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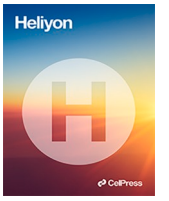

Research article

Human cerebral blood supply via circulus arteriosus cerebri: A scoping review on its variations and clinical implications

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ABSTRACT

Background: Circulus arteriosus cerebri (CAC), responsible for supplying blood to the brain, presents anatomical variations that have been associated with both haemorrhagic and ischemic strokes. Therefore, it is crucial to conduct comprehensive investigations and comparisons of the diverse variant components of the CAC, published in various journals, and analyze them to identify individuals at risk of cerebrovascular pathologies, thereby ensuring enhanced and timely treatment.

Methods: A scoping review according to the five-stage protocol by Arksey and O'Malley was performed between February and June 2023. Seven hundred and seventy-seven records were initially identified, and a total of 51 studies were finally included.

Results: This scoping review focuses on the anatomical variations of the CAC and their clinical implications on cerebrovascular disease and includes more original articles than review s. Consistent with previous findings, most of the records included small populations or samples, while only three records reported larger populations. Surprisingly, the populations enclosed in the included records consisted of autopsied cadaveric specimens more than living subjects. Finally, the qualitative analysis highlighted three main themes concerning the relationship between the normal CAC morphology and the cerebrovascular disease onset as well as the variant CAC morphology and its main features that might be also involved in these diseases. Finally, techniques that can be used to measure CAC have also been assessed.

Conclusion: Variations in the CAC, more common in the posterior part, with genetic and environmental factors influencing these variations impact cerebrovascular disorders. Understanding variants components of CAC can aid in improving brain surgeries and post-stroke care.

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1. Introduction

The brain is one of the most important organs of the human body. Due to the brain's high metabolic rate and activity, it is highly sensitive to ischemia and dependent upon adequate blood supply [1]. According to Shlobin [2] cerebrovascular diseases (CVDs) refer to any condition that affects the blood supply to the brain. These conditions may include stroke, aneurysms, vascular malformations, and arterial stenosis and are closely related to acute ischemic stroke and hemorrhagic stroke, which are the most feared complications of these diseases. Generally, the cerebral circulation is maintained by a network of arterial components known as the cerebral basal arterial network (CBAN), including the anteriorly positioned *circulus arteriosus cerebri* (CAC, known also as the Circle of Willis) [3]. Indeed, CAC, named after British clinician Thomas Willis (1621–1675), was first described by Herophilus of Chalcedon (335-280 BCE) and further detailed by Galen (131–201 CE), who hypothesized that following its formation, vital pneuma migrates to the carotid arteries into the rete mirabile in the brain, which in turn transforms the vital spirit into animal or psychic pneuma [4]. In the following centuries, alternating evidence confirmed or denied the existence of rete mirabile in the brain until Gabriele Falloppio (1523–1562) in his work *Observationes anatomicae* provided an accurate description of the blood supply to the brain [5]. Thomas Willis (1621–1675) in turn definitely demonstrated the pathophysiologic significance of CAC with autopsies and experimental surgeries [6]. In his work, *Cerebri Anatome*, he provided the classification of the cranial nerves and the description of the arterial pattern at the base of the brain widely known, even to the present day, as the circle of Willis [7].

The *circulus arteriosus cerebri* (CAC) is a polygonal anastomotic network of blood vessels that communicates with the posteriorly positioned vertebrobasilar (VB) arterial system located at the base of the brain that plays a crucial role in providing the cerebrum brain stem and cerebellum with enough collateral blood, especially when severe large vessel stenosis and occlusions occur. Previous evidence seemed to demonstrate that approximately one-third of ischemic strokes were caused by haemodynamic issues and resulted from severe stenosis or occlusion of the internal carotid artery, combined with an incomplete intracranial collateral network [8]. Over the past few decades, anatomical and radiological studies have assessed the typical pattern and variations of the CAC and VB network. It has been observed that the "typical pattern" occurs in 4.6–72.2 % of cases, and variations in prevalence may be explained by genetic, environmental, and haemodynamic factors, among others [8–12].

The total blood supply of the brain is not influenced by functional hemispheric lateralization and there is no asymmetry in arterial cross sectional area supplying the blood to the left and right cerebral hemispheres, as recently highlighted [13]. Blood irrigates the brain by two internal carotid arteries (ICAs) and two vertebral arteries (VAs) [1]. The cranial component of ICA bifurcates to form the middle cerebral artery (MCA) and the anterior cerebral artery (ACA) which supply the anterior, medial, and lateral aspects of the cerebral hemispheres bilaterally (i.e. frontal, parietal, and temporal aspects of the cerebrum) [1]. The two ACAs are joined by the anterior communicating artery (ACoA) [11]. The VAs anastomose forming the basilar artery which then divides into the left and right posterior cerebral artery (PCA) to supply the inferior, lateral and the posterior aspect of the cerebrum and the cranial aspect of the brainstem [12]. The posterior circulation is connected by the posterior communicating artery (PCoA) on each side [12]. This resulting arterial network is referred to as the CBAN or the cerebral arterial circle and is vital in providing collateral blood supply to the brain in the case of occluded or missing blood vessels [1,2,10]. A typical CAC is bilaterally symmetrical and is composed of a complete ring of blood vessels [11]. There may be variations in the CAC, for example, vessels may vary in distinction; often they are hypoplastic, duplicated, or can be absent [14]. In principle, it is likely that the structure of the CAC might play a role in the appearance and severity of cerebrovascular disease; in fact this is not the case, being the association between CV disease and CAC anatomy weak at least [1,11]. Nevertheless, it is important having knowledge of the variations in the CAC, especially for interventional radiologists and neurosurgeons performing shunt surgeries and to better identify those at risk of cerebrovascular morbidity for accurate diagnosis and adequate treatment [15]. Variations in the structure of the CAC could be genetically determined and occur during early embryonic development and persist post-natally, even if well designed recent study shows no association in this regard [16]. General CAC structure and morphology are remarkably similar in several animal species, particularly in non-human primates [17]. Observed variations in animal species mirror human variations [17]. Moreover, clinical studies are likely to associate CAC variability with cardiovascular diseases [18]. The incomplete formation of the cerebral artery network may increase the risk of ischemic stroke and worsen patient outcomes [8,18–20]. Additionally, patients with an incomplete CAC morphology are at a higher risk of intraoperative ischemic events [18]. Variations in the CAC have also been linked to the development of cerebral aneurysm [21,22]. It is important to note that, in addition to morphological features, the diameter of collateral vessels also plays a crucial role in the collateral capacity of the CAC. While a diameter of less than 1 mm was previously considered hypoplastic for anterior and posterior communicating arteries [23,24], recent clinical and mathematical studies suggest that the functional cross-flow threshold through these arteries is between 0.4 and 0.6 mm [25–28]. The understanding of the role of the components of CAC in cerebrovascular disease is limited, some of the existing studies rely on small, poorly defined participant groups, potentially hindering the reliability of their conclusions [29]. As far as the authors are concerned, only Hindenes [30] and coworkers and Qiu et al. [29] included more information on the variant CAC components in their studies based on the largest populations. Moreover, Hindenes and coworkers in the Tromsø Study assessed the variants CAC in a community-dwelling sample of 1864 subjects of both sexes. Consistent with other studies [31,32], the authors revealed 47 variants of the CoW and demonstrated that CoW frequencies were associated with age, not sex. It is probably caused by the reduction in cerebral blood flow with age [33], and eventually by the increase in tortuosity of blood vessels with age [34]. In contrast, the same authors did not find an association between sex and the frequencies of Circle of Willis (CoW) variants although evidence has been reported by others [10,35]. Consistent with Hindenes and coworkers, Qiu et al. investigated the morphology and variation of the CoW in healthy Chinese male adults and recruited 2246 Chinese male adults. In this population, the authors reported that the incidences of partial integrity and non-integrity of CoW were much higher [29]. Finally, it is worth mentioning the impact that the recent COVID-19 pandemic had on cerebrovascular disease onset, progression, and outcomes. In December 2019, in the Hubei province of

