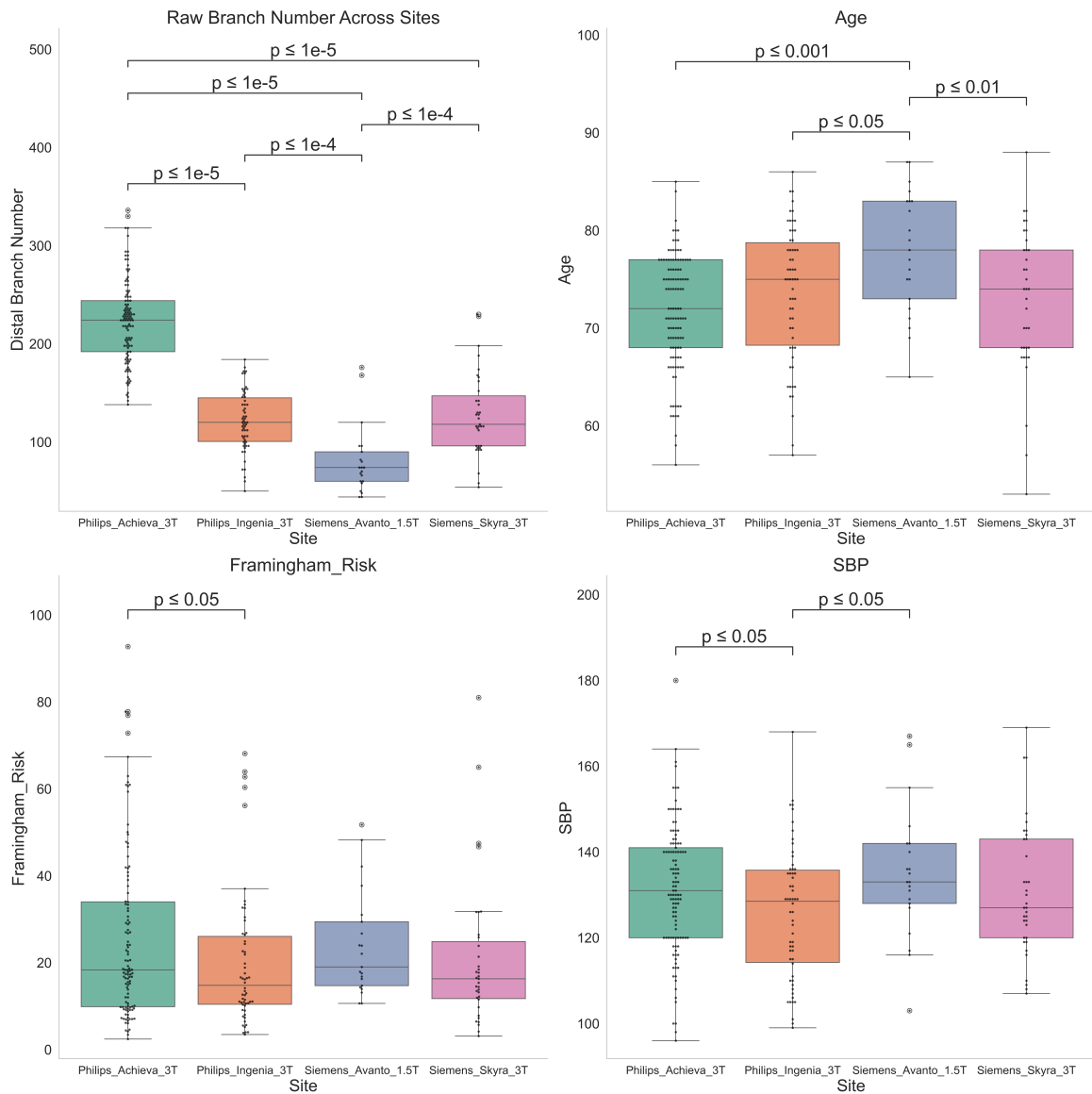


Figure 3.5: Comparison of key vascular and clinical metrics across four imaging sites. **Top left:** Raw distal branch number shows significant differences between all sites, with highest values observed at Philips_Achieva_3T. **Top right:** Age distribution varies across sites. **Bottom left:** Framingham Risk Score shows modest significant differences between some sites. **Bottom right:** SBP demonstrates differences between selected site pairs. P-values from pairwise statistical tests are indicated above the comparison brackets.

- γ_{jv} represents the additive site effect (location parameter)
- δ_{jv} represents the multiplicative site effect (scale parameter)
- ϵ_{ijv} is the error term, assumed to follow a normal distribution

The key advantage of ComBat is its ability to simultaneously address both location and scale effects while preserving biological variability. Additionally, ComBat employs empirical Bayes to stabilize the estimation of site-specific parameters when sample sizes within sites are limited, allowing information to be shared across features [16].

The ComBat-harmonized vascular feature Y_{ijv}^{ComBat} is calculated as:

$$Y_{ijv}^{\text{ComBat}} = \frac{Y_{ijv} - \hat{\alpha}_v - X_{ij}^T \hat{\beta}_v - \hat{\gamma}_{jv}}{\hat{\delta}_{jv}} + \hat{\alpha}_v + X_{ij}^T \hat{\beta}_v \quad (3.2)$$

This transformation effectively removes site-specific additive and multiplicative effects while preserving the biological relationships of interest.

3.5.4 Application to Brain Artery Network Features

We applied the ComBat harmonization procedure to our multi-site brain arterial network dataset comprising data from the CROP and Korean Dementia studies across four different scanner configurations: Philips_Achieva_3T (CROP), Philips_Ingenia_3T (Korean Dementia), Siemens_Avanto_1.5T (Korean Dementia), and Siemens_Skyra_3T (Korean Dementia). For each subject, vascular morphological features were extracted as described in Section 3.2. The harmonization was performed on key vascular features including total artery length and total branch number.

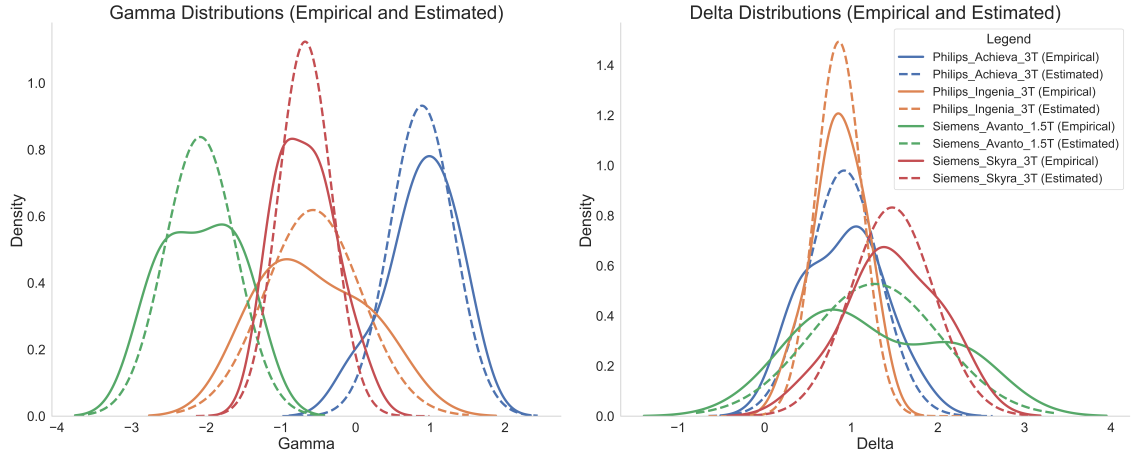


Figure 3.6: Prior distributions of site effect parameters estimated by ComBat for brain arterial network features. (a) Distributions of location parameters (γ) showing systematic shifts across scanning sites; (b) Distributions of scale parameters (δ) demonstrating differences in measurement variability between sites. Solid lines represent empirical distributions while dashed lines show the estimated prior distributions used in the empirical Bayes framework.

Figure 3.6 illustrates the empirical distributions of the site-specific parameters estimated by ComBat, alongside the prior distributions used in the empirical Bayes framework. The location parameters (γ) showed systematic shifts across sites, with the Philips_Achieva_3T scanner exhibiting the highest positive shift and Siemens_Avanto_1.5T showing the most negative shift for gamma. The scale parameters (δ) revealed notable differences in measurement variability, with Siemens_Avanto_1.5T demonstrating the widest variance and Philips_Ingenia_3T showing the narrowest variance distribution.

For comparison, we implemented two simpler harmonization approaches:

1. **Residuals method:** Direct removal of site effects via linear regression without considering biological covariates
2. **Adjusted Residuals method:** Removal of site effects via linear regression while adjusting for biological covariates

3.5.5 Evaluation of Harmonization Effectiveness

To assess the effectiveness of the ComBat harmonization procedure, we conducted several evaluations focusing on both the removal of scanner effects and the preservation of biological relationships.

Visualization of Scanner Effects Before and After Harmonization

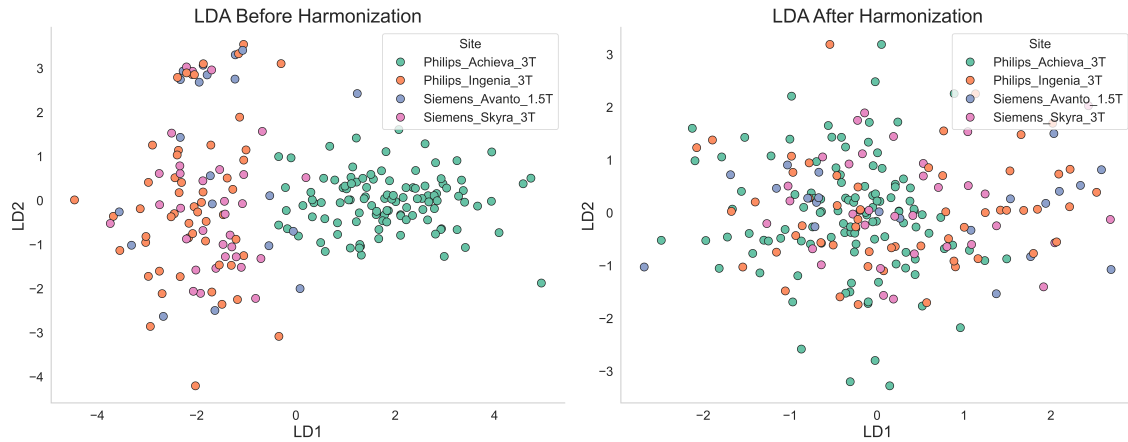


Figure 3.7: Visualization of scanner effects before and after harmonization using Linear Discriminant Analysis (LDA). (a) LDA before harmonization, showing clear clustering by scanner site with distinct separation between scanners; (b) LDA after ComBat harmonization showing substantial removal of scanner-related clustering, with data points from different scanners becoming well-intermixed in feature space.

As shown in Figure 3.7, we employed supervised Linear Discriminant Analysis (LDA) to visualize scanner effects before and after harmonization. Prior to harmonization, clear clustering by scanner was evident, with Philips_Achieva_3T (green) forming a distinct cluster separate from the other scanners. After ComBat harmonization, these scanner-related clusters were substantially diminished, with data points from different scanners becoming well-intermixed in the LDA projection, indicating successful removal of scanner-specific effects.

Table 3.4: ANOVA F-test p-values for scanner effects before and after harmonization

Feature	Raw Data	Residuals	Adjusted Residuals	ComBat
Total Branch Number	$p < 1.0\text{e-}50$	$p = 1.000$	$p = 0.959$	$p = 0.222$
Total Length	$p < 1.0\text{e-}30$	$p = 1.000$	$p = 0.997$	$p = 0.757$

Table 3.5: Bartlett’s test p-values for homogeneity of variances across scanners

Feature	Raw Data	Residuals	Adjusted Residuals	ComBat
Total Branch Number	$p = 0.040$	$p = 0.040$	$p = 0.040$	$p = 0.338$
Total Length	$p < 1.0\text{e-}09$	$p < 1.0\text{e-}09$	$p < 1.0\text{e-}09$	$p = 0.826$

Statistical Assessment of Harmonization

To quantitatively evaluate harmonization performance, we conducted several statistical tests, including ANOVA for assessing location effects and Bartlett’s test for assessing scale effects:

As shown in Tables 3.4 and 3.5, ComBat significantly reduced both location and scale effects across all vascular features. The raw data showed highly significant scanner effects ($p < 1\text{e-}5$) for all features. While the Residuals and Adjusted Residuals methods effectively addressed location effects ($p > 0.05$ for ANOVA), they were less successful in mitigating scale effects ($p < 0.05$ for Bartlett’s test), highlighting the advantage of ComBat’s comprehensive approach in addressing both location and scale effects ($p > 0.3$ for both tests across all features).

3.5.6 Preservation of Biological Associations

A critical requirement for any harmonization method is the preservation of legitimate biological relationships. Following the approach in Chen et al. [11], we examined the relationship between age and key vascular features before and after harmonization.

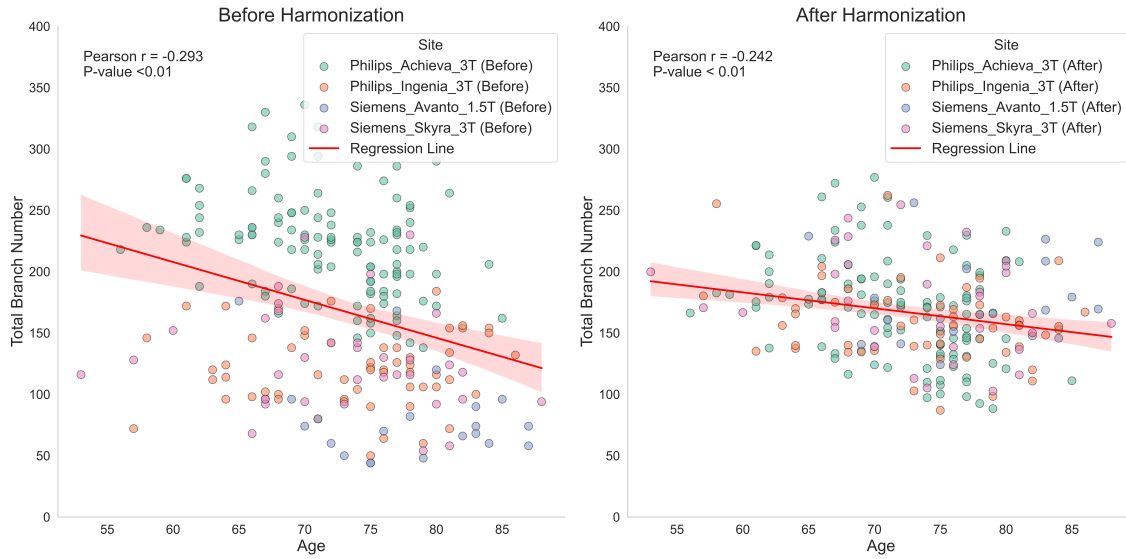


Figure 3.8: Relationship between total branch number and age before and after harmonization. (a) Before harmonization, showing a significant negative correlation ($r = -0.293$, $p < 0.01$) but with clear scanner-specific clustering affecting the relationship; (b) After ComBat harmonization, the biological relationship is preserved ($r = -0.242$, $p < 0.01$) while scanner-specific clustering is eliminated, resulting in a more homogeneous distribution across sites.

Figure 3.8 shows that ComBat harmonization not only preserved but enhanced the clarity of the biological relationship between total branch number and age. Before harmonization, the correlation between age and total branch number was $r = -0.293$ ($p < 0.01$), but scanner-specific clustering created artificial boundaries in the relationship. After ComBat harmonization, while the correlation coefficient was slightly reduced to $r = -0.242$, the p-value remained significant ($p < 0.01$), and importantly, the distribution of data points became more homogeneous across scanner sites, allowing for a more accurate assessment of the true biological relationship.

Table 3.6 quantifies these relationships, showing that the correlation coefficients between age and vascular features were largely maintained after ComBat harmonization. Notably, the simple Residuals method weakened these biological associations, with some correlations losing statistical significance, underscoring the importance of adjusting for biological covariates during harmonization.

Table 3.6: Correlation coefficients (r) between age and vascular features before and after harmonization

Feature	Raw Data	Residuals	Adjusted Residuals	ComBat
Total Branch Number	-0.293**	-0.208**	-0.215**	-0.242**
Total Length	-0.232**	-0.083	-0.086	-0.162*

* $p < 0.05$, ** $p < 0.01$

Table 3.7: Linear regression coefficients for age-related changes in vascular features after ComBat harmonization

Feature	Coefficient (per year)	95% CI	p-value
Total Branch Number	-1.350	[-2.099, -0.601]	$p < 0.001$
Total Length (mm)	-84.956	[-153.498, -16.415]	$p = 0.015$

3.5.7 Age-Related Changes in Harmonized Vascular Features

Using the harmonized data, we investigated age-related changes in brain arterial network features using linear regression models. Following the approach in Chen et al. [11], we adjusted for sex and examined two key vascular features most strongly associated with age.

Table 3.7 presents the regression coefficients for age-related changes in vascular features after ComBat harmonization. Consistent with Chen et al. [11], we found significant decreases in the total branch number (-1.350 branches per year, $p < 0.001$) and average order (-84.956 mm per year, $p = 0.015$) with increasing age. These age-related changes were consistently observed across different vascular territories, supporting the hypothesis that vascular aging affects the entire cerebral arterial network.

3.5.8 Implications and Limitations

ComBat harmonization successfully mitigated scanner-related variability in brain arterial network features while preserving and enhancing biological relationships. The harmonized dataset enables more robust cross-sectional analyses of age-related vascular changes, which

may serve as imaging biomarkers for cerebrovascular health.

Several limitations should be acknowledged:

1. ComBat assumes that scanner effects are consistent across all subjects at a given site, which may not hold for subjects with unusual vascular anatomy
2. While ComBat effectively addresses additive and multiplicative scanner effects, more complex non-linear effects may not be fully corrected
3. The current implementation treats each morphological feature independently, potentially neglecting inter-feature correlations
4. As with any harmonization method, there is a risk of removing legitimate biological variability that happens to correlate with scanner site

Despite these limitations, ComBat harmonization represents a significant methodological advance for multi-site studies of brain arterial networks, enabling more accurate assessment of vascular changes associated with aging and disease. The successful application of this approach to our dataset demonstrates the feasibility of pooling arterial network data across multiple sites and scanner configurations, opening avenues for larger-scale investigations of cerebrovascular health and pathology.