China, Wuhan was the center of an outbreak of pneumonia. A novel coronavirus (SARS- CoV-2) identified in January 2020 is the causative agent of this severe acute respiratory infection commonly spread through respiratory droplets and aerosol transmission [36], that caused a global pandemic and became a primary global health concern [37,38].Viral infection occurs when the viral Spike protein binds to the human cell surface receptor protein Angiotensin-Converting Enzyme-2 (ACE-2) which has a ubiquitous distribution in the organs [39]. This leads to the consequence that SARSCoV-2 infection may affect the lungs primarily, leading to respiratory failure but this infection simultaneously might also involve several organs, including blood vessels and the vascular system as recently reported [40].

This detailed scoping review thoroughly explores the notable anatomical variations present in the components of the Circle of Willis (CAC) and their profound impact on a range of cerebrovascular pathologies and clinical outcomes. The primary aim of this study was to conduct a comprehensive examination of the current body of literature in regards to the variant CAC and their association with various pathologies including aneurysms, meticulously analyze the available evidence, and identify specific areas that warrant further investigation and future considerations. This investigation seeks to shed light on the intricate relationship between variant components of CAC, their morphology, their diverse anatomical variances, and association with the cerebrovascular diseases, offering valuable insights for advancing our understanding in this crucial field of study.

2. Material and methods

According to the five-stage protocol by Arksey and O'Malley [41], Levac and coworkers [42], and Westphaln et al. [43], a scoping review was performed between February and June 2023 [44]. Afterward, the included records were screened and assessed for qualitative synthesis.

Since this study did not involve any type of human material (cells, tissues, organs, patients, or others), approval from the Ethics Committee was not required. Thus, the manuscript was not eligible for ethical review.

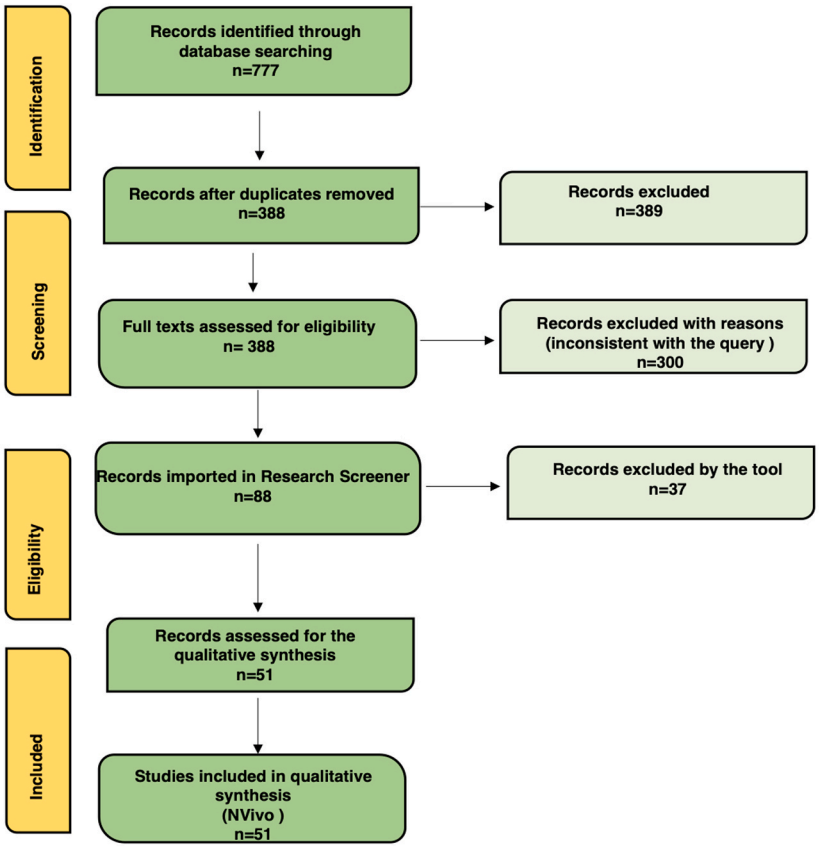

Fig. 1. Flowchart of the Reporting items for the systematic review adapted from the Preferred reporting items for systematic reviews (PRISMA) statement [45]. Researchers initially identified 777 records; 88 were included and further processed using the open, online Research Screener machine learning tool (Research Screener, 2021) and evaluated for qualitative synthesis using the NVivo qualitative data analysis software (QSR International Pty, Ltd., Melbourne, VIC, Australia).

Table 1
List of the Included Records. The table details the main features of the included records: authors, type of the study, and keywords. Note that 94 % of the included records have been classified as original articles while 6 % are represented by review articles.

Study details	Title	Type of study	Key words
Al-Hussain et al., 2001[a] [48]	Circle of Willis in adults	Original article	Circle of Willis, variations, adults.
Alastruey et al., 2007 [14]	Modelling the circle of Willis to assess the effects of anatomical variations and occlusions on cerebral flows	Original article	Circle of Willis, anatomical variation, collateral flow, one-dimensional modelling, pulse wave propagation.
Alpers et al., 1959 [14]	Anatomical studies of the circle of Willis in normal brain	Original article	Not available.
Ansari et al., 2011 [12]	A simple technique for morphological measurement of cerebral arterial circle variations using public domain software (Osiris)	Original article	Anatomy, cerebral arterial circle, anatomical variation, circle of Willis, methods.
Arjal et al., 2014 [49]	The study of fetal-type posterior cerebral circulation on multislice CT angiography and its influence on cerebral ischemic strokes	Original article	Cerebral angiography circle of Willis, posterior cerebral artery (PCA), hypoplasia, stroke.
Ayre et al., 2022[a] [50]	A new classification system for the anatomical variations of the human circle of Willis: A systematic review	Review article	Cerebrovascular anatomy, classification, neuroanatomy, variation.
Bahaddur et al., 2015 [51]	Anatomical variants of circle of Willis in South Indian population: A study by using magnetic resonance angiography	Original article	Prevalence, circle of Willis, arterial variants, anomalies, MR angiography.
Banga et al., 2018 [26]	Incomplete circle of Willis is associated with a higher incidence of neurologic events during carotid eversion endarterectomy without shunting	Original article	Circle of Willis, cerebral circulation, collateral circulation, stroke, carotid endarterectomy, selective shunting, computed tomography angiography, middle cerebral artery.
Burlakoti et al., 2017 [3]	The cerebral basal arterial network: Morphometry of inflow and outflow components	Original article	Cerebral arteries; circle of Willis; circulus arteriosus cerebri; internal carotid arteries; vertebral arteries.
Burlakoti et al., 2019 [13]	Asymmetries of total arterial supply of cerebral hemispheres do not exist	Original article	Anatomy, neuroscience.
Crompton et al., 1962 [16]	The pathology of ruptured middle-cerebral aneurysms with special reference to the differences between the sexes	Original article	Not available.
Cui et al., 2015[a] [52]	Anatomic variations in the anterior circulation of the circle of Willis in cadaveric human brains	Original article	Circle of Willis, anterior circulation, microanatomy, variation.
De Silva et al., 2011 [53]	Types of the cerebral arterial circle (circle of Willis) in a Sri Lankan population	Original article	Not available.
Dumitrescu et al., 2022 [54]	Anatomical study of circle of Willis on fresh autopsied brains. A study of a Romanian population	Original article	Circle of Willis, anatomical variant, hypoplasia, partially fetal artery, fenestration.
Eftekhar et al., 2006* [55]	Are the distributions of variations of circle of Willis different in different populations? – Results of an anatomical study and review of literature	Original article	Not available.
Enyedi et al., 2021 [15]	Circle of Willis: anatomical variations of configuration. A magnetic resonance angiography study	Original article	Circle of Willis, anatomic variation, magnetic resonance angiography.
Fawcett et al., 1905 [9]	The Circle of Willis: an examination of 700 specimens	Original article	Not available.
Feng et al., 2022* [56]	Association between anatomical variations of the circle of Willis and covert vascular brain injury in the general population	Original article	Circle of Willis, white matter hyperintensity, lacunes, cerebral microbleed, perivascular space.
Fields 1964 [57]	Aortocranial occlusive vascular disease (stroke)	Original article	Not available.
Gibello et al., 2019 [27]	Impact of the supra-aortic trunks and circle of Willis patency on the neurological compensation during carotid endarterectomy	Original article	Not available.
Gyöngyösi et al., 2022 [24]	The value of transcranial doppler monitoring of cerebral blood flow changes during carotid endarterectomy performed under regional anesthesia – A case series	Original article	Carotid endarterectomy, regional anesthesia, transcranial Doppler monitoring.
Gyöngyösi et al., 2023 [20]	Incomplete circle of Willis as a risk factor for intraoperative ischemic events during carotid endarterectomies performed under regional anesthesia – A prospective case-series	Original article	Carotid endarterectomy, circle of Willis, collateral ability, cross-clamping, local anesthesia.
Hashemi et al., 2013 [58]	Variations in the anatomy of the Willis' circle: A 3-year cross-sectional study from Iran (2006–2009). Are the distributions of variations of circle of Willis different in different populations? Result of an anatomical study and review of literature	Original article	Aneurysm, autopsy, circle of Willis, variation.
Henderson et al., 2000 [22]	Angiographically defined collateral circulation and risk of stroke in patients with severe carotid artery stenosis	Original article	Carotid stenosis, cerebral ischemia, collateral circulation risk.
Hindenes et al., 2020[a] [30]	Variations in the circle of Willis in a large population sample using 3D TOF angiography: The Tromsø Study	Original article	Not available.
Hoksbergen et al., 2000 [19]	Collateral configuration of the circle of Willis transcranial color-coded duplex ultrasonography and comparison with postmortem anatomy	Original article	Cerebral arteries, collateral circulation, hemodynamics, ultrasonography, Doppler, duplex, autopsy.

(*continued on next page*)

Table 1 (*continued*)