Chapter 4

ADVANCED IMAGING SEQUENCES FOR VASCULAR CHARACTERIZATION

4.1 Introduction and Rationale for Advanced Imaging Sequences

Comprehensive assessment of intracranial vasculature requires evaluation of multiple aspects: luminal stenosis, vessel wall conditions, and blood flow dynamics. Traditionally, this necessitates acquiring several different MRI sequences, including TOF-MRA, vessel wall imaging, and dynamic MRA sequences [46]. This multi-sequence approach presents several limitations: prolonged total acquisition time, potential misregistration between different image contrasts, and increased patient discomfort, all of which limit clinical application.

The development of advanced imaging sequences capable of simultaneously generating multiple image contrasts from a single acquisition offers significant advantages for neurovascular disease assessment [12]. Such sequences not only improve time efficiency but also ensure spatial registration between different contrasts, facilitating comprehensive analysis of the relationships between vessel morphology and hemodynamics.

The BAN represents a complex system of interconnected vessels whose analysis is crucial for understanding cerebrovascular health, aging processes, and neurological disorders [40]. Advanced imaging and analysis of these networks can provide insights into the mechanisms of vascular remodeling and its relationship with cardiovascular risk factors, which is particularly important for the early detection and management of cerebrovascular diseases [11].

Recent technological developments in MRI pulse sequence design, image reconstruction algorithms, and post-processing techniques have enabled significant advancements in this field [71, 69]. These innovations allow for more efficient data collection and the extraction of multiple complementary information from a single dataset, providing comprehensive characterization of the intracranial vasculature in clinically feasible scan times.

4.2 *iSNAP Sequence Development for Artery Characterization*

The intraCranial Simultaneous Non-contrast Angiography and intraPlaque hemorrhage (iSNAP) sequence represents a significant advancement in multi-contrast MRI for comprehensive intracranial vascular assessment [12]. Building upon the principles of the SNAP sequence originally developed for carotid artery imaging [69], iSNAP was specifically designed to simultaneously generate multiple image contrasts for intracranial vascular evaluation within a single, time-efficient acquisition.

The fundamental concept of iSNAP involves the use of pulsed ASL preparations followed by a 3D golden angle radial acquisition [8]. This approach enables reconstruction of different image contrasts at various inversion times along the magnetization recovery curve. The sequence employs two acquisitions, each with different inversion preparation: one with a small-slab inversion and another with a large-slab inversion. Through strategic data sharing and image subtraction between these two acquisitions, both static and dynamic information about the intracranial vasculature can be extracted [12].

The key features of iSNAP include:

1. Whole-brain coverage with isotropic spatial resolution
2. Simultaneous acquisition of dynamic MRA (dMRA) for hemodynamic assessment
3. Static MRA (sMRA) for anatomical evaluation of the arterial tree
4. Vessel wall imaging (VWI) for assessing vessel wall conditions
5. T1-weighted brain structural imaging

With a single acquisition time of approximately 6.5 minutes, iSNAP provides comprehensive intracranial vascular assessment that would otherwise require multiple separate sequences totaling 15-20 minutes of scan time [12]. This significant improvement in acquisition efficiency addresses a critical barrier to the clinical application of comprehensive vascular MRI protocols.

iSNAP Optimization for Frequency Offset Corrected Inversion (FOCI) Enhancement

The original iSNAP sequence employed standard hyperbolic secant (HS) inversion pulses for ASL preparation [12]. However, this implementation faced limitations related to the imperfect inversion profile of HS pulses, resulting in undesirable artifacts, particularly in dynamic MRA. The dynamic MRA component of iSNAP, which relies on subtraction between acquisitions with small-slab and large-slab inversions, suffered from residual soft tissue signal contamination in early time frames due to off-resonance effects and imperfect inversion slice profiles of the standard HS pulses [80].

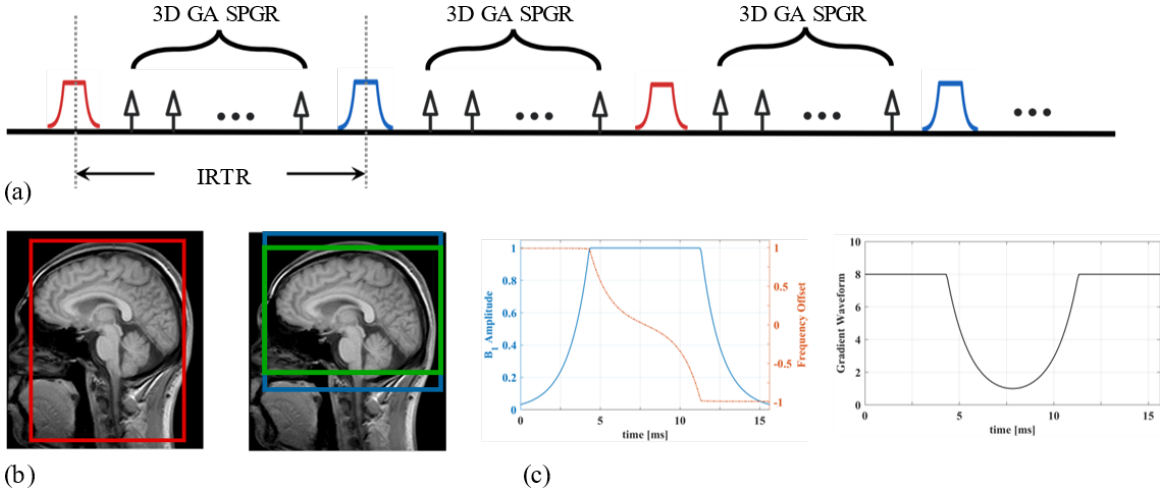


Figure 4.1: (a) An illustration of the sequence scheme of proposed method. Large slab (red RF pulse) and small slab (blue RF pulse) FOCI inversion pulses are performed alternately followed by 3D Golden angle (GA) radial spoiled gradient echo (SPGR); (b) Large inversion slab and small inversion slab are shown with red border and blue border. Green border is the actual imaging region which is set inside the small inversion slab; (c) Waveforms of FOCI pulse. Left side is the amplitude waveform and frequency offset curves, right side is the gradient waveform.

To address these limitations, an optimized version of iSNAP was developed using FOCI RF pulses instead of standard HS pulses [80]. FOCI pulses provide sharper transition bands in the slice profile, which is particularly beneficial for ASL-based techniques that rely on subtraction between labeled and control acquisitions [53, 66].

The FOCI-enhanced iSNAP implementation utilized C-shape FOCI pulses, which demon-

strate the sharpest transition band in both simulation and experimental results [75]. The FOCI pulse design involved modulating the gradient amplitude, RF amplitude, and resonance frequency offset using specific envelope functions [80]:

$$B_1^{FOCI} = A(t) \times \text{sech}(\beta t) \quad (4.1)$$

$$\Delta\omega^{FOCI} = -A(t) \times \mu\beta \tanh^{-1}(\beta t) \quad (4.2)$$

$$G(t) = A(t) \times G \quad (4.3)$$

where G is the constant gradient applied in standard HS pulse, β and μ were designed as 826s^{-1} and 6.2, with pulse duration $T = 15.3\text{ms}$. The maximum value of $A(t)$ was set according to gradient amplifier and RF specifications [80].

Phantom experiments demonstrated that FOCI-iSNAP produced significantly sharper transition bands on either side of the inverted region compared to HS-iSNAP [80]. In vivo experiments confirmed these findings, showing that FOCI-iSNAP effectively eliminated background artifacts in dynamic MRA, particularly in the first several frames where HS-iSNAP showed significant fat-related artifacts. This improvement is critical for accurate assessment of arterial filling patterns, especially in the early phase of contrast arrival.

The FOCI enhancement preserved all the multi-contrast capabilities of the original iSNAP sequence while substantially improving image quality, particularly for dMRA. The sMRA, vessel wall images, and T1-weighted structural images were all maintained with comparable quality to the original implementation, demonstrating the versatility and robustness of the optimized sequence [80].

Advanced Vessel Wall Reconstruction with iSNAP

While iSNAP successfully generates multiple image contrasts, the quality of vessel wall images has been a limitation compared to dedicated vessel wall imaging sequences [12]. This is primarily due to the highly undersampled 3D radial acquisition strategy and the k-space weighted image contrast (KWIC) reconstruction method originally employed for iSNAP [62].

To address this limitation, a novel low-rank-based reconstruction method was developed specifically for iSNAP [79]. This approach leverages the sharable structural information

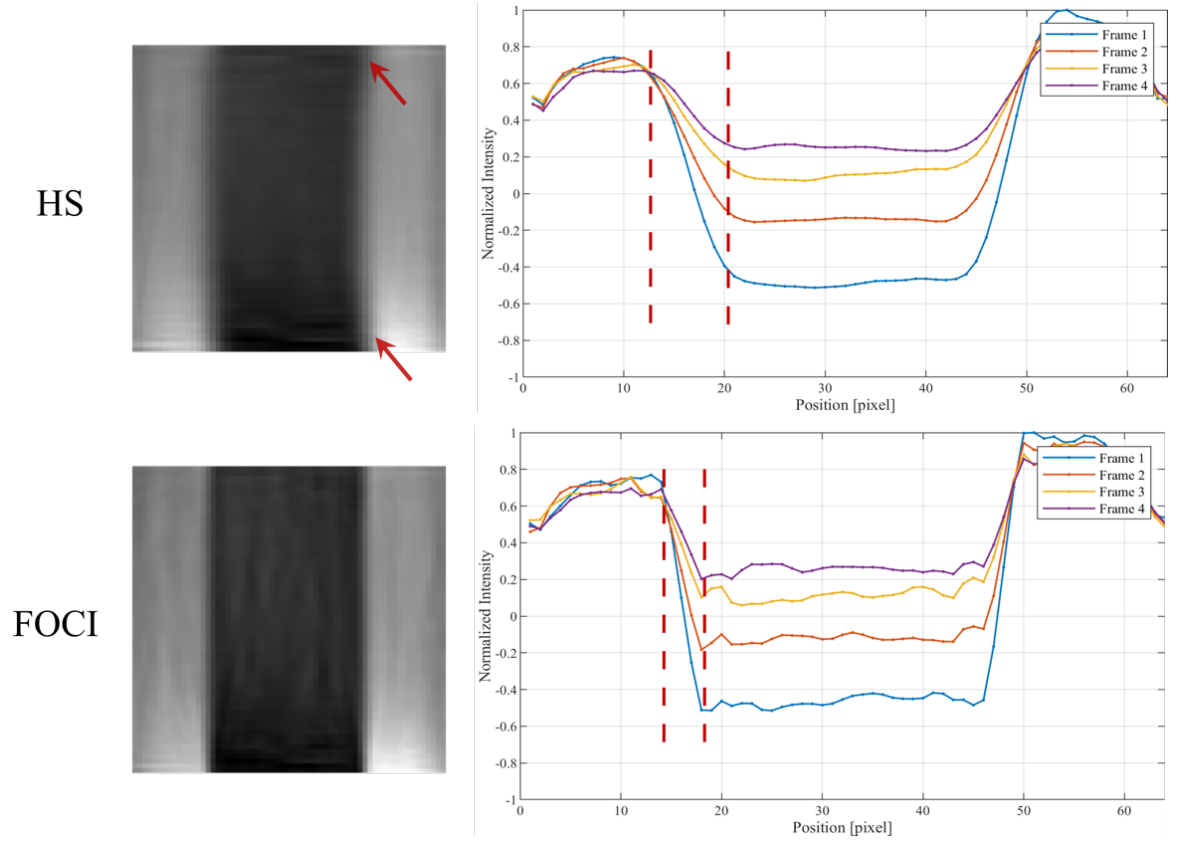


Figure 4.2: Measured inversion profiles. Readout excitation thickness is 137.5mm, small/large inversion slab thickness is 55/88mm. Left side is the first frame after applying small slab inversion pulse on phantom. Right side is the inversion profiles for different inversion pulse type for the first four frames. Transition bands of both HS and FOCI are outlined with red dotted line.

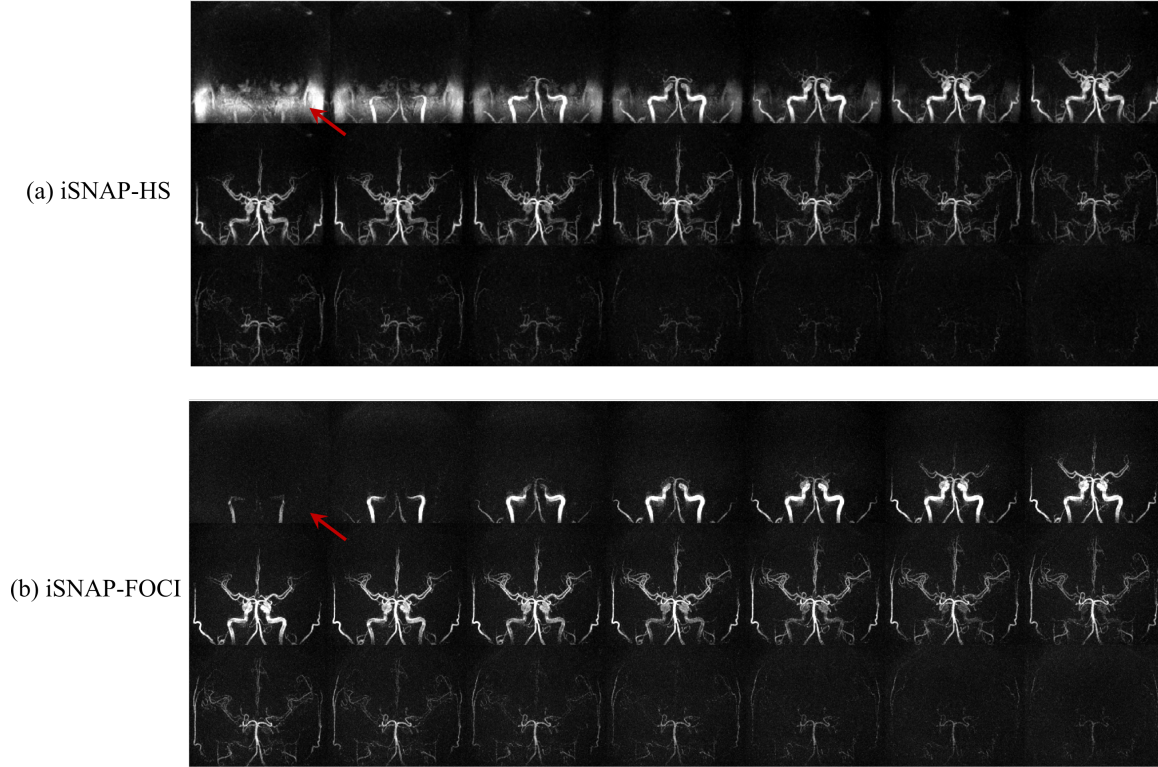


Figure 4.3: First frame of dMRA with readout excitation thickness 137.5mm, small/large slab inversion thickness 110/500mm. Small inversion slab is inside excitation region which can observe transition band in field of view.

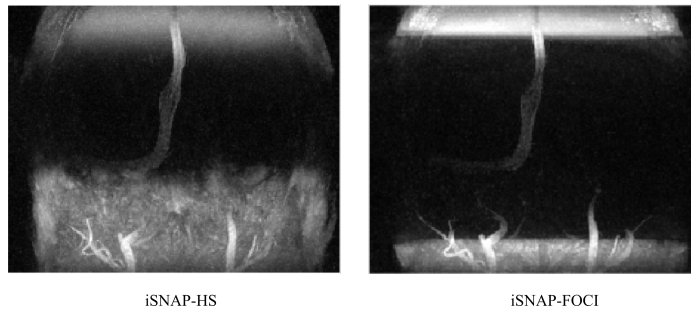


Figure 4.4: dMRA images obtained by (a) iSNAP-HS and (b) iSNAP-FOCI in healthy volunteer. Readout excitation thickness is 137.5mm, small/large inversion slab thickness is 154/500mm. Fat related artifacts are totally removed in the first frames.

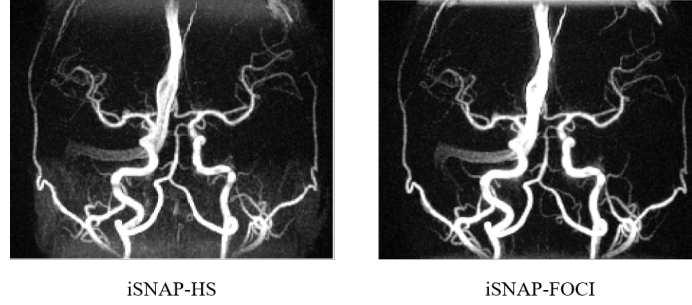


Figure 4.5: sMRA images obtained by iSNAP-HS and iSNAP-FOCI in healthy volunteer. Readout excitation thickness is 137.5mm, small/large inversion slab thickness is 137/500mm.

across time frames in the 4D dataset to facilitate reconstruction of high-quality vessel wall images while preserving hemodynamic information.

The low-rank reconstruction method involves constructing a 3D Hankel tensor for each frame and concatenating them for low-rank approximation, with a kernel size of $3 \times 3 \times 3$, targeted rank of 50, and 50 iterations [79, 59]. This approach, when compared to the original KWIC reconstruction, demonstrates several advantages:

1. Enhanced sharpness of vessel wall delineation, allowing better visualization of wall morphology
2. Reduced aliasing artifacts compared to KWIC reconstruction with fewer rings
3. Improved suppression of blood signal contamination from adjacent frames
4. Higher contrast-to-noise ratio (CNR) between vessel lumen and wall

Quantitative evaluation of vessel wall images from both reconstructions demonstrated that while there was no significant difference in vessel wall signal-to-noise ratio (SNR) between the two methods, the low-rank reconstruction provided significantly better suppression of blood signal [79]. This resulted in improved CNR between lumen and vessel wall, which is critical for accurate assessment of vessel wall pathology.