Study details	Title	Type of study	Key words
Hoksbergen et al., 2003 [25]	Assessment of the collateral function of the circle of Willis: Three-dimensional time-of- flight MR angiography compared with transcranial color-coded duplex sonography	Original article	Not available.
Iqbal et al., 2013 [11]	A comprehensive study of the anatomical variations of the circle of Willis in adult human brains	Original article	Not available.
Jain 2000 [59]	Asymmetry in cerebral perfusion from circle of Willis arterial variations in normal population	Original article	Perfusion, circle of Willis, cerebral anatomy, development.
Kalaria 2001 [60]	Advances in molecular genetics and pathology of cerebrovascular disorders	Original article	Apolipoprotein E, CADASIL, cerebral, amyloid, angiopathy, cerebrovascular disease, stroke, vascular malformations.
Kapoor et al., 2008[a] [17]	Variations in the configuration of the circle of Willis	Original article	Anterior cerebral, circle of Willis, communicating arteries, hypoplastic, posterior cerebral, variations.
Klimek-Piotrowska et al., 2013 [61]	Configurations of the circle of Willis: A computed tomography angiography based study on a Polish population	Original article	Cerebral arterial circle, computed tomography angiography, anatomic variations.
Kovač et al., 2014 [62]	Intracranial arterial variations: A comprehensive evaluation using CT angiography	Original article	Cerebral angiography, computed tomography angiography, intracranial aneurysm, diagnosis, Cerebral arteries abnormalities.
Krabbe-Hartkamp et al., 1998 [10]	Circle of Willis: Morphologic variation on three-dimensional time-of-flight MR angiograms	Original article	Not available.
Milenković et al., 1985 [63]	Asymmetry and anomalies of the circle of Willis in fetal brain. Microsurgical study and functional remarks	Original article	Not available.
Moritz et al., 2007 [23]	Accuracy of cerebral monitoring in detecting cerebral ischemia during carotid endarterectomy a comparison of transcranial doppler sonography, near-infrared spectroscopy, stump pressure, and somatosensory evoked potentials	Original article	Not available.
Orosz et al., 2009 [28]	Clinical applicability of a mathematical model in assessing the functional ability of the communicating arteries of the circle of Willis	Original article	Circle of Willis, transcranial color-coded duplex sonography, collateral capacity.
Orosz et al., 2022 [8]	Assessment of malformations, variations and diameters of vessels forming the circle of Willis – An autopsy study in a non-cerebrovascular cohort	Original article	Circle of Willis, autopsy, diameter, configuration.
Oumer et al., 2021 [18]	Association between circle of Willis and ischemic stroke: A systematic review and meta-analysis	Review article	Circle of Willis, ischemic stroke, association, systematic review and meta-analysis.
Prasad et al., 2017 [64]	Normal variants of the circle of Willis in patients undergoing CT angiography	Original article	Circle of Willis, CT angiography, variants.
Qiu et al., 2015 [29]	MRA Study on Variation of the Circle of Willis in Healthy Chinese Male Adults	Original article	Not available
Rhoton 2002 [65]	The supratentorial arteries	Original article	Not available.
Shaikh et al., 2018 [66]	MRA-based evaluation of anatomical variation of circle of Willis in adult Pakistanis	Original article	Anatomical variation, cerebral arteries, circle of Willis, 3D-TOF MR angiography, complete circle, anterior circulation, posterior circulation.
Silva Neto et al., 2012 [67]	Carotid siphon geometry and variants of the circle of Willis in the origin of carotid aneurysms	Original article	Intracranial aneurysm, carotid siphon, fetal communicating artery, A1 hypoplasia, carotid artery.
Sinha et al., 2014 [68]	Variation in the pattern of circle of Willis in human brain –A morphological study and review	Original article	Circulus arteriosus, internal carotid artery, vertebral artery, hypoplasia.
Songsaeng et al., 2010 [69]	Impact of anatomical variations of the circle of Willis on the incidence of aneurysms and their recurrence rate following endovascular treatment.	Original article	Not available.
Tanaka et al., 2006 [70]	Relationship between variations in the circle of Willis and flow rates in internal carotid and basilar arteries determined by means of magnetic resonance imaging with semiautomated lumen segmentation: Reference data from 125 healthy volunteers	Original article	Not available.
van Seeters et al., 2015 [21]	Completeness of the circle of Willis and risk of ischemic stroke in patients without cerebrovascular disease	Original article	Ischemic stroke, circle of Willis, carotid stenosis.
van Laar et al., 2006 [71]	Magnetic resonance evaluation of the cerebral circulation in obstructive arterial disease	Review article	Magnetic resonance imaging, cerebral blood flow, steno-occlusive disease.
Walcott et al., 2014 [72]	Zebrafish models of cerebrovascular disease	Original article	Aneurysm, arteriovenous malformation, cavernous malformation, moyamoya, stroke, zebrafish.
Yang et al., 2013 [73]	Regulation of pre-natal circle of Willis assembly by vascular smooth muscle Notch signaling	Original article	Notch signaling, angiogenesis, vascular smooth muscle cell, circle of Willis.

Abbreviations: *CT angiography*, computer-tomography angiography; *3D TOF angiography*, 3-dimensional time of flight angiography; *MR angiography*, magnetic resonance angiography; *MR angiograms*, magnetic resonance angiograms; *PCA*, posterior cerebral artery; *CADASIL*, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; and *3D-TOF MR* angiography, 3-dimensional time of flight magnetic resonance angiography.

[a] These records have been identified as seed articles.

2.1. Search strategy

The search strategy was conducted between February and June 2023. It was based on key search terms in the *PubMed* (US National Library of Medicine, National Institutes of Health, Bethesda, MD), *Biomed Central* (BioMed Central Ltd., Springer Nature, London, UK), *Scopus* (Elsevier B.V., Amsterdam, the Netherlands) academic search engines. The search strategy was designed by A.F.A. and validated by the senior author (M.V.).

2.2. Eligibility criteria

A literature search including the terms Circulus Arteriosus Cerebri OR Circle of Willis AND variation in the aforementioned search engines was carried out.

Inclusion criteria enclosed articles published in English and peer-reviewed journals and covered citations of the past twenty years. Therefore, few studies published before 1999 were included. Keywords related to these terms were identified. Moreover, the authors searched the reference lists of articles identified through this search strategy and selected additional publications that they deemed relevant.

2.3. Study selection and data extraction

Titles, abstracts, keywords, and full texts were reviewed by two authors (A.F.A. and V.P.). Eventually, conflicts between reviewers were discussed until a consensus was reached, and one of the senior authors was involved if needed. A total of 777 records were initially identified. After duplicate removal, a total of 388 papers were further processed. Moreover, only items in which the abstract unequivocally discussed the topic were included. Therefore, 300 records were excluded with reason and 88 were finally assessed for full-text screening and further qualitative analysis (vd. Fig. 1 for further details).

All articles, abstracts, and keywords, as well as the complete reference list, were analyzed. Moreover, priority was given to anatomy, imaging, and neuroanatomy descriptions, owing also to reference number constrain. Finally, the quality assessment was analyzed by two authors (M.V. and V.P.) and based on the STROBE guidelines for observational studies, as reported by Vandenbroucke and coworkers and von Helm and coworkers [46,47].