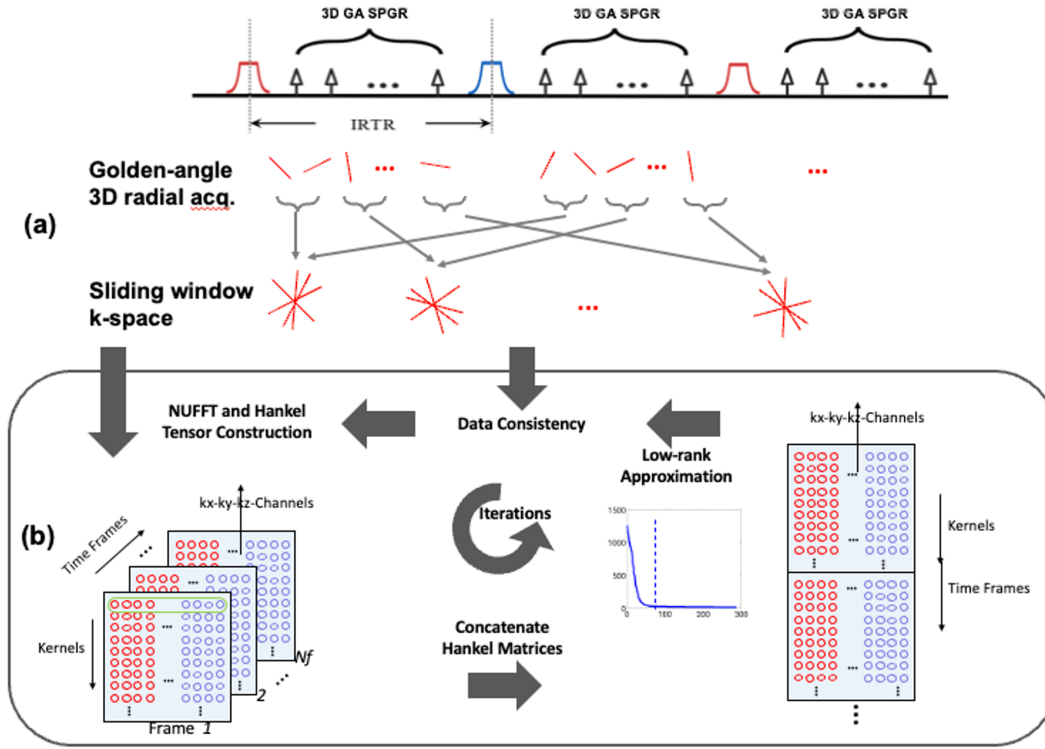


Figure 4.6: (a) An illustration of the proposed low-rank reconstruction method. (TR/TE=7.6/2.7 ms, excitation slab thickness=137.5 mm, flip angle=6°, voxel size=0.8 mm isotropic, total scan time=6.5min) (b) Image reconstruction: k-space data from 3D golden-angle radial trajectory can be combined using a sliding-window way for each time frame. During the reconstruction, a low-rank approximation is pursued with the original k-space data enforcing the data fidelity. Note: the number of frames can be manually selected by balancing the image signal-to-noise ratio (SNR) and temporal resolution.

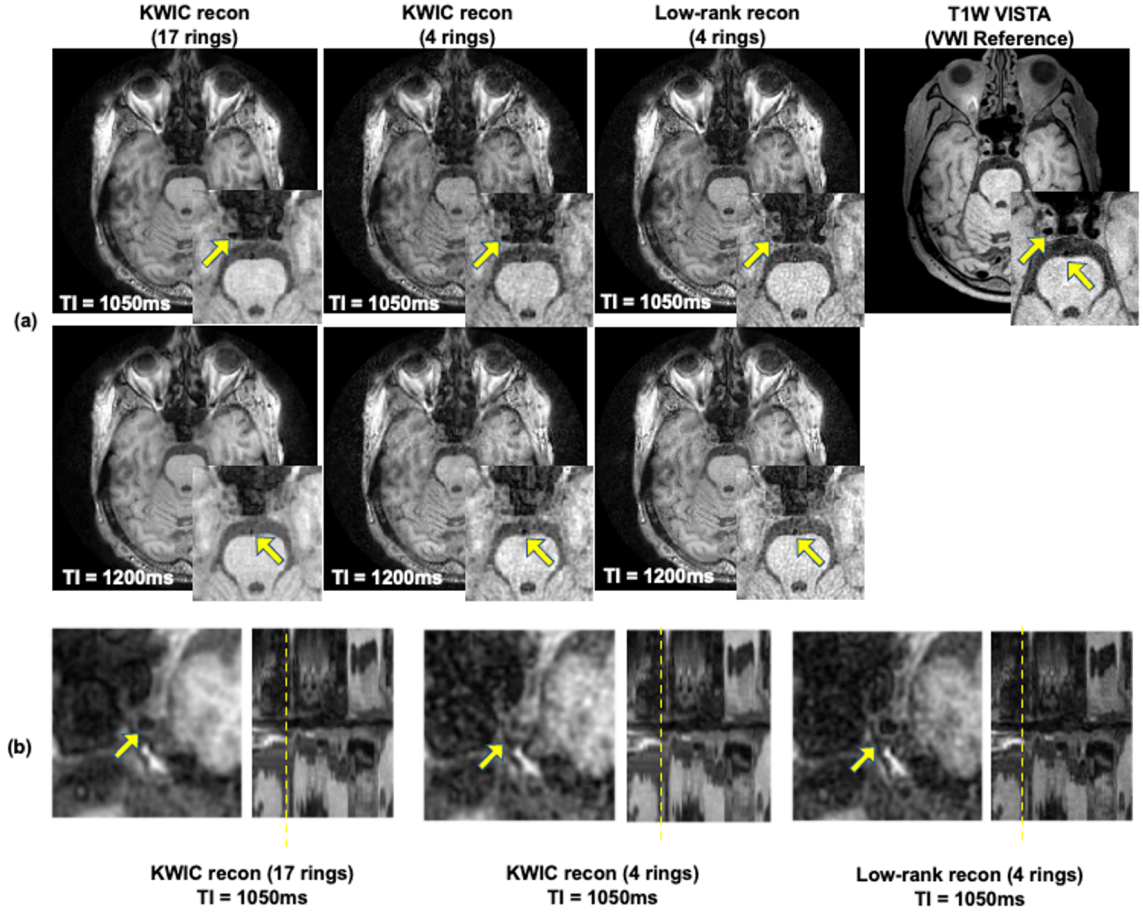


Figure 4.7: (a) Comparison of KWIC reconstruction using 17 rings (original implementation) and 4 rings, proposed low-rank reconstruction and the reference T1W VISTA in vessel wall visualization. (b) Zoom-in images for one cross-sectional image and MPR-view image of internal carotid artery (ICA) at $TI = 1050ms$. The proposed reconstruction provided sharper images with better visualization of the vessel wall (arrows). Moreover, the proposed method better suppressed blood signal compared to KWIC reconstruction, as can be seen in the MPR-view image.

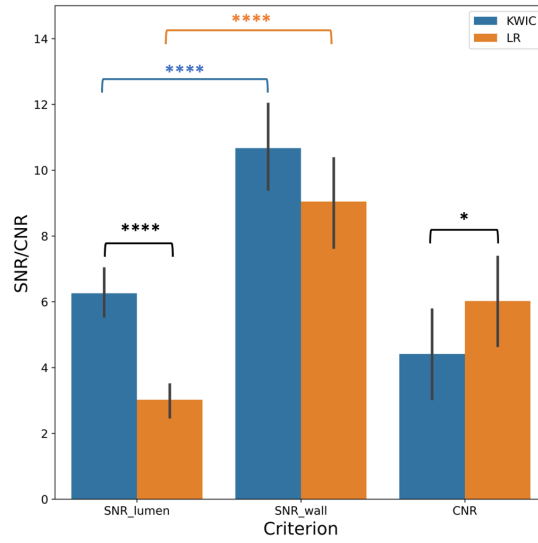


Figure 4.8: Bar chart of SNR / CNR values of KWIC vs low-rank (LR) reconstruction. Significant differences were observed between the SNRs of lumen and wall from both reconstruction methods, as well as between the SNRs of lumen from KWIC and LR methods. A less significant difference was observed between CNR from KWIC and LR methods. No significant difference was observed between SNR of the vessel wall from KWIC and LR methods. (**** indicates p-value less than 0.0001, * indicates p-value less than 0.05)

Importantly, the low-rank reconstruction preserved the hemodynamic information in the dMRA component of iSNAP. The time-to-peak (TTP) values derived from low-rank reconstructed dynamic MRA showed high correlation with those from KWIC reconstruction ($R = 0.83$), indicating that the temporal information was well preserved despite the substantial improvement in spatial image quality [79].

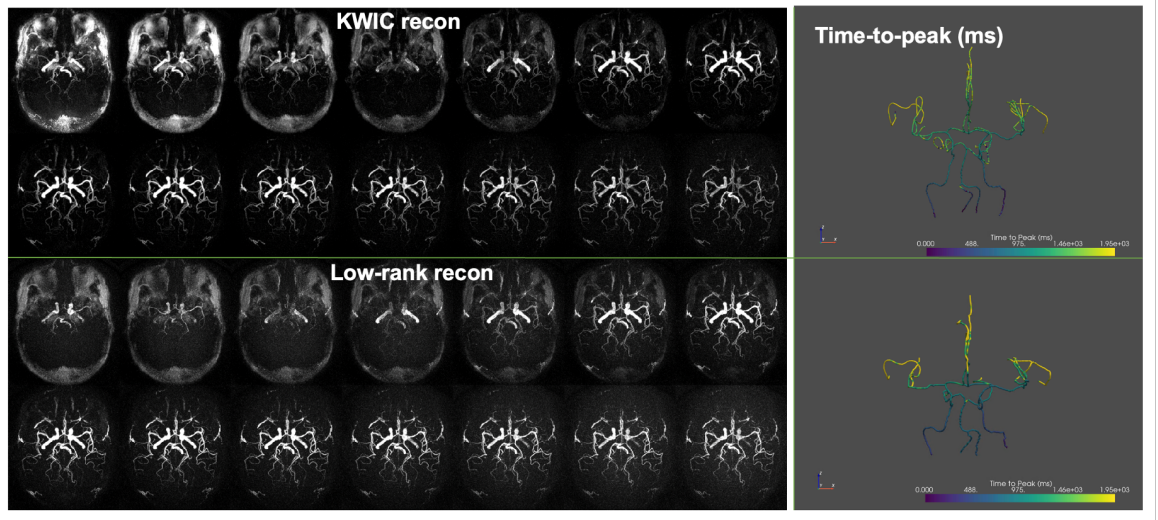


Figure 4.9: Comparison of the dMRA images reconstructed by KWIC and proposed low-rank method. The 3D time-to-peak map showed consistent patterns between the two reconstruction methods.

The advanced vessel wall reconstruction represents a significant enhancement to the iSNAP technique, addressing one of its primary limitations. This improvement enables more accurate assessment of vessel wall conditions, potentially improving detection and characterization of intracranial vascular pathologies such as atherosclerosis and other vessel wall abnormalities [52]. It clearly demonstrates the superior vessel wall delineation achieved with low-rank reconstruction compared to the original KWIC method [79].

In summary, the combination of FOCI pulse enhancement and low-rank reconstruction substantially improves the quality and utility of the iSNAP sequence for comprehensive intracranial vascular assessment. These advancements maintain the time efficiency of the original technique while addressing its limitations, bringing multi-contrast vascular MRI

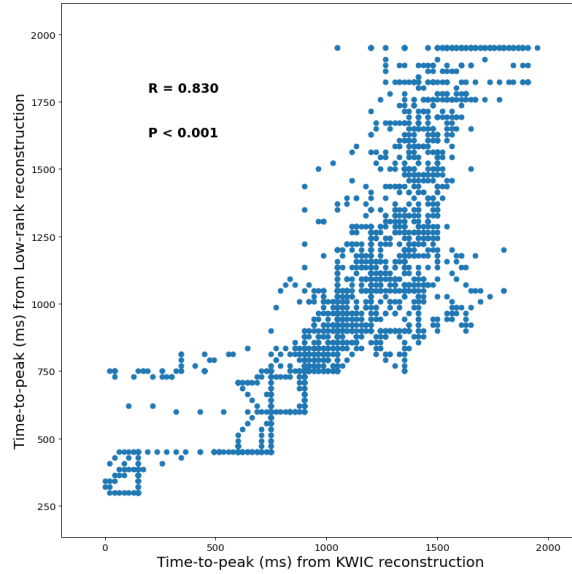


Figure 4.10: Correlation of time-to-peak map from KWIC and low-rank reconstruction methods. A high positive correlation ($r = 0.83$) was observed from KWIC and LR methods, indicating good agreement for hemodynamic information between the two different reconstruction methods.

closer to routine clinical application.

4.3 CineMerge Sequence for Arterial Pulsatility

4.3.1 CineMerge Acquisition and Implementation

The CineMerge sequence represents a significant advancement in MRI technology for visualizing and quantifying vascular pulsatility. This 3D isotropic black-blood MRI technique enables high-resolution imaging of vessel wall motion throughout the cardiac cycle with remarkable temporal and spatial resolution while maintaining adequate blood suppression [82, 34, 3]. The sequence utilizes a sophisticated approach combining Motion-Sensitized Driven Equilibrium (MSDE) preparation with a rapid gradient echo readout during the approach to spoiled steady state [2, 82].

The implementation of CineMerge involves peripheral pulse gating (PPG) for cardiac triggering, supplemented by ECG monitoring. Each heartbeat captures multiple segments

(typically around ten), corresponding to distinct cardiac phases [82, 3]. This implementation provides isotropic spatial resolution of $1 \times 1 \times 1 \text{ mm}$ (interpolated to $0.5 \times 0.5 \times 0.5 \text{ mm}$), covering a substantial field of view ($20 \times 20 \times 16 \text{ cm}$) to encompass the entire cerebral vasculature of interest, as shown in Figure 4.11.

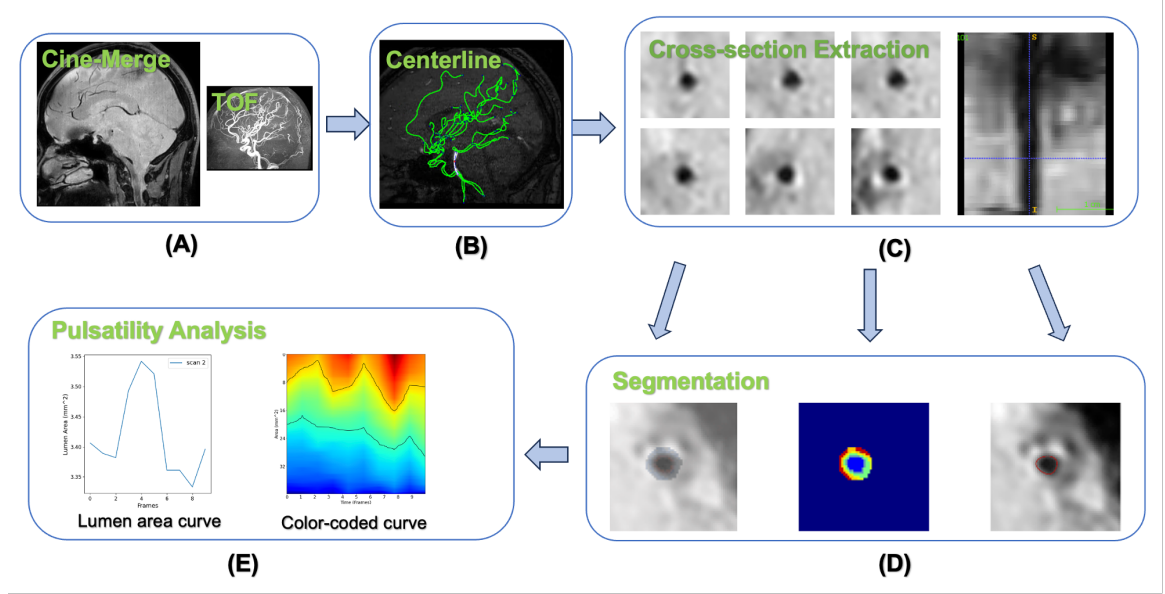


Figure 4.11: The pipeline for generating basilar artery (BA) lumen contours on 3D Cine MERGE multi-frame images. (a–c) centerline tracing result of selected arteries from automated tracing algorithm; (d) manual artery labeling for BA using iCafe; (e) lumen contours were manually drawn. The centerlines are extracted from MRA images, and the surface of BA is segmented from CineMerge images.

The scan parameters are carefully optimized to balance signal-to-noise ratio, blood suppression efficiency, and scan time. Typically, a GRE TR/TE of 10/4ms is employed with a flip angle of 6 degrees, resulting in a remarkably short scan time of approximately 4.5 minutes [82]. This efficiency is achieved through a MSDE preparation scheme that utilizes flow dephasing gradients in all three orthogonal directions with a cumulative first moment of $1574 \text{ mT ms}^2/\text{m}$, sufficient for suppressing blood signal while maintaining vessel wall visibility.

For optimal image quality, the centerlines of Circle-of-Willis arteries are traced on TOF-MRA images using specialized software iCafe, and these centerlines are then transferred to

the CineMerge dataset [82, 34]. This approach facilitates the reformation of cross-sectional images perpendicular to the vessel centerline, allowing precise measurement of lumen area changes throughout the cardiac cycle.

Post-processing involves a transformer-based deep learning model for segmentation of lumen and wall boundaries, followed by a novel approach that accounts for sub-pixel signal changes with time [82]. Lumen area quantification involves pixel counting within the identified lumen, with color-coded visualization enhancing interpretation, as demonstrated in Figure 4.12.

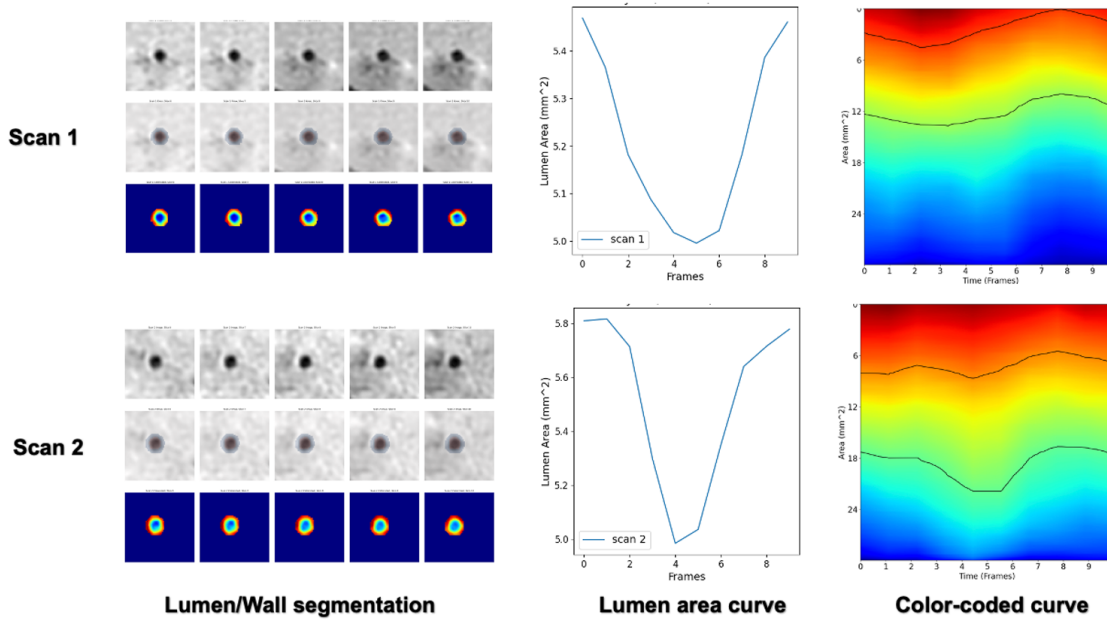


Figure 4.12: Reproducibility result: comparison between scan and rescan on top half of basilar artery (BA). The comparison includes segmentation results, lumen area curve, and color-coded plot.