The records included in this study are listed in Table 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart [45] was utilized for the report of findings (Fig. 1). All the authors agreed on the final number of studies included.

2.4. Qualitative analysis

According to the Grounded Theory methodology [74,75], the authors extensively discussed the foundations of their query before formulating the research question: "How important is it to know the variant components of the CAC for an efficient, effective, and safe clinical practice?"

The inclusion of records in the qualitative synthesis was performed using the online Research Screener machine learning tool for systematic reviews [76]. The sample in this qualitative analysis was represented by the records assessing the relationship between the anatomical variation of the CAC and the cardiovascular diseases.

Initially, the data set imported into the Research Screener machine learning tool was represented by the 88 records assessed for qualitative analysis. Credibility and reliability were ensured by debriefing and triangulation.

After exhaustive discussion among team members, 7 seed articles were identified [18,30,48,50,52,55,56]. According to the instructions, the library created with the 88 records assessed for qualitative analysis was uploaded to the tool to be further analyzed. Moreover, 37 abstracts from the library counted less than 100 words, and no missing abstracts were automatically removed by the tool. Therefore, a final set of 51 abstracts was further analyzed.

Two reviewers (A.F.A. and V.P.), and an external expert who has full experience in qualitative research independently flagged the abstract. Conflicts were discussed between reviewers and managed accordingly. The senior author (A.B.) was involved if needed. The final qualitative synthesis included 51 records. Subsequently, members of the team (A.F.A., A.B., M.V and V.P.) independently coded and categorized the data into themes and subthemes, which were debated on a regular basis.

Open codes were developed, and themes and subthemes were generated using the trial version of NVivo qualitative data analysis software package (QSR International Pty, Ltd., Melbourne, VIC, Australia) [77,78]. These themes were reviewed by all authors to ensure they were fully consistent with the research question. The flowchart of the Reporting items for the systematic reviews (adapted from the Preferred reporting items for systematic reviews (PRISMA) statement) is reported below (Fig. 1).

3. Results

As previously reported, 777 records were initially identified, and a final set of 51 records were assessed for the qualitative synthesis. Of those, 94 % have been classified as original articles while 6 % are represented by review articles. Moreover, among the original articles, only 3 records have been clearly defined as cross-sectional studies [51,58,66] and only Hindeners et al. [30], as a cohort study. Additionally, consistent with previous findings [29], most of the records included small populations or samples (<350) [11,12,51,53–55,58,61,64,66,68], while only three records reported larger populations [17,29,30]. Surprisingly, the population enclosed in the records consisted of cadaveric specimens [11,12,17,53,54,58,68,79] more than living subjects [29,30,61,64,66,80]. Finally, the

included records were analyzed in terms of three main codes that have been discussed in the following paragraphs: 1) the normal CAC morphology; 2) the abnormal CAC morphology and its main features; 3) techniques that can be used to measure CAC (Fig. 2). Themes and subthemes are discussed in the following paragraphs.

3.1. Cerebrovascular disease

Cerebrovascular disease occurs due to an impairment in vessels that supply blood to the brain [60]. Around 80 % of cerebrovascular disease occurs due to ischemic strokes and the remaining 20 % from haemorrhages, which can be intracerebral or subarachnoid [17]. An ischemic stroke occurs when a thrombus/embolus occludes an artery to the brain causing a reduction in blood flow, thus depriving the brain from oxygen and glucose, critical to keep it alive [59]. There are two forms of haemorrhages: intracerebral haemorrhage due to hypertension and subarachnoid haemorrhage as a result of aneurysm rupture [59]. The severity of ischaemic damage depends upon the size, type and arrangement of vessels [60]. These events might be neurologically devastating and result in permanent damage, increasing the rate of disability or morbidity [72]. Furthermore, evidence has clearly demonstrated a link between CAC variations and the development of cerebrovascular diseases [17,25,71].

3.2. Normal CAC morphology

There is a substantial variability in the morphology of CAC, as reported [10,25]. A normal circle is defined as one with all the vessels intact and forming a complete ring, usually polygonal in shape and symmetrical [11].

Hashemi et al. found that 69 out of 200 (34.5 %) of Iranian study population had a normal CAC (by conventional gross anatomy dissection); this was similar in number to Natraj Prasad et al. who, out of 65 patients, found that 23 (35.4 %) of patients had typical CAC anatomy [58,64]. In contrast, a study of CAC variation via autopsy in India by Sinha and co-workers found that 62 out of 80 specimens (77.5 %) showed a typical CAC, that is, a complete, symmetrical, and normal caliber [68]. Interestingly, a Polish study by Klimek-Piotroska et al. found that in 250 subjects, only 16.8 % presented with a normal CAC [61]. This variation in reported numbers of normal or typical CAC morphology among various studies could be due to sample size, study populations, or diversity in nomenclature [11,51,55,58,61,64,66,81]. However, it is important to note that variations exist and likely have a functional significance. Further research on larger populations to determine the full effect of genetic, environmental, regional, and haemodynamic factors are warranted. Included records assessing the incidence of normal CAC configuration have been reported in Table 2.

3.3. Techniques to measure the circulus arteriosus cerebri (CAC)

Many studies have utilized different methods and techniques to measure the structure of the CAC. Autopsy of cadaveric brains have been used to evaluate CAC anatomy and vessel structure. Various studies have utilized this method [11,12,17,53–55,58,81]. Usually, specimens with head trauma and brain injuries are excluded. Dissection involves removing the brain through careful transection, preserving the brain specimen in 10 % formalin for fixation then careful dissecting and revealing of the arteries from the base of the brain. Observations of shape, size, completeness, symmetry, and any abnormalities are recorded. The length and diameter of vessels making up the CAC are also measured. However, a limitation is that the results are based on autopsy studies and are not physiologically reflective of the normal population and vary from researcher to researcher as to what technique, instrument, measurement tool to use