4.3.2 Clinical Relevance of Pulsatility Metrics

The clinical significance of intracranial vascular pulsatility extends far beyond traditional blood flow assessments. While velocity pulsatility has been extensively documented, the pulsatility related to vessel wall compliance and diameter changes has remained relatively

understudied until recent advancements [82, 34]. The ability to accurately measure these parameters provides crucial insights into cerebral vasculature’s mechanical behavior and overall vascular health.

Our recent studies have revealed that intracranial arterial wall pulsatility serves as a promising biomarker for various cerebrovascular conditions, including aneurysm risk assessment [34]. The distinct patterns of pulsatility observed in different arterial locations underline the highly nuanced nature of cerebral vascular dynamics, as illustrated in Figure 4.13.

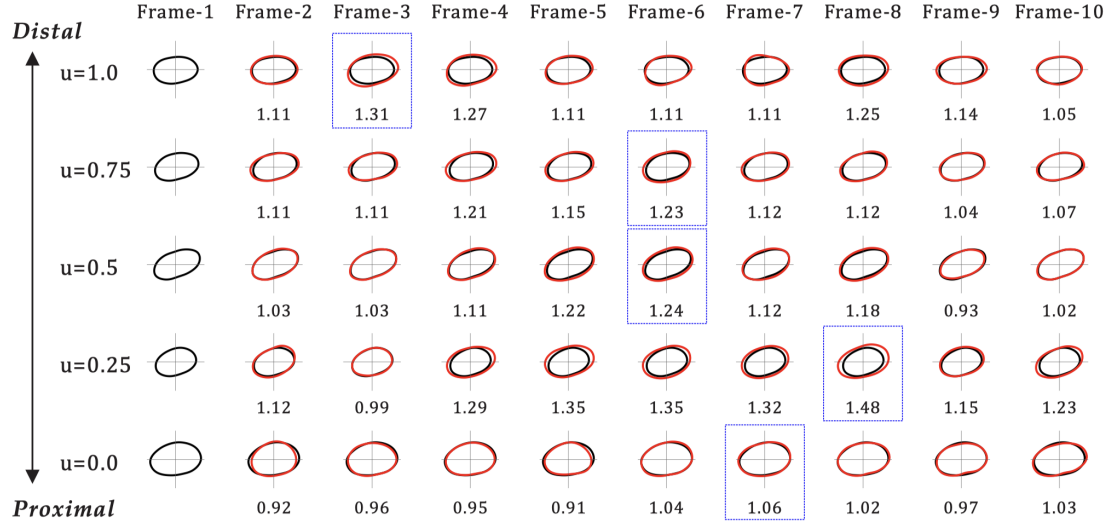


Figure 4.13: BA cross sections over the cardiac cycle showing the cross sections uniformly spaced along the u axis for each of the 10 frames acquired. The initial cross sections are shown as the reference state (black curves), overlaid with the current state (red curves). The ratio between the initial and current cross-sectional perimeter for each cross section is also indicated. The maximum value for each cross section is highlighted in blue box, which revealed a peristaltic-like temporal sequence in BA deformations.

Quantitative analysis using CineMerge shows reproducible lumen area change curves across different arterial segments. Notable observations from our studies include that longitudinal stretches are generally contractile and show minimal variation over the cardiac cycle ($\lambda_u \approx 0.98 - 1.02$), while circumferential stretches exhibit significant extensional deformations up to approximately 10-11% ($\lambda_v \approx 1.11$) [34]. Interestingly, shear deformations

remain consistently negligible, indicating that arterial wall motion is predominantly in the circumferential direction, as shown in Figure 4.14.

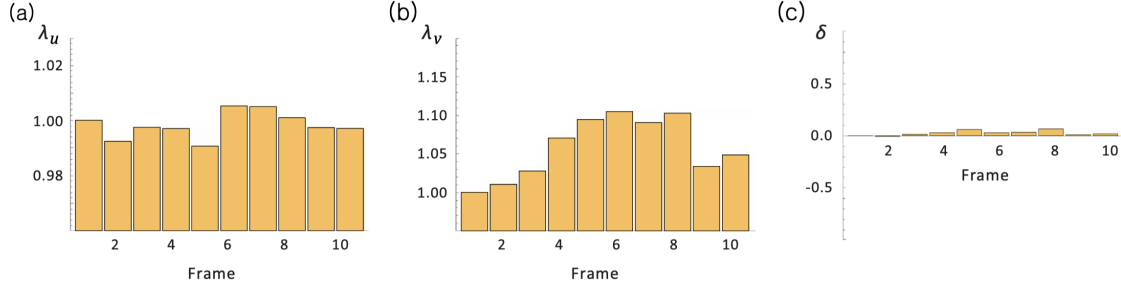


Figure 4.14: The deformation analysis measured over the cardiac cycle: (a) stretch in the longitudinal direction λ_u , (b) stretch in the circumferential direction λ_v , and (c) angle changes δ (shown in degrees).

The pulsatility index for lumen area, calculated using the formula $(max - min)/mean$ across the cardiac cycle, provides a quantitative measure that correlates with vessel wall properties such as stiffness and compliance [82]. This metric shows reproducible results when comparing repeated scans, as demonstrated in Table 4.1, establishing its reliability for longitudinal studies.

Table 4.1: Reproducibility of Pulsatility Index from Cine Black Blood Imaging.

Territory	Scan 1	Scan 2	Abs. Diff.	% Diff.
BA	0.284 ± 0.086	0.283 ± 0.123	0.09	3.18
VA_L	0.209 ± 0.050	0.228 ± 0.047	0.02	8.48
VA_R	0.246 ± 0.121	0.214 ± 0.126	0.03	13.9

Of particular interest is the observation of a peristaltic-like temporal sequence in basilar artery deformations, where the maximum circumferential perimeter length occurs at different time points along the length of the vessel (Figure 4.13) [34]. This phase lag in pulsatility suggests that the artery deforms asynchronously over the cardiac cycle, possibly due to variations in local mechanical properties or the influence of branching vessels.

The implications of these findings extend to multiple clinical domains. Abnormal pulsatility patterns may serve as early indicators of vascular pathology before morphological changes become apparent. Figure 4.15 illustrates the average minimum and maximum BA endoluminal surface deformations observed in our studies, highlighting significant circumferential expansion.

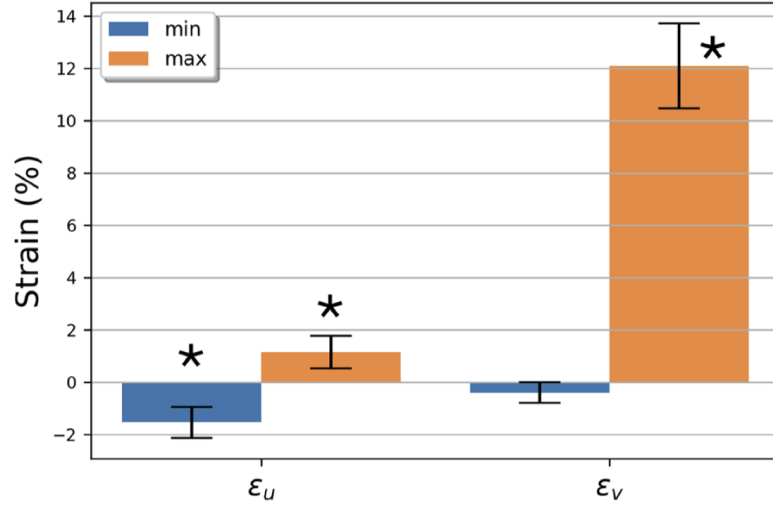


Figure 4.15: Average minimum and maximum BA endoluminal surface deformations from the $n=3$ normal BA studied. Here, the deformations were expressed as a strain $\epsilon_i = 100 * (\lambda_i - 1)$, $i = u, v$, to facilitate comparisons. While the maximum and minimal axial strains ϵ_u were statistically different from 0, their magnitudes were generally small ($\sim 1\%$). The minimum circumferential strains ϵ_v were not different from zero. In contrast, the maximum circumferential strains (ϵ_v) were both large ($\sim 12\%$) and statistically different from 0.

The integration of lumen area pulsatility measurements with traditional velocity assessments offers a more comprehensive evaluation of cerebrovascular function and may enhance our ability to predict and manage conditions such as aneurysms, dementia, and stroke [34, 82]. The reproducibility of these pulsatility measurements, as validated through our test-retest experiments, further confirms CineMerge as a reliable tool for both research applications and potential clinical use.

In summary, the CineMerge technique provides a robust approach to quantifying in-

tracranial vascular pulsatility through direct measurement of lumen area changes. This novel aspect of vascular mechanics, previously difficult to assess *in vivo*, offers valuable complementary information to traditional flow velocity measurements, promising advancements in the diagnosis and treatment of cerebrovascular diseases.

4.4 Limitations and Implications for Large-scale Studies

While significant advancements have been made in vascular imaging techniques, several limitations persist that impact the feasibility of large-scale studies. The advanced sequences described in this chapter—iSNAP and CineMerge—offer tremendous potential for comprehensive vascular assessment but remain primarily in the research domain rather than clinical practice.

The primary constraint for large-scale implementation stems from limited accessibility to these novel sequences, which are currently available only at specialized research centers with advanced MRI hardware and expertise. Meanwhile, the previous Chapter on large-scale TOF-MRA datasets demonstrates the feasibility of collecting substantial morphological data across multiple centers. However, TOF-MRA provides only basic morphological biomarkers without capturing the functional and hemodynamic information accessible through iSNAP’s dMRA or CineMerge’s pulsatility measurements.

This dichotomy between widespread availability of basic morphological imaging and limited access to advanced functional imaging creates both challenges and opportunities. **The morphological biomarkers derived from large-scale TOF-MRA datasets serve as observable endpoints, while the hemodynamic and functional measurements from advanced sequences help elucidate the underlying mechanisms driving these morphological changes.** For instance, the vessel wall abnormalities detectable through iSNAP’s vessel wall reconstruction or the arterial pulsatility quantifiable through CineMerge may explain the stenosis, dilation, or tortuosity observed in TOF-MRA.

Chapter 5

GRAPH-BASED APPROACHES FOR ARTERIAL NETWORK ANALYSIS

5.1 *Introduction to Graph-based Models*

The human BANs represents one of the most complex vascular systems in the body, with numerous clinical conditions associated with its structural and functional characteristics. Traditional analysis methods often struggle to capture the intricate patterns and relationships within these networks. Graph-based approaches offer a natural framework for modeling vascular structures, where vessels can be represented as edges and bifurcations as nodes.

BANs exhibit intrinsic graph-like properties that make them particularly well-suited for graph-theoretic analysis. The topology of these networks which includes features such as connectivity patterns, hierarchical organization, and collateral pathways, contains valuable information about both normal physiology and pathological states. Graph theory provides mathematical tools to quantify these structural properties and their relationship with clinical outcomes.

Recent advances in graph-based machine learning, particularly GNNs, have opened new possibilities for analyzing complex networks in healthcare. Unlike traditional statistical approaches that rely on predefined graph metrics, GNNs can learn relevant features directly from the data, potentially uncovering novel biomarkers and relationships not captured by conventional analysis.

5.2 *Graph Model for Hemodynamic Analysis in Circle-of-Willis*

The Circle of Willis (COW) is a crucial mechanism for cerebral collateral circulation. When principal conduits fail, it plays a pivotal role in maintaining cerebral blood flow and extending the treatment window before revascularization [37]. As the primary collateral circulation

mechanism in the brain, the COW bridges the interhemispheric blood flow pathways and connects anterior and posterior circulations, providing rapid response to cerebral blood flow alteration in acute vascular events [38]. Therefore, a comprehensive evaluation of both the structure and blood flow of COW is important for the diagnosis and treatment of cerebrovascular diseases.

Due to the wide availability of angiography techniques such as DSA, CTA, and MRA, the patency and caliber of the arterial segments in COW have been extensively explored regarding their characteristics and clinical relevance [29]. However, the blood hemodynamics within these segments have been less studied in clinical practice, largely attributed to the difficulty in measurement.

5.2.1 Methodology

A novel approach was developed to estimate flow direction within the COW using ASL-dMRA and graph-based analysis [76]. This method employed three principal methodologies to determine time curve shifts from ASL-dMRA:

1. **Graph Modeling:** The arterial network of COW was represented as a graph, with nodes representing points on the arterial centerlines and edges representing vessel segments. This representation improved characterization of the inherent connections between arteries and served as a low-pass filter to reduce noise in the time signals.
2. **Bootstrap Strategy:** This statistical resampling technique was used to estimate flow patterns from high-dimensional data, reducing variance and uncertainty in the prediction results.
3. **Ensemble Learning:** Four different analysis strategies were employed and combined to derive robust flow direction estimates, improving predictive performance through integration of multiple approaches.

Fig. 5.1 illustrates the overall workflow of the approach, showing ASL-dMRA images, centerline tracing results, labeled COW arteries, and time signals along vessel centerlines.

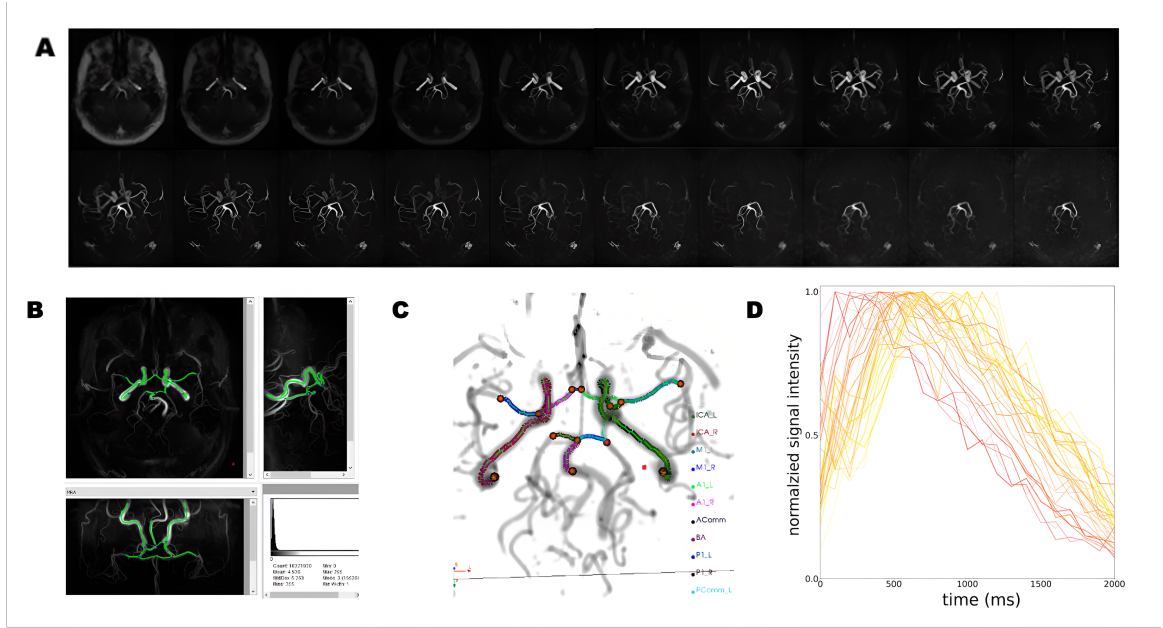


Figure 5.1: (A) Representative ASL-dMRA images obtained by the iSNAP sequence. (B) Centerline tracing results based on the tMIP of dMRA. (C) The labeled COW arteries for flow direction estimation. (D) Time signals along the centerline of ICA, measured from ASL-dMRA. The red ones correspond to the proximal sites of ICA, while the light yellow ones correspond to the distal sites.

The flow direction within the COW can be predicted by estimating the time curve shift and identifying the source of the signal profile that reaches the peak earlier.

5.2.2 Ensemble Strategies

For each arterial segment, four ensemble strategies were employed to calculate the flow direction independently:

As shown in Fig. 5.2, the target artery was divided into halves, with each half connected to the adjacent artery. The flow direction was determined by analyzing correlations between different parts:

1. Strategy 1: Calculate correlation between the adjacent artery and the first half of the target artery, and between the first half and second half of the target artery.

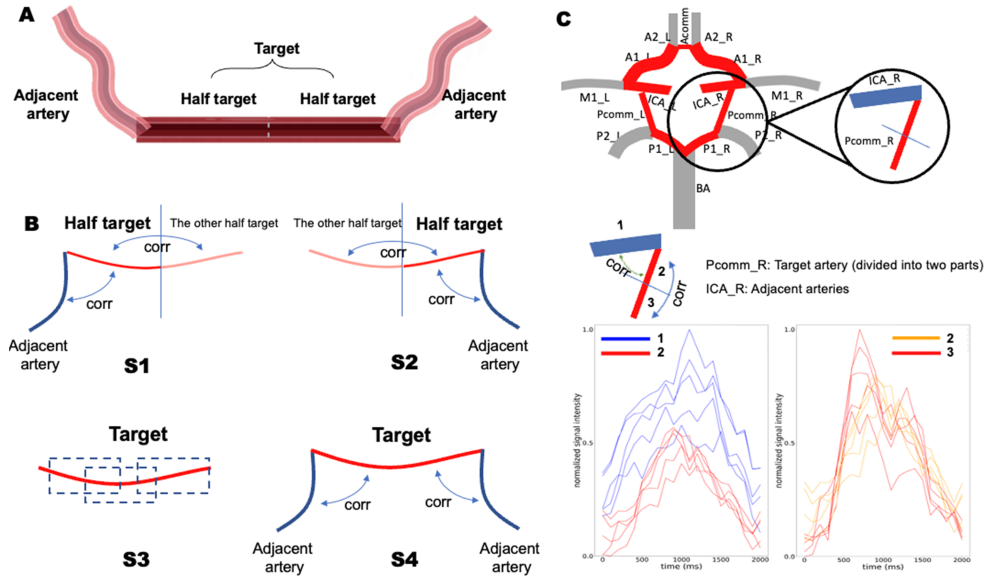


Figure 5.2: The four strategies employed to estimate flow direction of COW arteries based on ASL-dMRA. (A) Illustration of different parts of the target artery and its adjacent arteries. (B) Schematics showing how the correlation coefficients were calculated for flow direction. (C) An example showing how to derive flow direction for the target artery (right posterior communicating arteries (PcomAs)) from strategy 1 in the COW. The correlation between the adjacent artery (right ICA, #1) and the first half of the target artery (#2) was first calculated, and then the correlation between the first half of the target artery (#2) and the other half of the target artery (#3) was calculated.

2. Strategy 2: Similar to Strategy 1 but focusing on the other side of the target artery.
3. Strategy 3: Calculate correlation between distance and time-to-peak within the target artery.
4. Strategy 4: Calculate correlation between the adjacent arterial segment and the target artery instead of dividing into halves.

Table 5.1: Length, radius, and correct prediction counts for arterial segments ($n = 52$)

Arterial Segment	Length (mm)	Radius (mm)	Accuracy
ICA_R	89.8 ± 16.9	2.7 ± 0.4	98.07% (51/52)
ICA_L	87.9 ± 15.2	2.8 ± 0.3	98.04% (50/51)
A1_R	18.3 ± 3.4	1.9 ± 0.3	95.65% (44/46)
A1_L	17.5 ± 2.3	1.9 ± 0.3	97.78% (44/45)
AcomA	4.2 ± 1.8	1.8 ± 0.4	78.26% (18/23)
PcomA_R	15.1 ± 3.2	1.8 ± 0.4	86.67% (13/15)
PcomA_L	14.9 ± 4.1	1.9 ± 0.3	94.44% (17/18)
P1_R	11.7 ± 4.7	2.2 ± 0.4	88.10% (37/42)
P1_L	10.9 ± 4.3	2.2 ± 0.3	88.10% (37/42)

5.2.3 Results

Among 52 subjects with atherosclerotic disease, 340 arterial segments in COW were evaluated, including ICAs, A1, P1, anterior communicating artery (AcomA), and posterior communicating arteries (PcomAs). The developed method achieved an overall accuracy of 95.47%, sensitivity of 80.00%, and specificity of 96.34% when compared to flow directions derived from 3D phase-contrast (PC) MR imaging.

Table 5.1 shows the length and radius of the COW arteries measured from ASL dMRA, as well as the accuracy of flow prediction for each arterial segment. The method performed particularly well for major vessels like ICAs and A1 segments, with accuracy exceeding 95%, while the accuracy for smaller communicating arteries was somewhat lower.

Table 5.2 shows the performance of each individual strategy and the combined approach. While individual strategies showed varied performance (accuracy ranging from 47.60% to 78.44%), the ensemble approach significantly improved overall performance, highlighting the value of combining multiple analysis techniques.

Fig. 5.3 presents the results of ablation studies exploring the effects of sampling time and number of sampling points on estimation performance. The optimal parameter combi-

Table 5.2: Accuracy, sensitivity, and specificity of the 4 strategies, along with overall performance metrics

Strategy	Accuracy	Sensitivity	Specificity
s1	47.60% (159/334)	80.56% (29/36)	43.96% (131/298)
s2	60.48% (202/334)	30.56% (11/36)	68.79% (205/298)
s3	78.44% (262/334)	61.11% (22/36)	80.54% (240/298)
s4	56.29% (188/334)	75.00% (27/36)	55.37% (165/298)
Overall	92.80% (310/334)	83.33% (30/36)	93.96% (280/298)

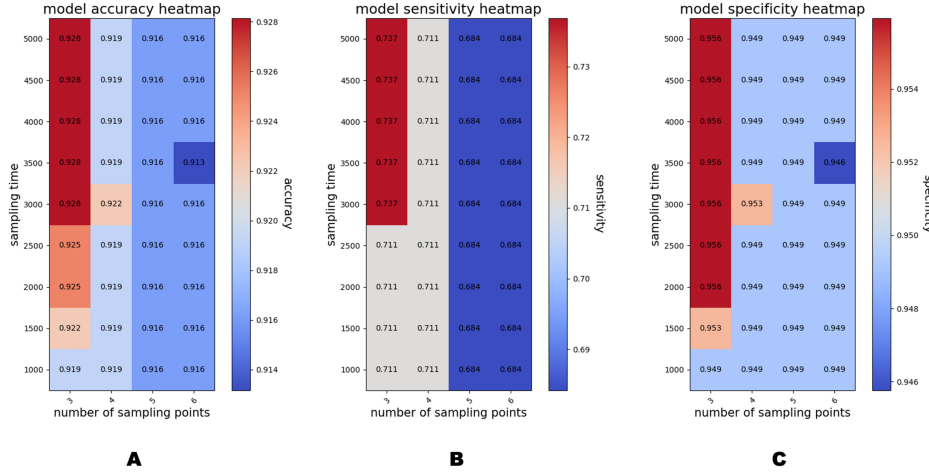


Figure 5.3: Accuracy (A), sensitivity (B), and specificity (C) of the flow direction estimation in the ablation study, in which different sampling time and the number of sampling points were used.

nations were identified as a sampling time of 3000 and 3 sampling points, which balanced computational efficiency with estimation accuracy.

5.3 Graph Neural Networks for Vascular Analysis

GNNs have emerged as powerful tools for analyzing graph-structured data, with demonstrated success across various domains. Their ability to learn from both node features and graph topology makes them particularly well-suited for analyzing anatomical structures like the brain arterial network.

Several key characteristics of BANs make GNN approaches especially appropriate:

1. **Natural graph structure:** The branching pattern of arteries naturally forms a graph with meaningful topology.
2. **Multi-scale features:** Arterial networks contain information at multiple scales, from individual vessel segments to global network patterns.
3. **Edge-centric information:** In BANs, critical clinical features (e.g., radius, tortuosity, length) often reside in edges rather than nodes.
4. **Hierarchical organization:** Blood vessels exhibit clear hierarchical patterns from major feeding arteries to distal branches.

5.3.1 Graph Convolutional Networks

Graph Convolutional Networks (GCNs) extend the concept of convolutional neural networks to graph-structured data. The key operation in GCNs is neighborhood aggregation, where each node's representation is updated by combining information from its neighbors [35].

For a brain arterial network represented as a graph $G = (V, E)$ with node features X , a typical GCN layer performs the following operation:

$$H^{(l+1)} = \sigma(D^{-\frac{1}{2}} \hat{A} D^{-\frac{1}{2}} H^{(l)} W^{(l)}) \quad (5.1)$$

Where:

- $H^{(l)}$ is the node feature matrix at layer l

- $\hat{A} = A + I$ is the adjacency matrix with self-connections
- D is the degree matrix of $\hat{A}$
- $W^{(l)}$ is a trainable weight matrix
- σ is a non-linear activation function

While effective for many graph learning tasks, standard GCNs face limitations when applied to BANs:

1. They operate primarily on node features, whereas key vascular characteristics are often associated with edges
2. They struggle to capture long-range dependencies across the network
3. They lack the ability to explicitly model hierarchical relationships

5.3.2 Graph Attention Networks

Graph Attention Networks (GATs) address some limitations of GCNs by introducing attention mechanisms that allow nodes to weigh their neighbors differently [67]. This approach enables more flexible information aggregation and can potentially capture more complex relationships.

In a GAT layer, the attention coefficient between nodes i and j is computed as:

$$\alpha_{ij} = \text{softmax}_j(e_{ij}) = \frac{\exp(e_{ij})}{\sum_{k \in N(i)} \exp(e_{ik})} \quad (5.2)$$

Where e_{ij} is typically computed as:

$$e_{ij} = \text{LeakyReLU}(a^T [Wh_i \parallel Wh_j]) \quad (5.3)$$

The updated node features are then calculated as:

$$h'_i = \sigma \left(\sum_{j \in N(i)} \alpha_{ij} W h_j \right) \quad (5.4)$$

For BANs, GATs offer advantages in their ability to focus on the most relevant vessel connections. However, like GCNs, standard GATs are primarily designed for node-centric learning and may not fully leverage the edge features critical for vascular analysis.

5.3.3 Graph Transformers

Graph Transformers (GTs) extend the self-attention mechanism of transformer architectures to graphs, allowing for global information exchange across all nodes regardless of their proximity in the graph [17]. This capability is particularly valuable for modeling long-range dependencies in complex networks like the BAN.

A key advantage of graph transformers is their ability to incorporate both local (through optional message passing) and global (through self-attention) information. The general structure of a graph transformer layer follows:

$$H^{(l+1)} = \text{MultiHeadAttention}(\text{LN}(H^{(l)})) + H^{(l)} \quad (5.5)$$

$$H^{(l+2)} = \text{FFN}(\text{LN}(H^{(l+1)})) + H^{(l+1)} \quad (5.6)$$

Where LN is layer normalization and FFN is a feed-forward network.

In the context of brain arterial networks, graph transformers can potentially overcome the limitations of GCNs and GATs by:

1. Capturing long-range dependencies between distant vessel segments
2. Modeling global circulation patterns
3. Reducing the over-smoothing problem common in deep GNNs

However, standard graph transformers still face challenges in modeling the hierarchical structure inherent to vascular networks and effectively incorporating edge features.

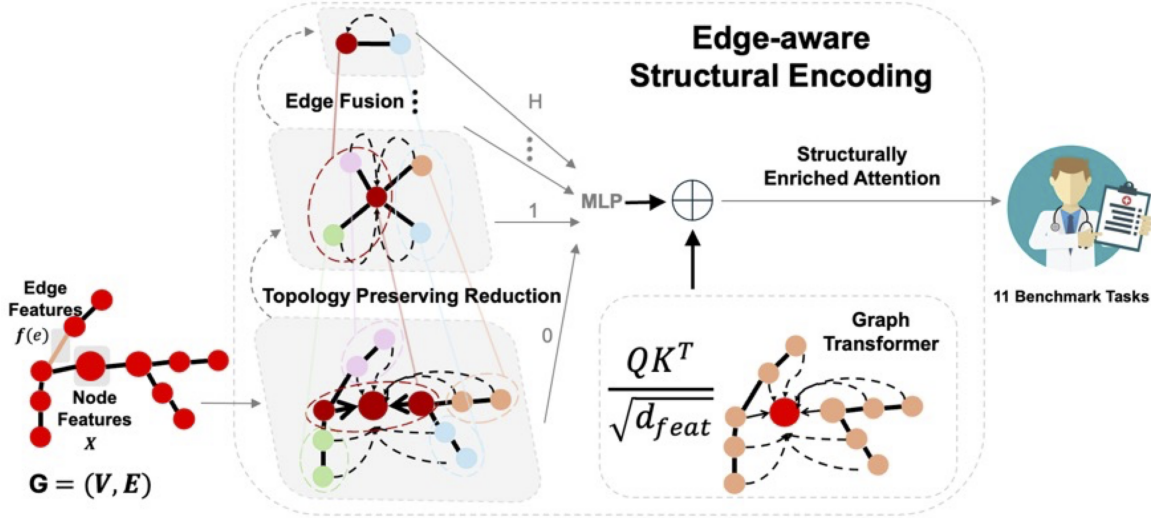


Figure 5.4: Architecture of the proposed hierarchical graph transformer (HGT) with edge-aware structural encoding. The framework processes a vascular graph through hierarchical structural encoding pathways, transforming edge features into multi-level representations. These encodings are integrated with standard transformer attention, producing structurally enriched attention for capturing hierarchical information of the graph.

5.3.4 Novel Adaptations for Brain Arterial Network

To address the specific challenges of modeling brain arterial networks, a hierarchical graph transformer (HGT) with edge-aware structural encoding has been proposed [77]. This model incorporates several key innovations to effectively process vascular graph data:

As shown in Fig. 5.4, the HGT model incorporates:

1. **Edge-Aware Structural Encoding:** Unlike standard GNN approaches that focus primarily on node features, HGT explicitly incorporates edge features through a dedicated encoding pathway. This is particularly important for BANs, where critical arterial attributes such as radius, tortuosity, and length are associated with edges rather than nodes.
2. **Topology-Preserving Reduction:** A specialized graph reduction technique preserves the essential vascular branching structure while eliminating redundant nodes from continuous vessel segments, focusing on bifurcation and terminal nodes.

3. **Multi-Level Edge Fusion:** To capture multi-scale structural information, a heavy-edge matching algorithm generates a hierarchy of graphs at different levels of abstraction. A composite function that favors merging of thick and short segments—a biologically meaningful heuristic for vascular networks—guides this process:

$$m(e) = \frac{r(e)^2}{l(e)} \quad (5.7)$$

where $r(e)$ is the radius and $l(e)$ is the length of edge e .

4. **Structurally Enriched Attention:** The multi-level edge encoding is processed to generate an attention bias, allowing the model to modulate attention based on hierarchical structural information:

$$\text{Attn}(X) = \text{softmax} \left(\frac{QK^T}{\sqrt{d_{feat}}} + B \right) V \quad (5.8)$$

where B is a bias matrix constructed from multi-level structural encodings.

5.4 Training and Validation Strategies

Developing effective graph-based models for arterial network analysis presents several methodological challenges. To address these challenges, specialized training approaches have been implemented:

1. **Cross-Validation:** A 5-fold cross-validation strategy is employed for both classification and regression tasks to ensure robust model evaluation.
2. **Data Augmentation:** To enhance training power while managing computational time, augmentation techniques are applied with a multiplier of 5. These techniques include adding Gaussian noise (std=0.01) to node coordinates and performing random node sampling to simulate variability in arterial density.

Table 5.3: Regression performance across tasks (MAE↓/R²↑)

Model	Age	HDL	LDL	TC	SBP	DBP	FRS
GCN	4.81±0.38	4.48±0.40	4.74±0.45	4.47±0.50	5.03±0.81	4.49±0.51	4.36±0.27
	0.43±0.08	0.51±0.06	0.46±0.10	0.51±0.09	0.40±0.18	0.51±0.08	0.53±0.05
GAT	2.42±0.28	2.47±0.23	2.37±0.21	1.30±0.05	2.46±0.21	2.42±0.23	2.46±0.20
	0.84±0.03	0.83±0.03	0.84±0.03	0.95±0.00	0.83±0.03	0.84±0.03	0.84±0.03
GT	4.29±0.42	3.95±0.37	4.22±0.48	3.96±0.52	4.57±0.79	3.98±0.49	3.84±0.31
	0.65±0.07	0.72±0.05	0.67±0.11	0.70±0.10	0.62±0.17	0.73±0.09	0.74±0.06
GPS	3.51±0.31	3.22±0.23	3.44±0.37	3.10±0.22	3.68±0.49	3.36±0.32	3.52±0.38
	0.72±0.05	0.78±0.04	0.73±0.05	0.84±0.03	0.79±0.06	0.81±0.05	0.82±0.04
HGT	2.12±0.21	2.15±0.18	2.05±0.15	1.10±0.04	2.27±0.18	2.12±0.20	2.05±0.18
(ours)	0.88±0.02	0.87±0.03	0.89±0.03	0.97±0.00	0.86±0.03	0.88±0.02	0.89±0.02

3. **Hyperparameter Tuning:** Automated grid search managed by tools like Neural Network Intelligence (NNI) with cosine learning rate schedulers optimizes model configuration.

5.5 Performance Evaluation and Model Comparison

5.5.1 Regression Performance

Table 5.3 presents regression performance across various tasks, comparing standard GNN architectures with the proposed HGT model. For all regression targets—including age, blood lipid levels (HDL, LDL, TC), blood pressure (SBP, DBP), and cardiovascular risk score (FRS)—HGT consistently achieves the lowest Mean Absolute Error (MAE) and highest coefficient of determination (R²).

5.5.2 Classification Performance

Tables 5.4 and 5.5 show classification performance across various tasks. For all classification targets—including smoking status, diabetes, hypertension, and FRS level—HGT consistently achieves superior performance, particularly in terms of AUC. Notably, the HGT model demonstrates not only better performance but also more stable results, as evidenced

Table 5.4: Classification performance across tasks (Micro-F1/Macro-F1/AUC)

Model	Smoking	Diabetes	HT
GCN	72.40±4.38/71.16±5.08/81.79±2.12	74.38±4.69/73.19±5.34/82.51±2.83	74.38±4.14/73.43±4.65/82.36±1.53
GAT	72.39±3.72/71.12±4.30/80.59±3.61	71.37±6.63/69.41±7.44/80.06±3.74	71.14±1.90/69.64±1.54/79.09±1.39
GT	77.48±4.41/76.21±5.12/82.85±2.18	79.42±4.73/78.24±5.29/83.58±2.79	79.45±4.22/78.51±4.71/83.41±1.60
GPS	74.71±8.51/72.88±8.40/77.42±4.12	74.68±10.36/74.53±10.39/80.75±10.13	70.68±8.45/69.90±12.19/78.75±5.32
HGT (ours)	75.64±1.70/74.82±1.61/83.23±1.41	76.84±1.45/75.35±1.42/84.12±1.31	76.53±1.39/75.24±1.36/83.82±1.23

Table 5.5: Classification performance for FR level prediction (Micro-F1/Macro-F1/AUC)

Model	FR Level
GCN	74.38±4.14/73.43±4.65/82.36±1.53
GAT	69.63±3.46/67.76±2.98/79.93±3.25
GT	79.47±4.19/78.49±4.68/83.40±1.55
GPS	74.68±8.31/72.12±8.69/79.75±10.92
HGT (ours)	76.23±1.23/74.92±1.26/83.45±1.12

Table 5.6: Ablation studies on FR level prediction (Micro-F1/Macro-F1/AUC)

Metrics	Full Model	w/o Hier. Enc.	w/o Virtual Node	w/o Art. Feat.	Endpts + Bifurc.
Micro-F1	76.23±1.23	74.68±8.31	75.53±1.20	52.45±3.41	50.67±1.51
Macro-F1	74.92±1.26	72.12±8.69	73.32±1.42	37.89±4.60	36.12±1.72
AUC	83.45±1.12	79.75±10.92	81.15±1.78	60.23±5.50	58.46±1.63

by the smaller standard deviations across multiple runs.