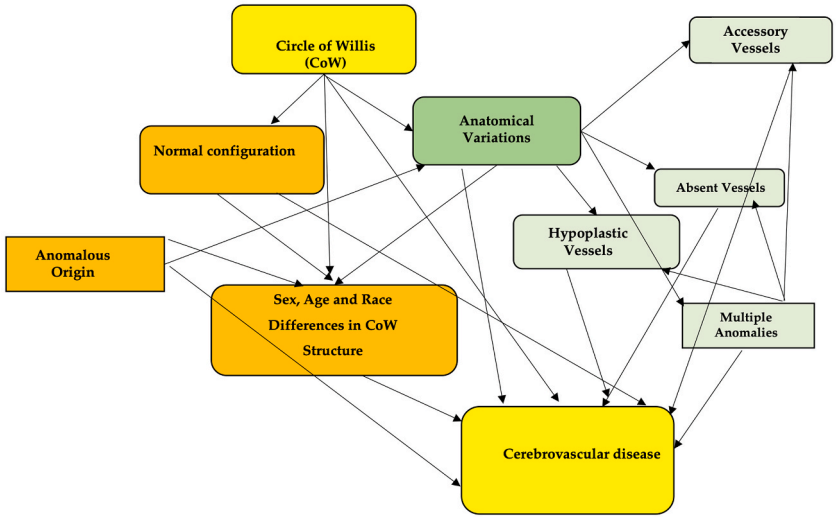

Fig. 2. Node diagrams based on NVivo qualitative data analysis software output (QSR International Pty, Ltd., Melbourne, Victoria, Australia). The larger boxes have been used to identify themes, the smaller to define subthemes.

Table 2
List of the included records reporting the incidence of normal configuration of vessels in the CAC in different populations. *CAC*, Circulus Arteriosus Cerebri. *M*, males. *F,* females. *ACA*, Anterior Cerebral Artery. *gender details not included.

Study details	Study population characteristics	Sample characteristics	Type of study	Incidence of normal ACA (%)	CAC testing methods
Bahaddur et al., 2013 [51]	Indian subjects	healthy subjects (N = 300; 198 M; 102F)	Cross-sectional	16.6	Magnetic resonance angiography
Eftekhar et al., 2006 [55]	Iranian males	cadaveric specimens (N = 102; 102 M)	Not available (	29	Gross anatomy
Hashemi et al., 2013 [58]	Iranian subjects	cadaveric specimens (N = 200*)	Cross-sectional	14	Gross anatomy
Hindenes et al., 2020 [30]	Norwegian population	healthy subjects (N = 1,864, 874 M; 990F)	cohort study	11,9	Magnetic resonance angiography
Iqbal et al., 2013 [11]	Indian subjects	cadaveric specimens (N = 50*)	Not available	48	Gross anatomy
Kapoor et al., 2008 [17]	Indian subjects	cadaveric specimens (N = 1000*)	Not available	45.2	Gross anatomy
Klimek-Piotrowska et al., 2013 [61]	Polish subjects	healthy subjects (N = 250; 129 F and 121 M)	Not available	16.8	Computer tomography angiography
Natraj Prasad et al., 2017 [64]	Nepalese subjects	healthy subjects (N = 65*)	Not available	35.4	Computer tomography angiography
Qiu et al., 2015 [29]	Chinese males	healthy subjects (N = 2246; 2246 M)	Not available	78.58	Magnetic resonance angiography
Shaikh et al., 2018 [66]	Pakistani subjects	healthy subjects (N = 135; 70 M; 65F)	cross-sectional	22.2	Magnetic resonance angiography
Sinha et al., 2014 [68]	Indian subjects	cadaveric specimens (N = 80*)	Not available	77.5	Gross anatomy

[66]. Accuracy of studies investigating intracranial vasculature on cadavers, depends upon the technical preparation of specimens [58].

Magnetic Resonance Angiography (MRA) including contrast-enhanced, time-of-flight, and phase contrast, has been used to investigate the anatomy of the circulus arteriosus cerebri by van Laar and coworkers in 2006 [71]. This technique is useful in determining anatomic and haemodynamic aspects of cerebral circulation, however, these diameter measurements have to be interpreted with a degree of caution as the actual blood vessel lumen may be underestimated due to slower blood flow by the side of the wall [71]. Benefits of MRA include its non-invasive, non-contrast and non-radiation quality allowing a unique and useful opportunity to image living individuals [66]. Similarly, computed tomographic angiography (CTA) has also been used as a reliable non-invasive method of evaluating the CAC with high sensitivity (81–90 %) and specificity (93 %) respectively [62,65]. However with MRA and CTA, limitations include limited resolution which sometimes make distinguishing circulus arteriosus cerebri variations difficult [12].

Just as there are different methods to study the CAC, there are various discrepancies in defining terminology. There are disagreements among researchers about the definition of hypoplasia. Some consider it hypoplasia when the diameter of a blood vessel is < 1.5 mm [22]. Whereas, others consider hypoplasia when the diameter is < 1 mm [53,55,58,66].

3.4. Abnormal CAC morphology

In the past, Fields commented that the variations in the segments of the CAC developed prenatally, and although genetic factors are vital, random chemical biochemical or physical factors are also responsible [57]. Similarly, Milenkovic et al. also observed that variations in the CAC are genetically determined and begin to develop embryonically and persisting into post-natal life [63]. Certainly, factors such as genetics, race, environment, amplitude of neck movement, haemodynamic factors and occlusion may cause or modify variations and anomalies of the CAC [11]. Indeed, a study performed in two independent family groups with familial aneurysms, found that the incomplete PCoA variation was more common within families rather than between, thus suggesting that this variation in the CAC was heritable [71]. In mice, knock out Notch signalling pathways caused an impaired anterior anastomosis and loss of symmetry in the CAC structure, suggesting that the Notch signalling pathway may play a role in CAC variations [73]. In 2014, Arjal et al. analyzed the risk of patients with partial and full fetal-type posterior cerebral artery to ischemic strokes on multislice computed tomographic angiography and demonstrated that those patients could be more prone to develop ischemic strokes [49]. Surprisingly, Oumer and co-workers [18] in a recent review and meta-analysis evaluated evidence on the association between the variations of CAC and ischemic stroke using the available studies. They involved 2718 participants and concluded that there was a non-significant positive association between CAC variation and ischemic stroke.

Subthemes concerning the most common anomalies in CAC morphology will be addressed in the following paragraphs.