5.5.3 Ablation Studies

Table 5.6 presents ablation studies examining the contribution of different components to the overall model performance. Removing hierarchical encoding reduces performance, indicating its importance for capturing multi-scale features. Without the virtual node, information flow is disrupted. Removing arterial features (length, tortuosity, radius) causes severe



Figure 5.5: Visualization of node and edge attention importance in BAN for age prediction across three subjects of increasing age (48, 67, and 88 years). The intensity of red coloring indicates higher attention weights.

degradation, confirming these attributes' critical role. Using only bifurcation and endpoint nodes (post topology-preserving reduction) similarly impairs performance.

5.5.4 Visualization of Attention Patterns

Fig. 5.5 shows the visualization of attention patterns in the HGT model for age prediction across subjects of different ages. Notably, distal arterial branches exhibit higher attention weights, which aligns with prior studies showing that aging particularly affects distal vasculature [78]. This visualization demonstrates the model's ability to focus on clinically relevant vascular features when making predictions.

5.6 Limitations and Methodology Considerations

Despite their promise, graph-based approaches for arterial network analysis face several important limitations:

1. **Anatomical Variability:** Graph models may not fully capture the extensive anatomical variability inherent to diseased populations, potentially limiting robustness in cases with atypical vascular anatomy.

2. **Validation Requirements:** Novel methodologies require extensive validation against established clinical and imaging standards, which can be challenging to obtain for specialized vascular measurements.
3. **Computational Complexity:** Graph neural networks, particularly transformers with attention mechanisms, can be computationally intensive when applied to large vascular networks with hundreds of nodes and edges.
4. **Interpretability Challenges:** While graph-based models can achieve high predictive performance, ensuring clinical interpretability remains challenging, particularly for complex architectures like graph transformers.
5. **Data Scarcity:** Limited availability of large-scale, well-annotated vascular network datasets remains a significant obstacle to developing and validating advanced graph-based models.

Future methodological improvements should focus on enhancing adaptability to rare anatomical configurations, addressing scalability challenges for widespread clinical implementation, and strengthening the biological plausibility of model operations to improve both performance and interpretability.

5.7 Summary

Graph-based approaches offer powerful frameworks for analyzing the complex structural and functional characteristics of BANs. From classical graph theoretical measures to advanced neural network architectures, these methods provide unique capabilities to quantify vascular patterns and their associations with clinical conditions.

Recent innovations in GNNs address many of the specific challenges inherent to vascular network analysis. By explicitly incorporating edge features, capturing hierarchical relationships, and modeling both local and global vascular patterns, these specialized architectures achieve superior performance in predicting various cardiovascular risk factors from brain arterial network structure.

The continued advancement of graph-based methods for arterial network analysis promises to enhance our understanding of vascular-systemic relationships while establishing foundations for more precise, personalized cardiovascular risk stratification. This work demonstrates that brain arterial network structure contains **rich information about systemic cardiovascular health that can be effectively decoded using specialized graph neural network architectures.**

Chapter 6

CLINICAL BIOMARKER DISCOVERY FROM BRAIN ARTERIAL NETWORKS

6.1 *Classical Morphological Biomarkers*

Our investigation into non-invasive cerebrovascular biomarkers began with the analysis of classical morphological features of the cerebral arterial network. Building upon established literature exploring the relationship between cerebrovascular health and cognitive function [26, 84], we specifically focused on the medium-to-large distal arteries—a vascular domain positioned between the well-studied proximal large arteries and the microvascular bed.

In a prospective longitudinal study of 27 subjects with high cardiovascular risk, we examined the relationship between morphological features of cerebral arteries, as measured by TOF-MRA, and cognitive function, as assessed by the Montreal Cognitive Assessment (MoCA) [78]. Subjects underwent baseline and 12-month follow-up evaluations, allowing us to analyze not only cross-sectional associations but also longitudinal changes in both vascular morphology and cognitive performance.

6.1.1 *Quantification Approach*

We utilized the iCafe software [10] to extract three primary morphological features: **Artery Length**, **Branch Number**, **Tortuosity**.

These features were derived from two non-contrast-enhanced MRA sequences: TOF and SNAP. Each feature was further categorized by arterial territory (anterior, middle, and posterior cerebral arteries) and anatomical position (proximal versus distal to the A1-A2, M1-M2, and P1-P2 connection points).

Table 6.1: Clinical characteristics of the enrolled subjects (N = 27)

Variable	Mean $\pm$ SD or N (%)
Age	72.5 $\pm$ 10.2
Male	19 (70)
BMI (kg/m ²)	28.0 $\pm$ 3.7
Hypertension	17 (63)
Systolic blood pressure (mm Hg)	145.7 $\pm$ 12.5
Diastolic blood pressure (mm Hg)	80.6 $\pm$ 10.0
Use of antihypertensive drug	17 (63)
Diabetes	1 (4)
Smoking	13 (48)

6.1.2 Key Findings

Our analysis revealed several significant associations between cerebrovascular morphology and cognitive function:

1. Changes in global medium-to-large artery length and branch numbers, as measured on SNAP MRA, were significantly associated with alterations in MoCA scores ($r = 0.55$, $P = 0.003$ and $r = 0.71$, $P < 0.001$, respectively).
2. These associations remained significant after adjusting for potential confounding factors including age, total brain volume, white matter lesion volume, hypertension, diabetes, smoking, and obesity.
3. Territorial analysis showed that morphological changes in the posterior cerebral artery (PCA) territory demonstrated the strongest correlation with cognitive changes. SNAP PCA artery length change ($r = 0.69$, $P < 0.001$) and branch number change ($r = 0.77$, $P < 0.001$) were both significantly associated with MoCA score changes after Holm-Bonferroni correction.

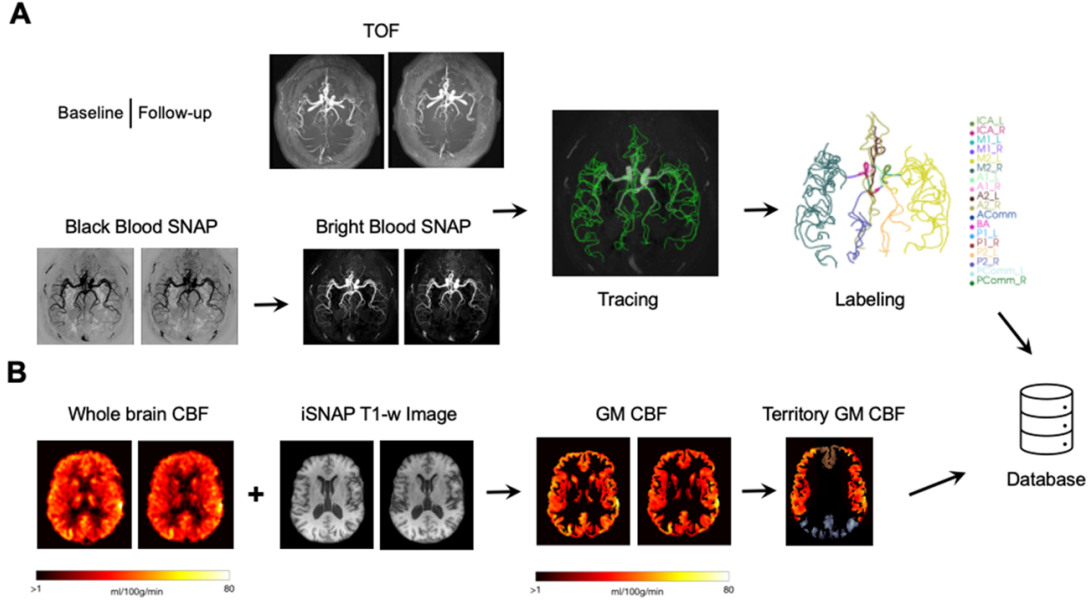


Figure 6.1: The overall workflow of image post-processing for TOF, SNAP, and ASL perfusion-weighted image. (A) Workflow in iCafe based method: SNAP is first transformed to a bright blood image and then a pre-trained segmentation model is used for vessel segmentation. A novel deep open snake tracker model is used to trace the vessels for both TOF and bright blood SNAP. The final step is to label different arteries for calculating territorial vascular features. (B) Workflow for CBF post-processing: grey matter (GM) cerebral blood flow (CBF) is segmented from whole-brain CBF using the T1-w image. Then, territorial CBFs (anterior communicating artery, ACA; middle cerebral artery, MCA; and posterior cerebral artery, PCA) are calculated.

4. No significant associations were found between changes in gray matter cerebral blood flow (GM CBF), as measured by arterial spin labeling (ASL), and changes in MoCA scores.

6.1.3 Comparison of Imaging Techniques

The differential sensitivity of SNAP versus TOF in detecting cognition-relevant vascular changes warrants particular attention. SNAP's superior performance likely stems from its enhanced sensitivity to slow flow in distal arteries [?], capturing hemodynamic alterations that may precede detectable changes in tissue-level perfusion. This technical advantage

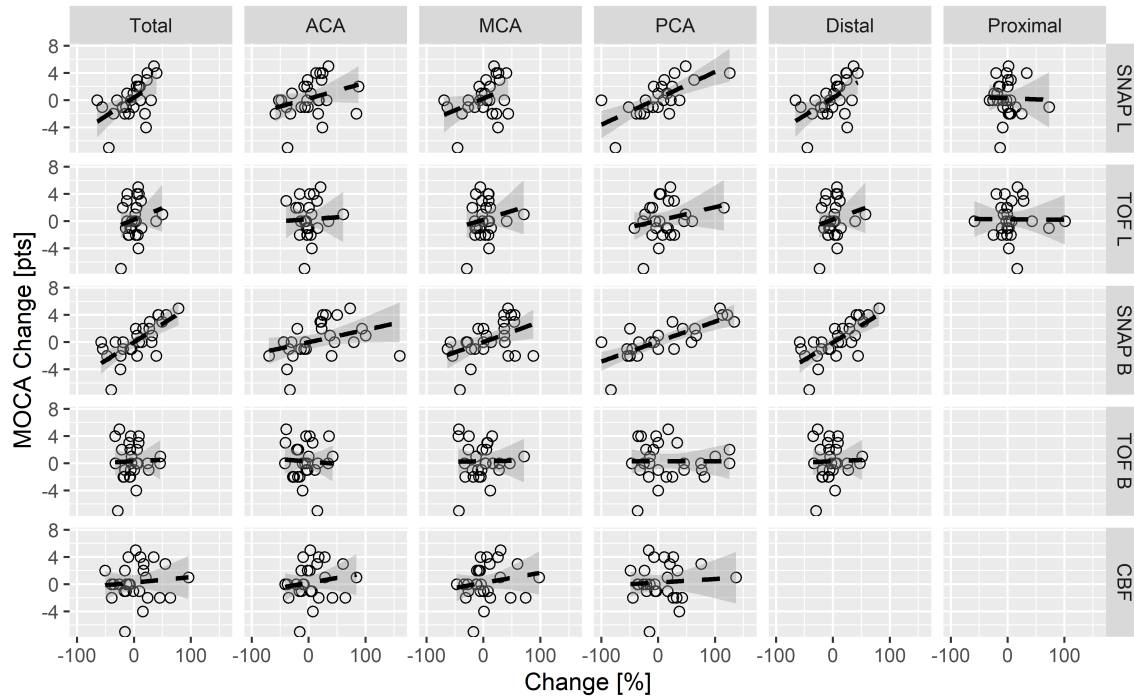


Figure 6.2: Univariable regression associations between the percentage of total, proximal, and territorial distal SNAP artery length change, TOF artery length change, ASL GM CBF change, and changes in MoCA scores (L represents length, B represents branch number). A significant positive association was found between the percentage of total SNAP artery length change and changes in MoCA scores in the whole population ($r = 0.55$, $P = 0.003$), while the percentage of total TOF artery length change and ASL GM CBF change were not significantly associated with changes in MoCA scores. A significant association between the percentage of SNAP distal artery length change and changes in MoCA scores ($r = 0.55$, $P = 0.003$) was obtained, while no significant association was seen between TOF distal artery length change and changes in MoCA scores. A significant positive association between the percentage of SNAP PCA branch number change and MoCA score change was obtained ($r = 0.7$, $P < 0.01$ and still significant after Bonferroni-Holm correction).

enables SNAP to visualize more distal arterial segments and to better reflect subtle changes in cerebrovascular physiology.

6.1.4 Limitations of Classical Morphological Biomarkers

Despite demonstrating significant associations with cognitive function, classical morphological biomarkers exhibit several limitations:

Table 6.2: Linear regression summary between different vascular features and MoCA score change in different sequences

Predictors	Model 1		Model 2	
	β (95% CI)	P-value	β (95% CI)	P-value
SNAP, artery length change	0.7 (0.3–1.1)	0.002	0.8 (0.3–1.3)	0.003
TOF, artery length change	0.2 (−0.3–0.7)	0.371	0.3 (−0.4–0.9)	0.389
ASL, GM CBF change	0.2 (−0.2–0.7)	0.336	0.5 (−0.2–1.2)	0.343
SNAP, branch number change	0.8 (0.5–1.2)	<0.001	1.0 (0.6–1.3)	<0.001
TOF, branch number change	0.0 (−0.5–0.6)	0.930	0.0 (−0.6–0.6)	0.958
SNAP, tortuosity change	−0.2 (−0.8–0.4)	0.510	−0.4 (−1.1–0.4)	0.321
TOF, tortuosity change	−0.3 (−0.8–0.1)	0.174	−0.3 (−0.9–0.3)	0.271

Model 1 = adjusted for age and baseline total white matter lesion (WML) volume and total brain volume.

Model 2 = Model 1 + other risk factors (hypertension + diabetes + smoking + obesity).

Bold P-values are still significant after Holm-Bonferroni correction.

1. They provide surface-level descriptors without capturing the underlying topological organization and connectivity patterns of the vascular network.
2. These features do not explicitly account for the complex relationships between different segments within the vascular network.

These limitations highlight the need for more sophisticated analytical approaches that can better characterize the complex architecture of cerebral arterial networks and their relationship to cognitive function. As we will explore in subsequent sections, graph-based approaches offer a promising framework for addressing these shortcomings by explicitly modeling vascular topology and leveraging deep learning to identify more subtle and complex biomarkers.

6.2 Intracranial Arterial Calcification and Cerebral Blood Flow

Building upon our investigation of classical morphological biomarkers, we extended our research to explore the relationship between intracranial arterial calcification and cerebral

Table 6.3: Territory linear regression summary between different vascular features and MoCA score change

Model	ACA		MCA		PCA	
	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value
Model 1						
SNAP, artery length change	0.2 (−0.2–0.8)	0.201	0.6 (0.1–1.0)	0.012	0.7 (0.4–1.1)	<0.001
TOF, artery length change	0.0 (−0.5–0.5)	0.983	0.2 (−0.3–0.7)	0.378	0.3 (−0.2–0.8)	0.265
SNAP, branch number change	0.3 (−0.2–0.8)	0.168	0.5 (0.1–1.0)	0.0158	0.8 (0.4–1.0)	<0.001
Model 2						
SNAP, artery length change	0.5 (−0.2–1.1)	0.130	0.7 (0.2–1.1)	0.012	0.8 (0.3–1.2)	0.002
TOF, artery length change	−0.1 (−0.7–0.6)	0.870	0.2 (−0.3–0.8)	0.389	0.3 (−0.3–1.0)	0.257
SNAP, branch number change	0.4 (−0.1–1.0)	0.120	0.8 (0.3–1.3)	0.003	0.8 (0.5–1.2)	<0.001

Model 1 = adjusted for age and baseline total white matter lesion (WML) volume and total brain volume.

Model 2 = Model 1 + other risk factors (hypertension + diabetes + smoking + obesity).

Bold P-values are still significant after Holm-Bonferroni correction.

blood flow in patients with high cardiovascular risk. This study offers complementary insights into the structural and functional characteristics of cerebral vasculature that may contribute to cognitive impairment.

6.2.1 Study Rationale

The vascular biomechanics, encompassing both blood flow and vessel integrity, plays a significant role in the management of cognitive function [78]. While our previous investigations demonstrated associations between vascular morphology and cognitive performance, the impact of large vessel pathology—particularly arterial calcification—on cerebral blood

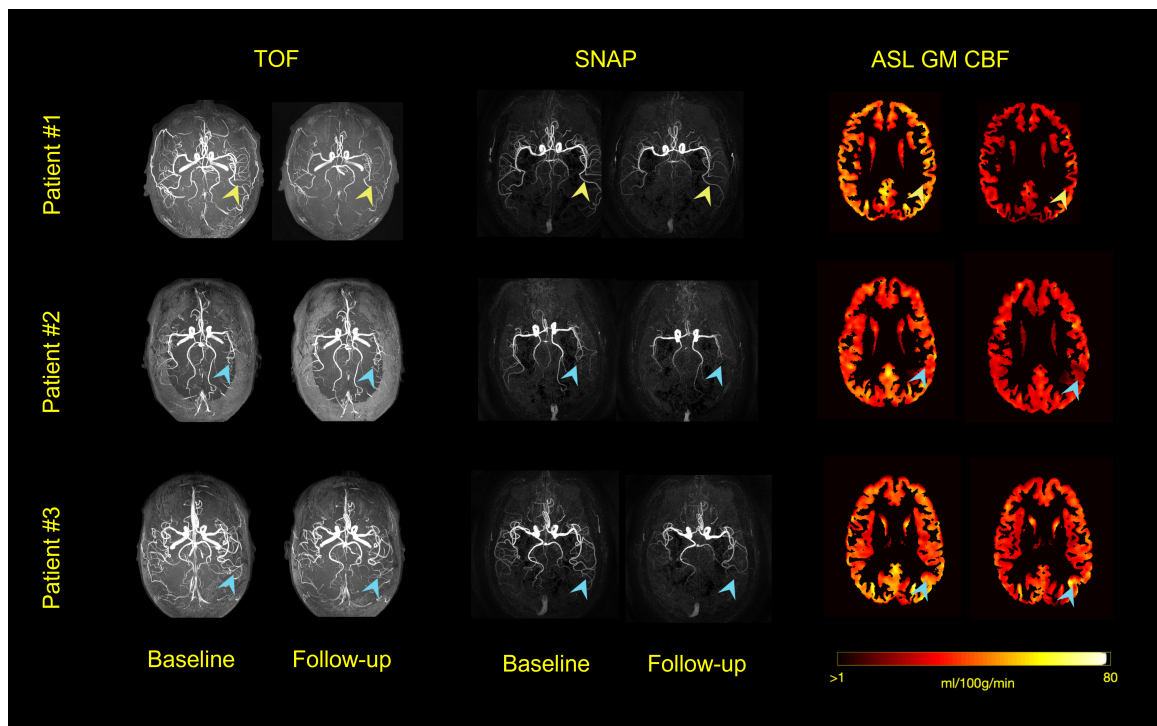


Figure 6.3: 3D TOF, 3D SNAP, and ASL perfusion-weighted images of three representative subjects. Blue arrows point out the inconsistent change between SNAP and TOF, ASL GM CBF, while yellow arrows point out the consistent change in SNAP, TOF, and ASL GM CBF. The first subject had a decreased MoCA score from 23 to 18, with consistent artery length reduction in the posterior cerebral artery (PCA) and middle cerebral artery (MCA) territories in TOF and SNAP, along with a global reduction in GM CBF. The second subject had a decreased MoCA score from 29 to 26, with artery length reduction in MCA and PCA territories in SNAP but no obvious artery length change in TOF, and GM CBF decrease in PCA territory. The third subject had a decreased MoCA score from 29 to 22, with obvious artery length reduction in the MCA and PCA territories in SNAP but no obvious change in TOF and GM CBF.

flow and cognitive decline remains an underexplored area of research.

Prior evidence has corroborated a connection between intracranial arterial calcification and cognitive function [18], but the mechanisms underlying this relationship remain unclear. We hypothesized that calcification might affect distal arterial flow, potentially contributing to cognitive impairment through altered hemodynamics rather than through changes in tissue-level perfusion.

6.2.2 Methodological Approach

We enrolled 27 subjects from the Intraplaque hemorrhage study, all with $>15\%$ carotid stenosis by ultrasound. The clinical characteristics of these subjects were the same as those in our previous investigation (Table 6.1).

All MR studies were conducted on a 3.0-T Philips Ingenia CX scanner (Philips, Best, The Netherlands) with a 32-channel array head coil. The imaging protocol included:

- 3D TOF: voxel size $0.5 \times 0.5 \times 1 \text{ mm}^3$, TR/TE 20/3.5 ms
- SNAP: voxel size 0.8 mm isotropic, TR/TE 11/5.6 ms
- T1: voxel size 0.6 mm isotropic, TR/TE 10/6 ms

Image analysis involved preprocessing using previously-developed tools—MOCHA [21] and iCafe [10]. The deep learning model was then used to predict calcification from 2D cross-sectional slices generated at each point on the centerlines [70].

For statistical analysis, we applied univariable regression models and partial linear regression models, adjusting for CBF measured from ASL, WML volume, and other potential confounding factors including age, hypertension, diabetes, smoking, and history of stroke or TIA.

6.2.3 Key Findings

Our analysis revealed several significant relationships between arterial calcification and vascular morphology:

1. Significant negative correlations were found between SNAP total distal branch number and the number of calcified regions ($R = -0.493$, $p = 0.010$) and between SNAP total distal length and calcium volume ($R = -0.439$, $p = 0.025$).
2. These correlations remained significant in both univariable regression and partial regression models after adjusting for GM CBF and other factors ($p = 0.014$, 0.039 , 0.001 , 0.026 for partial regression models).

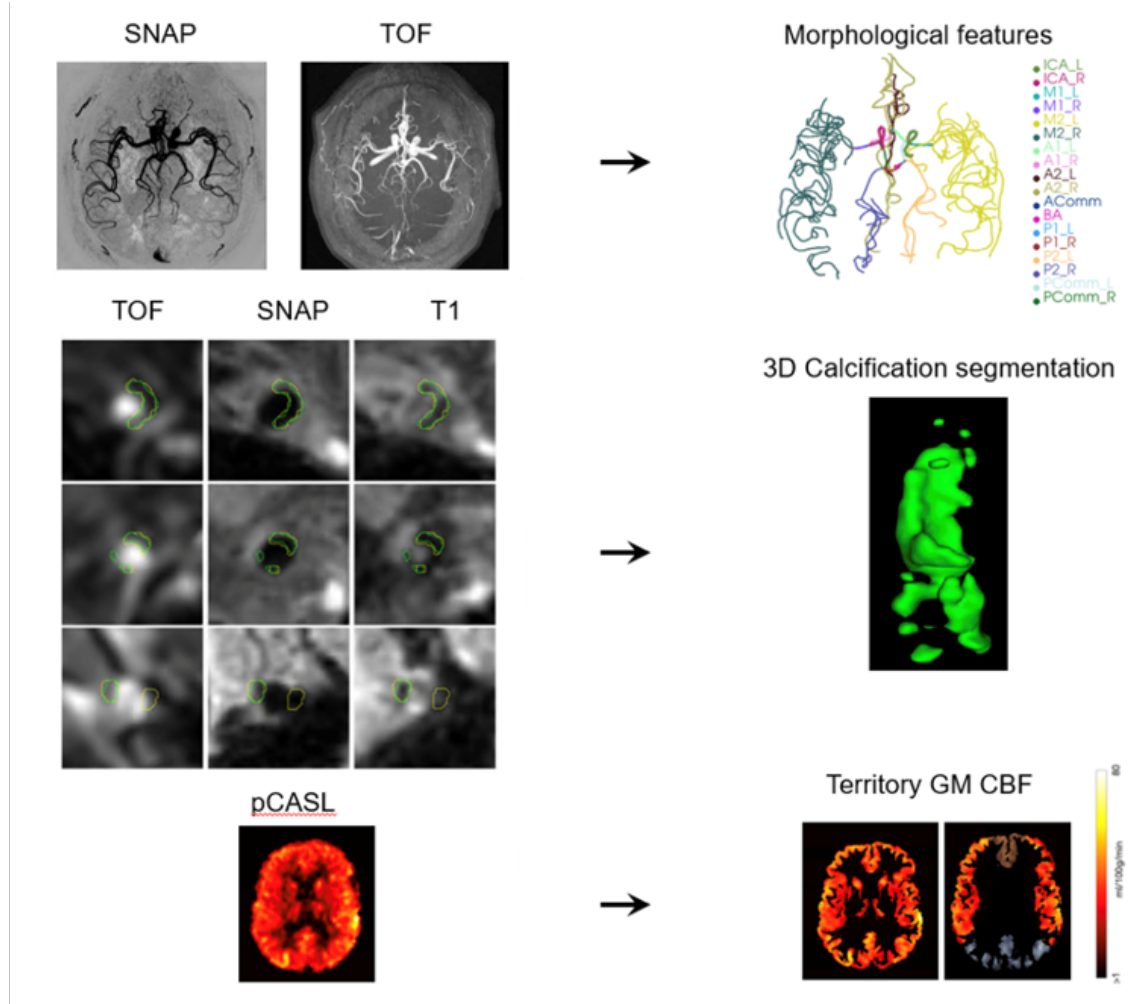


Figure 6.4: Multi-contrast MRI processing approach. Vascular morphology-associated blood flow characteristics are captured using the iCafe [10]. Number of distal branches and the length of distal arteries from the whole-brain TOF and SNAP were calculated. Subsequently, TOF, SNAP, and T1 are registered to generate cross-sectional images with MOCHA [21] around the lumen area, guided by the centerline produced from iCafe. The deep learning model then predicts a 2D calcification map which is subsequently reconstructed into 3D. Territory CBF is computed from pCASL images in line with the standard ASL setting.

3. Significant correlations were also obtained between TOF distal branch number, distal artery length and number of calcified regions in univariable regressions models, but after adjusting for CBF and other factors, only the correlation between TOF total distal artery length and number of calcified regions remained significant ($p = 0.027$).

Table 6.4: Linear regression summary between different calcification features and morphological features from SNAP

Outcome: Total distal branch number of SNAP						
Predictors	Model 1		Model 2		Model 3	
	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value
Cal Vol	-0.4 (-0.8–0.0)	0.056	-0.4 (-0.7–0.0)	0.061	-0.3 (-0.7–0.0)	0.039
No. of Cal regions	-0.5 (-0.9–0.1)	0.010	-0.5 (-0.8–0.1)	0.010	-0.4 (-0.7–0.0)	0.026
Observations	27		27		27	
R ² / R ² adjusted	0.144 / 0.109		0.245 / 0.180		0.775 / 0.670	
Outcome: Total distal artery length of SNAP						
Predictors	Model 1		Model 2		Model 3	
	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value
Cal Vol	-0.4 (-0.8–0.1)	0.025	-0.4 (-0.8–0.1)	0.025	-0.4 (-0.8–0.1)	0.014
No. of Cal regions	-0.6 (-0.9–0.2)	0.002	-0.6 (-0.9–0.2)	0.001	-0.5 (-0.8–0.2)	0.001
Observations	27		27		27	
R ² / R ² adjusted	0.193 / 0.159		0.314 / 0.254		0.758 / 0.643	

Model 1 = Univariable regression

Model 2 = Adjusted for GM CBF

Model 3 = Model 2 + WML volume + other risk factors (age + hypertension + diabetes + stroke)

4. Notably, no significant correlation was found between calcium features and CBF directly.

6.2.4 Implications for Cerebrovascular Health and Cognition

These findings suggest that intracranial arterial calcification is a potential factor affecting blood flow in distal arteries, particularly as captured by SNAP imaging. The negative correlations between calcification features and distal artery morphology indicate that increased arterial calcification is associated with reduced distal artery length and branch number, pointing to potential mechanisms of vascular remodeling in response to calcification.

Interestingly, the lack of direct correlation between calcification and CBF suggests that

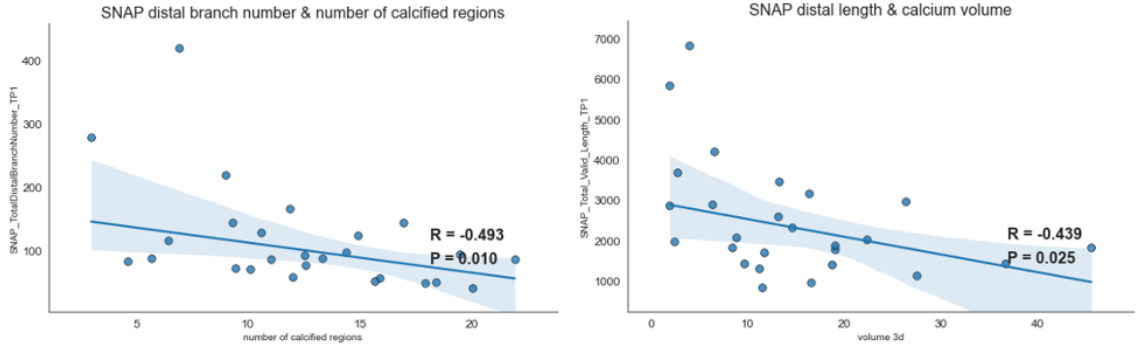


Figure 6.5: Correlation maps showing the relationship between arterial calcification and vascular morphology. (A) The correlation between the total distal branch number of SNAP and the number of calcified regions. (B) The correlation between the total distal length of SNAP and the volume of calcification.

the impact of calcification on cognitive function is more related to distal artery perfusion than tissue-level perfusion. This finding aligns with our previous observations regarding the differential sensitivity of SNAP versus perfusion measures in detecting cognition-relevant vascular changes.

6.2.5 Limitations and Future Directions

While our findings provide valuable insights into the relationship between intracranial arterial calcification and cerebral blood flow, several limitations should be acknowledged:

1. The relatively small sample size ($N = 27$) limits the statistical power of our analyses and the generalizability of our findings.
2. The cross-sectional nature of this analysis precludes determination of causal relationships between arterial calcification, vascular morphology, and cognitive function.
3. The current analysis focused on global measures of calcification and vascular morphology; more detailed regional analyses between calcium and blood flow should be conducted in the future.

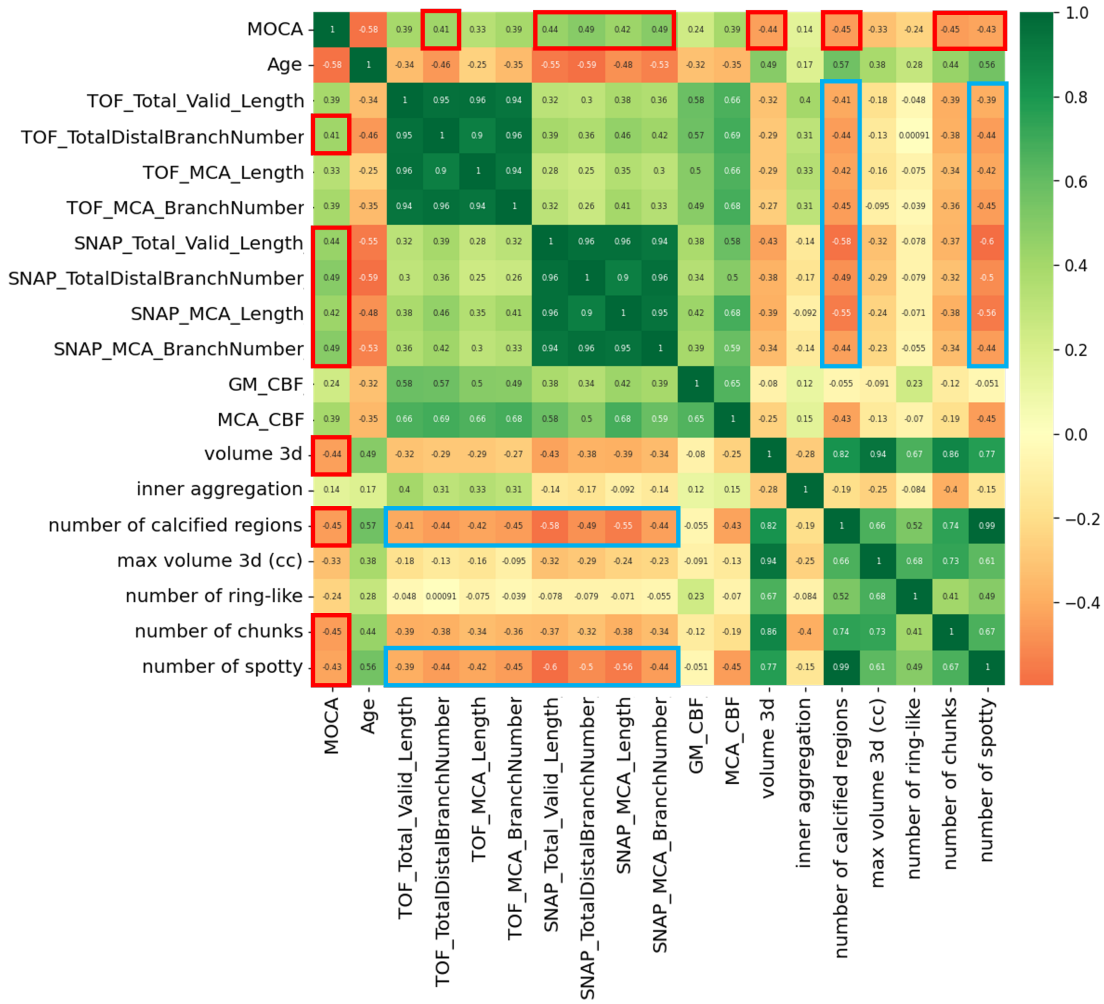


Figure 6.6: The correlation heatmap illustrating the associations among MoCA score, blood flow attributes derived from TOF, SNAP, and pCASL, and features of calcification. Red boxes denote a moderate to strong correlation (positive or negative) between MoCA scores and either blood flow or calcification features, whereas blue boxes represent the correlation between blood flow characteristics and calcification features.

Future research should aim to address these limitations through larger, longitudinal studies and more sophisticated analytical approaches that can better characterize the regional and network-level interactions between arterial calcification, vascular morphology, and cerebral blood flow. Additionally, the integration of these findings with the graph-based

approaches discussed in subsequent sections may provide a more comprehensive understanding of the complex relationships between cerebrovascular structure, function, and cognitive performance.

6.3 Ablation Studies for Biomarker Identification in Brain Arterial Networks

While classical morphological biomarkers provide valuable insights into cerebrovascular health, they rely on predefined features. To discover more comprehensive biomarkers, we conducted systematic ablation studies to identify which aspects of brain arterial networks contribute most significantly to clinical predictions. These studies explore feature importance, topological significance, and task-specific patterns using GNNs.

6.3.1 Experimental Design

We analyzed brain arterial networks from our curated BAN dataset, containing detailed vascular structures with clinical annotations for gender, hypertension, diabetes, smoking status, and Framingham risk level. Each network contained approximately 400-600 nodes representing the arterial vasculature. For simplicity, only classification tasks were involved and only GCN and GAT models were considered in the ablation experiments.

Our experimental framework followed a systematic approach to evaluate:

1. **Feature ablation:** Assessing the contribution of specific vascular characteristics (length, diameter, tortuosity) to model performance
2. **Cross-model validation:** Comparing patterns across GCN and GAT

All experiments used 5-fold cross-validation with consistent data splits to ensure fair comparison across conditions. Performance was measured using AUC, accuracy, and F1 score.

6.3.2 Feature Ablation Results

Feature ablation experiments revealed distinct patterns of importance across different vascular characteristics. Table 6.5 presents the impact of individual features on model perfor-

Table 6.5: Individual Feature Impact (AUC Improvement over Baseline)

Feature	GCN Impact	GAT Impact	Mean Impact	Consistency Score
Length	+29.20	+29.03	+29.12	0.98
Diameter	+11.20	+10.99	+11.10	0.95
Tortuosity	-0.20	+0.14	-0.03	0.36
Position (Node)	-0.0520	-0.0555	-0.0538	0.93

Table 6.6: Feature Combination Effect (AUC Scores)

Feature Combination	Smoking	Risk Category	Diabetes	Hypertension	Gender
pos+length+tortuosity+diameter	83.6	83.4	83.6	83.9	83.4
pos+length+diameter	83.2	83.6	84.0	83.5	83.9
NoNode+length	82.9	82.6	82.9	82.5	83.1
NoNode+length+diameter	82.4	82.6	82.6	82.6	82.5
NoNode+length+tortuosity+diameter	60.1	59.5	60.0	59.7	59.3

mance, measured as AUC improvement over baseline.

Length emerged as the most influential feature, providing an average AUC improvement of 29.10 across all tasks and models. This finding was remarkably consistent across different classification tasks with a consistency score of 0.98. Vessel diameter showed moderate positive impact (mean improvement of 11.10), while tortuosity demonstrated minimal influence on predictive performance.

Interestingly, node position information alone showed a slight negative impact, suggesting that raw spatial coordinates without accompanying edge features may introduce noise rather than signal for clinical prediction tasks.