3.4.1. Hypoplastic vessels

In the majority of studies, the most common variation of the CAC was hypoplasia or absence of a vessel, specifically the PCoA [17,55,65,66,68]. Iqbal et al. reported that 24 % of CAC studied showed hypoplastic vessels [11]. Natraj Prasad et al. observed hypoplastic PCoA in 26.2 % cases [64], van Laar et al. have reported hypoplasia or absence of PCoA in <40 % of cases [71], Hashemi et al. reported 41.5 % unilateral and bilateral hypoplasia of PcoA [58]. Hypoplasia of the ACoAs were not as common, De Silva et al. [53] as well as

Hashemi and coworkers [58] reported 14 % of cases each and other similar studies have reported 11 % 17 through to 1.25 % [68]. From the studies reported, it is more common to have a variant in the posterior portion of the CAC compared to the anterior portion, particularly, affecting the PCoA most commonly [64,66]. More recently, Dumitrescu and coworkers [54] first demonstrated hypoplasia in the Romanian population. These hypoplastic vessels can occur unilaterally or bilaterally and occur with other forms of anomalies. Also, Orosz et al. [8,8], applied the <1 mm diameter threshold to the CAC in a cohort from a Central European population and demonstrated that this diameter might represent a reference value for the Central-European population. Converserly, Hindenes and coworkers [30] did not differentiate between missing and hypoplastic segments since the hypoplastic segment might somehow provide some collateral flow to the brain.

Table 3 list the records assessing the incidence of cerebral hypoplastic vessels reported in this review. Please note that according to Orosz et al. [8],defined as vessels with <1 mm diameter except in the case of <0.5 mm.

3.4.2. Absent vessels

The anterior part of the CAC is a frequent site of aneurysm formation [52]. A mathematical 1-D model has calculated that a CAC without the first component of ACA (A1) and a complete occlusion of the contralateral ICA seems to have the most reduced cerebral outflow [1]. The reported incidence of absent vessels in the CAC of normal brains ranges from 0.6 % to 17 % [14]. Moreover, Fawcett and co-workers reported 3.8 % absent PCoAs from a study of 700 autopsies [9]. In contrast, De Silva et al. found no incidence of absent PCoAs in a study of 225 autopsies [53]. Finally, Iqbal and colleagues reported their least common anomaly of the CAC, was the absence of one (6 %) or the other PCoA [11]. However, upon closer observation, discovered minute anastomosis between the filiform twigs arising from the PCA and ICA 4, which is consistent with previous findings of Alpers and colleagues [6].

3.4.3. Accessory vessels

Iqbal and colleagues found accessory vessels were present, namely in the form of duplications or triplications of at least one of the components of the CAC. There was an accessory vessel present in 12 % of the circles (n = 50) [11]. Interestingly these duplications occurred more frequently in the anterior portion of the CAC, specifically in the ACoA (8 %) and ACA (4 %) [11]. A triplicate of the ACA was found to be the only anomaly in one circle and part of multiple anomalies in another circle [11].

3.4.4. Anomalous origin

The presence of the embryonic derivation of the PCA from the ICA was found in 10 % of circles [11].

Table 3
List of the included records reporting the incidence of cerebral hypoplastic vessels. *Hypoplastic defined as vessels with <1 mm diameter except in the case of #<0.5 mm [8]. *ACA*, Anterior Cerebral Artery. *ACoA*, Anterior Communicating Artery. *PCA*, Posterior Cerebral Artery, *PCoA*, Posterior Communicating Artery. **sex details not included.

Study details	Sample characteristic	Type of study	Incidence of hypoplastic* vessels (%)				
			PCoA	PCA	ACoA	ACA	CAC testing methods
Ansari et al., 2011 [12]	Iranian population cadaveric specimens (N = 132 fetuses = 3; neonates = 12; infants = 15, adults = 102**)	Not available	59.8	6.8	10.7	–	Gross anatomy and image digitization
De Silva et al., 2011 [53]	Sri Lankan population cadaveric specimens (N = 225**)	Not available	34.5	1.2	14	3	Gross anatomy
Dumitrescu et al., 2022 [54]	Romanian population cadaveric specimens (N = 96**)	Not available	5.2	0.51	0.51	–	Gross anatomy
Eftekhar et al., 2006 [55]	Iranian population cadaveric specimens (N = 102; 102 M)	Not available	60	1.	11	1	Gross anatomy
Hashemi et al., 2013 [58]	Iranian population cadaveric specimens (N = 200**)	Cross-sectional	41.5	–	14	4.5	Gross anatomy
Hindenes et al., 2020 [30]	Norwegian population (N = 1,864, 874 M; 990F)	cohort study	–	–	–	–	Magnetic resonance angiography
Iqbal et al., 2013 [11]	Indian population cadaveric specimens (N = 50**)	Not available	10#	6	4#	4	Gross anatomy
Kapoor et al., 2008 [17]	Indian population cadaveric specimens (N = 1000**)	Not available	16.7	10.6	2.1	1.7	Gross anatomy
Klimek-Piotrowska et al., 2013 [61]	Polish population healthy subjects (N = 250; 129 F and 121 M)	Not available	27	1	2	0	Computer tomography angiography
Natraj Prasad et al., 2017 [64]	Nepalese population healthy subjects (N = 65**)	Not available	26.2	–	12.3	–	Computer tomography angiography
Qiu et al., 2015 [29]	Chinese males healthy subjects (N = 2246; 2246 M)	Not available	48.22	3.16	–	2.49	Magnetic resonance angiography
Shaikh et al., 2018 [66]	Pakistani population healthy subjects (N = 135; 70 M; 65F)	Cross-sectional	38.5	24	–	–	Magnetic resonance angiography
Sinha et al., 2014 [68]	Indian population cadaveric specimens (N = 80**)	Not available	6.25	–	1.25	1.25	Gross anatomy

3.4.5. Multiple anomalies

In the study performed by Iqbal et al., 24 % of CACs demonstrated a single anomaly in one of the component vessels [11]. Multiple anomalies were found in 28 % of the circles with multiple anomalies, 20 % had two anomalies and 8 % had more than two anomalies. The most common of these anomalies was a hypoplastic PCoA with opposite embryonic derivation of the posterior [11]. Similar evidence was highlighted by Dumitrescu and co-workers who were the first to describe CAC variability in Romanian population [54].

3.5. Sex, age and race differences in CAC structure

Bahaddur et al. reported that variants in the CAC are more common in women and younger (<50 years) compared to older individuals [51]. This is in contrast with Kapoor et al. who observed that females have complete CAC more commonly (52.4 %) than males (42.8 %) [17]. However, Sinha et al. observed no statistical significance in regard to sex and age [68]. Other studies have simply not considered sex and age. Thus, more studies regarding these factors and their relation to variations in the CAC are required.