Table 6.6 shows the performance of different feature combinations across various clinical tasks. The optimal feature combinations consistently included length and diameter, with the most effective configuration being the combination of all features (length, diameter, tortuosity) with position information. This indicates that while some features may not be strongly predictive individually, they contribute synergistically in combination.

Table 6.7: Model Agreement on Feature Importance

Aspect	Pearson Correlation	Spearman Correlation
Edge Features	0.994	0.975
Node Features	0.982	1.000
Overall Features	0.989	0.986

6.3.3 Cross-Model Validation

To ensure the robustness of our findings, we compared results between GCN and GAT models. The inter-model correlation analysis revealed strong agreement in feature importance patterns (Pearson $r = 0.989$), indicating that the identified biomarkers represent fundamental properties of the vascular network rather than model-specific artifacts.

Table 6.7 shows the agreement metrics between GCN and GAT models. Agreement was particularly strong for edge features ($r = 0.994$), with both models identifying length as the most important characteristic.

The high consistency across models reinforces the validity of the identified vascular biomarkers and suggests that these findings likely generalize to other graph-based approaches.

6.3.4 Clinical Implications

These ablation studies provide several clinically relevant insights:

1. **Vascular length as a primary biomarker:** The strong and consistent importance of vessel length across all tasks suggests that overall arterial path length may be a fundamental biomarker for various clinical conditions. This aligns with our findings in Section 6.1, which showed significant associations between artery length changes and cognitive function.
2. **Vessel diameter as a secondary indicator:** The moderate importance of diameter suggests this feature provides complementary information to length, potentially

reflecting different aspects of vascular remodeling in pathological conditions.

3. **Limited utility of tortuosity:** Despite traditional emphasis on tortuosity in clinical assessments, our findings suggest that when analyzed across the entire brain arterial network, tortuosity provides minimal additional predictive value beyond length and diameter.

6.3.5 *Comparison with Classical Biomarkers*

The comprehensive ablation studies extend and complement the findings from classical morphological biomarkers presented in Section 6.1. While the classical approach identified significant associations between artery length, branch number, and cognitive function in specific vascular territories (particularly the PCA), our GNN-based ablation studies provide a more systematic quantification of feature importance across multiple clinical prediction tasks.

Both approaches highlight the importance of vessel length as a primary biomarker, suggesting this feature captures fundamental aspects of cerebrovascular health. However, our ablation studies additionally quantify the relative importance of diameter and tortuosity, and identify optimal levels of network simplification for clinical prediction tasks.

6.3.6 *Conclusion*

This systematic analysis of brain arterial networks through ablation studies has identified several key vascular characteristics that serve as potential biomarkers for clinical prediction tasks. Vessel length emerged as the most informative feature, with diameter providing complementary information, while tortuosity showed limited additional value.

These findings extend beyond the traditional morphological biomarkers by providing quantitative evidence for the relative importance of different vascular characteristics and their interactions. The consistency of these patterns across different models and tasks suggests that they represent fundamental properties of brain arterial networks rather than methodological artifacts.

Future work should focus on validating these findings in larger, more diverse populations and investigating whether the identified biomarkers correlate with specific pathophysiological mechanisms.

Chapter 7

DISCUSSION, STRATEGIC INTEGRATION, AND CONCLUSION

7.1 Summary of Thesis Contribution

This thesis has made several significant contributions to the field of neurovascular research by developing a comprehensive framework for analyzing brain arterial networks (BANs). These contributions span multiple domains, including dataset curation, advanced imaging techniques, computational modeling, and biomarker discovery.

7.1.1 Large-scale Harmonized Brain Arterial Network Dataset

A primary contribution is the curation of a large-scale, multi-site, harmonized BAN dataset that enables robust cross-sectional analyses across populations.

The key innovations that facilitate dataset curation include:

- Development of VesselVoyager, an interactive 3D platform for annotating, visualizing, and quantifying intracranial arteries from TOF-MRA. Comparative analysis demonstrated that VesselVoyager achieved strong agreement with established tools like iCafe ($\text{ICC} \geq 0.85$) while significantly reducing annotation time, particularly for distal or faint vessels.
- Creation of the Brain Artery Visualization & Analysis (BAVA) platform, a web-based resource providing interactive visualization and exploration of the harmonized dataset. This platform implements a modern web application architecture combining a FastAPI backend with a Streamlit frontend, enabling researchers to access the data through standard web browsers without complex software installations.
- Implementation of ComBat harmonization to address scanner- and protocol-induced variability across multiple acquisition sites. This approach successfully mitigated both

location effects (systematic shifts in mean values) and scale effects (differences in measurement variability), enabling more accurate assessment of true biological relationships.

The resulting dataset provides unprecedented opportunities for investigating the relationships between cerebrovascular structures and various health outcomes, addressing a critical gap in the field.

7.1.2 Advanced Imaging Sequences for Comprehensive Vascular Assessment

The thesis has advanced the field of neurovascular imaging through the development and optimization of novel MRI sequences that overcome limitations in conventional approaches:

- Further optimization of iSNAP using Frequency Offset Corrected Inversion (FOCI) pulse enhancement and advanced low-rank reconstruction methods substantially improved image quality, particularly for dynamic MRA and vessel wall visualization.
- Quantitative measurement methods developed for the CineMerge sequence, provides high-resolution 3D isotropic black-blood imaging of vessel wall motion throughout the cardiac cycle, enabling direct measurement of vascular pulsatility. This technique revealed novel insights into the mechanical behavior of intracranial arteries.

These advanced imaging sequences extend our ability to characterize cerebrovascular health beyond static morphological features, providing complementary functional information that may serve as early biomarkers for various neurovascular conditions.

7.1.3 Graph-based Models for Vascular Analysis

A major methodological contribution of this thesis is the development of specialized graph-based approaches for analyzing brain arterial networks:

- Development of a novel graph-based method for estimating flow direction within the Circle of Willis using ASL-dMRA and ensemble learning strategies.

- Develop a hierarchical graph transformer (HGT) with edge-aware structural encoding, specifically tailored to the unique characteristics of brain arterial networks. This architecture incorporates several key innovations, including edge-aware structural encoding, topology-preserving reduction, multi-level edge fusion, and structurally enriched attention, addressing limitations of standard graph neural network approaches.
- Comprehensive evaluation demonstrating the superior performance of the specialized HGT model compared to standard graph neural network architectures across various regression and classification tasks.

These graph-based approaches provide a powerful framework for modeling and analyzing the complex structural and functional properties of brain arterial networks, enabling more precise characterization of vascular patterns and their associations with clinical conditions.

7.1.4 Clinical Biomarker Discovery

The thesis has made significant contributions to the discovery and validation of clinical biomarkers derived from brain arterial networks:

- Identification of significant associations between morphological changes in cerebral arteries and cognitive function in a longitudinal study of subjects with high cardiovascular risk.
- Systematic feature ablation studies revealing vessel length as the most influential feature for clinical prediction tasks across different graph neural network architectures.

These findings extend beyond traditional morphological biomarkers by providing quantitative evidence for the relative importance of different vascular characteristics and their interactions, with strong consistency across different models suggesting they represent fundamental properties of brain arterial networks.

7.2 *Broader Clinical and Methodological Implications*

The contributions of this thesis have significant implications for both clinical practice and methodological approaches in neurovascular research.

7.2.1 *Advancing Precision Medicine in Cerebrovascular Health*

The comprehensive characterization of brain arterial networks enabled by our framework has important implications for precision medicine approaches to cerebrovascular diseases:

Foundation for Early Prevention: Our population-based approach reveals that vascular alterations may precede clinical symptoms, creating opportunities for preventive intervention. The reversible nature of many vascular features suggests that early modifications to risk factors could potentially restore healthier vascular patterns before permanent damage occurs. This is particularly significant given our findings that changes in artery length and branch numbers correlate with cognitive function, potentially serving as early biomarkers before tissue-level perfusion changes are detectable.

Longitudinal Analysis Capabilities: Our framework enables tracking of vascular changes over time, providing crucial insights into disease progression and treatment response. This longitudinal perspective offers a more dynamic understanding of cerebrovascular health than traditional cross-sectional approaches, potentially allowing clinicians to identify concerning trajectories before clinical deterioration becomes apparent.

Personalized Risk Stratification: Our graph-based models effectively leverage the high-dimensional information inherent in brain arterial networks to predict cardiovascular risk factors with greater accuracy than traditional approaches. By capturing the complex hierarchical structure and connectivity patterns of cerebral vasculature, these models can identify subtle, patient-specific vascular signatures that may indicate elevated risk, enabling more targeted preventive strategies and interventions.

7.3 *Limitations*

Despite the significant contributions of this thesis, several limitations should be acknowledged.

7.3.1 Dataset Limitations

Demographic Representativeness: The current dataset primarily consists of middle-to-late aged individuals of East Asian heritage, representing a spectrum from community-dwelling individuals to those with specific neurovascular conditions. This demographic profile may limit the generalizability of findings to other populations, particularly younger individuals or those with different genetic backgrounds. Future work should prioritize expanding the dataset to include more diverse populations across different age groups, ethnicities, and socioeconomic statuses.

Selection Bias in Clinical Cohorts: The inclusion of specific clinical cohorts (hypertensive individuals, patients with cognitive impairment) may introduce selection biases that influence the observed relationships between vascular features and health outcomes. To mitigate this limitation, future studies should incorporate population-based sampling approaches to establish more representative normative ranges for vascular biomarkers.

7.3.2 Technical Limitations

Resolution Constraints: Current MRA techniques, even with advanced sequences like iSNAP, face resolution limitations that restrict detailed visualization of small perforating arteries and the microvasculature. These smaller vessels play crucial roles in various neurovascular conditions, particularly small vessel disease. Integration with complementary higher-resolution techniques, such as 7T MRI, could address this limitation.

Computational Complexity: The graph neural network approaches developed in this thesis, particularly the hierarchical graph transformer, are computationally intensive when applied to large vascular networks with hundreds of nodes and edges. Optimization techniques such as network pruning, weight quantization, or development of more efficient attention mechanisms could address these computational challenges.

7.3.3 Methodological Limitations

Ground Truth Validation: Validation of vascular features extracted from MRA remains challenging due to the lack of a true gold standard for in vivo human cerebral vasculature.

Comparison with alternative imaging modalities like digital subtraction angiography or validation against post-mortem specimens could strengthen confidence in the accuracy of extracted features, though each approach has its own limitations.

Causal Inference: While our analyses demonstrate significant associations between vascular features and clinical outcomes, establishing causal relationships remains challenging. The observed correlations may reflect bidirectional relationships or shared underlying factors rather than direct causal pathways.

Model Interpretability: Despite efforts to visualize attention patterns and perform feature importance analyses, the interpretability of complex graph neural network models remains a challenge. This limits the immediate clinical applicability of these approaches, as clinicians typically require clear, mechanistic explanations for diagnostic or prognostic assessments.

7.4 *Concluding Remarks*

The brain’s vascular system remains one of the most intricate and clinically relevant biological networks in the human body. By developing a comprehensive framework for analyzing brain arterial networks—from advanced imaging acquisition to sophisticated computational modeling—this thesis has contributed to bridging the gap between neuroimaging and clinical neuroscience. The graph-based perspective introduced here provides a natural and powerful approach for representing and analyzing cerebrovascular structure and function, opening new avenues for understanding the complex relationships between vascular patterns and brain health.

The tools, datasets, and methodologies developed in this work establish a foundation for future research in this domain. The Brain Artery Visualization & Analysis platform, in particular, creates opportunities for collaborative research and knowledge sharing across the neurovascular community, potentially accelerating discoveries in this critical area of neuroscience.

As our understanding of the brain’s vascular architecture continues to evolve, the integration of advanced imaging, graph theory, and machine learning promises to yield increasingly precise biomarkers for early detection, risk stratification, and therapeutic monitoring

in cerebrovascular diseases. This thesis represents a step toward realizing that promise, with the ultimate goal of improving outcomes for the millions of individuals affected by cerebrovascular conditions worldwide.

Appendix A

DATASET ORGANIZATION AND DISTRIBUTION

This appendix details the organization, file formats, and distribution mechanisms for the Brain Artery Network dataset. The dataset has been structured to support reproducible research across multiple computational frameworks while ensuring long-term accessibility and version control.

A.1 Dataset Components and File Formats

The Brain Artery Network dataset consists of four primary components, each serving a specific role in the research pipeline:

A.1.1 Raw MRA Data

Raw Magnetic Resonance Angiography (MRA) data captures the original 3D vascular imaging acquired from research participants. This component is provided in the following format:

- **File format:** NIfTI compressed format (`.nii.gz`)
- **Dimensions:** $256 \times 256 \times 160$ voxels (typical resolution)
- **Voxel size:** $0.8 \times 0.8 \times 1.0$ mm (may vary slightly by acquisition protocol)
- **Intensity range:** 16-bit grayscale values
- **Anonymization:** All DICOM metadata containing protected health information (PHI) has been removed, and each scan is identified only by a unique study ID

Each MRA file is named according to the convention `subject_[ID]_mra.nii.gz`, where [ID] corresponds to the unique subject identifier used throughout the dataset.

A.1.2 Multi-label Artery Segmentation Data

The segmentation component contains volumetric masks delineating the brain artery network with anatomical labels. These segmentations were generated using the AICafe pipeline described in Section 3.3 and manually verified for anatomical accuracy.

- **File format:** NIfTI compressed format (`.nii.gz`)
- **Dimensions:** Identical to the corresponding raw MRA
- **Value encoding:** Integer values with the following label scheme:
 - 0: Background
 - 1: Internal Carotid Artery (ICA), Right
 - 2: Internal Carotid Artery (ICA), Left
 - 3: Middle Cerebral Artery (MCA), Right
 - 4: Middle Cerebral Artery (MCA), Left
 - 5: Anterior Cerebral Artery (ACA), Right
 - 6: Anterior Cerebral Artery (ACA), Left
 - 7: Posterior Cerebral Artery (PCA), Right
 - 8: Posterior Cerebral Artery (PCA), Left
 - 9: Vertebral Artery (VA), Right
 - 10: Vertebral Artery (VA), Left
 - 11: Basilar Artery (BA)

Each segmentation file is named `subject_[ID]_seg.nii.gz` to maintain direct correspondence with the raw MRA data.

A.1.3 Brain Arterial Network Graph Data

The graph representation encodes the brain artery network as a mathematical graph structure, with nodes representing bifurcation points or endpoints and edges representing arterial segments.

- **File format:** Graph Exchange XML Format (`.gexf`)
- **Node attributes:**
 - `id`: Unique identifier
 - `x`, `y`, `z`: 3D coordinates (in mm, corresponding to the raw MRA space)
 - `type`: Node classification (bifurcation or endpoint)
 - `label`: Anatomical region
- **Edge attributes:**
 - `source`, `target`: Connected node IDs
 - `length`: Physical length of the vessel segment (mm)
 - `diameter`: Average diameter of the vessel segment (mm)
 - `tortuosity`: Measure of vessel curvature
 - `vessel_type`: Anatomical classification

Each graph file is named `subject_[ID]_graph.gexf`, maintaining the subject ID correspondence across all data types.

A.1.4 Clinical and Demographic Data

Clinical and demographic information provides essential context for understanding the relationship between brain artery morphology and neurovascular health.

- **File formats:** Provided in two formats for different use cases:

- Comma-Separated Values (`.csv`) for easy import into statistical software
- SQLite database (`.db`) for relational queries and integration with the BAVA platform

- **Data fields:** Include but are not limited to:

- `subject_id`: Unique subject identifier
- `age`: Subject age at time of scan
- `sex`: Biological sex
- `hypertension`: Hypertension status (yes/no)
- `diabetes`: Diabetes status (yes/no)
- `smoking`: Smoking history
- `moca_score`: Montreal Cognitive Assessment score (when available)
- `cohort`: Study cohort designation (BRAVE, CROP, etc.)
- `scanner_info`: MRI scanner type and field strength

The clinical data is provided as `clinical_data.csv` and `subjects_all.db` at the dataset root level.

A.2 Data Distribution on Dryad

The Dryad Digital Repository provides a permanent, citable archive for the Brain Artery Network dataset with the following features:

A.2.1 Dataset Organization

The dataset on Dryad is organized hierarchically to facilitate systematic access:

```
brain_artery_network/
+-- README.md           # Dataset documentation
+-- clinical_data.csv    # Clinical and demographic data
+-- subjects_all.db      # SQLite database of all subjects
```

```

+-- raw_mra/                                # Raw MRA data directory
|   +-- subject_001_mra.nii.gz
|   +-- subject_002_mra.nii.gz
|   +-- ...
+-- segmentation/                          # Artery segmentation directory
|   +-- subject_001_seg.nii.gz
|   +-- subject_002_seg.nii.gz
|   +-- ...
+-- graph/                                 # Network graph directory
    +-- subject_001_graph.gexf
    +-- subject_002_graph.gexf
    +-- ...

```

The Dryad submission includes comprehensive metadata to enhance discoverability and usability:

- **Title:** "Brain Artery Network: A Multi-modal Dataset for Neurovascular Research"
- **Authors:** Full author list with ORCID identifiers
- **Abstract:** Overview of dataset contents and research applications
- **Keywords:** Curated terms for search optimization including "cerebrovascular", "neuroimaging", "MRA", "graph neural networks"
- **Related works:** Links to associated publications
- **Funding information:** Grant identifiers and acknowledgments

The README.md file provides detailed documentation including:

- Data acquisition protocols

- Processing pipeline description
- File format specifications
- Variable definitions and units
- Usage examples and code snippets
- Citation guidelines

A.2.2 Version Control and DOI Assignment

The Dryad repository supports dataset versioning with unique Digital Object Identifiers (DOIs) for each major release:

- **Initial release:** <https://github.com/BrainArteryNetwork/BAVA>
- **Version history:** Maintained with release notes detailing additions and modifications
- **Citation format:** Standardized citation format provided for academic reference

Major updates to the dataset will receive new DOI versions while maintaining backward compatibility wherever possible.

A.3 Usage Guidelines and Citations

Researchers using the Brain Artery Network dataset are requested to follow these guidelines:

- **Attribution:** Cite the dataset using the provided citation format
- **Limitations:** Acknowledge the dataset's limitations and cohort characteristics
- **Derivatives:** Share derivative works and improvements when possible
- **Feedback:** Report issues or suggestions through the provided channels

All usage should comply with the Creative Commons Attribution 4.0 International License (CC BY 4.0) applied to the dataset.

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