Hashemi et al. found that there were no major differences in studies reported from the Iranian population compared to the French and Moroccan populations when the most common variation was considered, that is hypoplasia of the PCoAs, suggesting that anatomical variation in CAC not different amongst races and ethnicities of different populations [58]. In contrast, De Silva et al. reported significant variations in CAC morphology among intra and inter-ethnic groups including Asian, African, and Caucasian populations [53]. However, as discussed earlier there have been variations in reported numbers, especially for normal CAC morphology. Iranian studies have reported 29 % [55] and 34.5 % [58] cases of normal circles in their study population. An Indian study reported 16.6 % 25 similar to that of the 14 % observed in Sri Lankan population [53]. Some Indian studies have reported about 45.2 % [68] and up to 77.5 % of cases of normal CAC morphology [68]. A Polish study reported 16.8 % of normal CAC morphology [61]. The wide range in prevalence of normal CAC morphology in various races is clinically important and warrants further studies and research to confirm the influence of genetics and the environment as a factor in altering CAC. However, the definition of hypoplasia, methods of collection, measurement and data assessment differ among these anatomical studies, which hinder comparisons between the studies. It appears evident that it is crucial to establish an international standard of definition for the variation and quantitative measures of the diameters of the vessels of the CAC, so that it is possible for accurate comparisons of data between studies in the literature.

4. Discussion: clinical implications

A mathematical model involving 1-D pulse wave propagation performed by Alastruey et al. observed that the CAC system is ineffective in the collateral pathways through the communicating vessels are vital to provide adequate blood flow to the brain of healthy subjects [1]. Of note, this modelling study finds that the CBAN system does not need the collateral blood flow and that occlusion of the VAs seems to be substantially less dramatic than ICAs occlusions.

The communicating arteries become especially important in CAC variations in case of missing first components of ACA or PCA, or when there is an occlusion in an ICA or VA [1]. The ACoA pathways becomes critical when an ICA is occluded, compared to the PCoA pathways which is a similar finding in a study by Hoksbergen et al. [1,19]. If, however, a VA is occluded, the PCoAs become more important collateral route as a compensatory mechanism of the CBAN system [1,3].

The variations in the structure of the CAC are clinically important. For example, a narrower carotid siphon, or a fetal PCoA circulation have an effect on haemodynamic stress and thus influencing the formation of PCoA and AcoA aneurysms [64]. Similarly, in severe occlusive diseases of the internal carotid artery, the components of CAC would provide the collateral blood flow in the system [64]. Therefore, patients with variants of the circle with less efficient circulation will have a higher risk of transient ischaemic attack and stroke compared to their counterparts, with more efficient collaterals, thus improved circulation [25]. Data suggests that certain CAC variations contribute to the development of aneurysms [67,69]. Hypoplasia or an absence of segments of the CAC and higher haemodynamic sheer stress may promote aneurysm formation [70]. Asymmetry of the anterior cerebral arteries (A1 segments) have been associated with aneurysms of the ACoA [67,69]. Similarly, a foetal type posterior cerebral circulation has been linked with aneurysms of the PCoA [67,69]. Aneurysms can develop at any age in the presence of variations in the brain arterial network [82]. Early detection of variations in brain arteries in infants using a non-invasive/safe Doppler ultrasound technique has been recommended and continuing screening regularly as needed [82].

Finally, the authors are aware of the caveats of their study represented a limited keyword search that did not expressly include ‘cerebrovascular disease’. Nevertheless, they purposely limited their search strategy to PubMed (US National Library of Medicine, National Institutes of Health, Bethesda, MD), Biomed Central (BioMed Central Ltd., Springer Nature, London, UK), Scopus (Elsevier B. V., Amsterdam, the Netherlands), search engines to maximize and relevance and, increase the quality of their analysis.

5. Conclusion

Variations in the cerebral basal arterial network (CBAN) are common within the general population and it is worth noting that variations in the posterior part of the *circulus arteriosus cerebri* (CAC) are more common than those in the anterior portion.

Anatomical variations in the CBAN are genetically determined, developing during the intricate process of early embryonic development and persisting throughout post-natal life. However, these variations are not solely influenced by genetics; racial, environmental, and haemodynamic factors may also interplay with genetic predispositions. Recent studies have revealed that variations are more commonly found in the posterior components of the CAC compared to the anterior sections, with posterior communicating arterial hypoplasia being the most prevalent variation observed. Variations in the components of CBAN are significantly associated

with cerebrovascular disorders like aneurysms and strokes. A detailed understanding of these variant components could contribute to improved management of these diseases and pave the way for further research. These deviations from the ~~normal anatomy~~ in the CAC can significantly impact the frequency of occurrence, the severity of symptoms experienced, the choice of treatment, and the overall recovery process for patients with cerebrovascular disorders such as aneurysms and strokes.

A thorough understanding of the variations in the components of the CBAN and their link to pathologies like aneurysms is crucial for health professionals, like neurosurgeons and neuro-interventional radiologists. This knowledge is valuable in performing procedures like aneurysm coiling and other vascular interventions, requiring a high degree of precision and a nuanced understanding of the complexities involved.

Gaining a thorough and in-depth understanding of these atypical manifestations of the CAC (cerebral aneurysm complex) holds significant importance in the realm of healthcare, especially for specialized professionals like neurosurgeons and neuro-interventional radiologists. This comprehensive knowledge becomes particularly valuable as they meticulously plan and execute intricate procedures such as coiling aneurysms and performing various vascular interventions, necessitating a keen eye for detail and a nuanced appreciation of the complexities involved in the treatment of these conditions.

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Adilah F. Ahmad: Writing – original draft, Investigation, Conceptualization. **Francesco M. Galassi:** Writing – review & editing, Formal analysis. **Arjun Burlakoti:** Writing – review & editing, Validation, Investigation. **Mauro Vaccarezza:** Writing – review & editing, Validation, Investigation. **Veronica Papa:** Writing – review & editing, Validation, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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List of abbrevations

*CAC*circulus arteriosus cerebri.
*CBAN*cerebral basal arterial network.
*ICAs*internal carotid arteries.
*VAs*vertebral arteries.
*MCA*middle cerebral artery.
*ACA*anterior cerebral artery.
*ACoA*anterior communicating artery.
*PCA*posterior cerebral artery.
*PCoA*posterior communicating artery.
*MRA*magnetic resonance angiography.
*CTA*computed tomographic angiography.

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