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# Diagnosis of Symptomatic Intracranial Atherosclerotic Disease

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## Abstract

Intracranial atherosclerotic stroke differs from extracranial atherosclerotic stroke in many aspects, including risk factors and stroke patterns. It occurs in association with in situ thrombotic occlusion, artery-to-artery embolism, branch occlusion, and hemodynamic insufficiency. Intracranial atherosclerotic stenosis (ICAS) could have only been diagnosed by transcranial Doppler (TCD) and transcranial color-coded sonography (TCCS), which are burdened by a risk of bias, or catheter angiography (DSA), which, on the contrary, is very precise, but rarely it is done in clinical practice due to its invasiveness. Computed tomography angiography (CT-A) and magnetic resonance imaging angiography (MR-A) have increased the identification of ICAS in a wider stroke population.

**Keywords:** intracranial atherosclerotic stenosis (ICAS), transcranial Doppler (TCD), transcranial color-coded sonography (TCCS), catheter digital subtraction angiography (DSA), computed tomography angiography (CT-A), magnetic resonance imaging angiography (MR-A)

## 1. Epidemiology, natural history, and risk factors of intracranial atherosclerotic disease

### 1.1 The incidence of intracranial atherosclerotic disease (ICAD)

Intracranial atherosclerosis is one of the most important causes of stroke worldwide [1]. All major intracranial arteries are affected by atherosclerotic disease, and between 6 and 50% of all world ischemic strokes are the result of ICAD [2]. Intracranial arterial atherosclerotic stenosis (ICAS) represents the most advanced stage of ICAD, and thus nonstenotic ICAD is much more common than stenotic ICAD [3].

Regarding the incidence of ICAD, it varies especially by ethnicity. Population groups which are at high risk for ICAS include: Asians (30–50% of all new ischemic strokes) [4], Hispanics, and population of African descent; conversely, the risk is lower in Caucasians (8–10% of all new ischemic strokes) [5]. The reason for racial differences is still unclear. The main hypotheses include: low lipid levels and high blood pressure (susceptibility to intracranial and intracerebral vascular disease);

high lipids and high blood pressure (susceptibility to extracranial occlusive vascular lesions); and diabetes mellitus and metabolic syndrome (for ICAS) [2, 6, 7]. Other studies include inherited susceptibility of intracranial vessels to atherosclerosis [8], acquired differences in the prevalence of risk factors [5], differential responses to the same risk factors [9], and different genetic susceptibility [7]. It is also possible that misclassifying patients with adult-onset Moya-Moya disease (MMD) as having ICAD may partly explain the high prevalence of ICAD in Asians [10]. A genome-wide linkage analysis and an exome analysis identified the strongest susceptibility gene for MMD in East Asian people: ring finger 213 (RNF213) [10]. An important role in the emergence of these ethnic differences can be represented by the lifestyle: the pattern of ischemic stroke is changing in Asian patients; due to the westernized lifestyle, the number of extracranial cervical disease is rising [11].

## **1.2 Prognosis of asymptomatic intracranial atherosclerotic disease (ICAD)**

Regarding the prevalence of asymptomatic ICAD in general population, information is still limited, in the absence of large clinical trials [12]. The atherosclerotic process develops silently over years, until its lesions suddenly become symptomatic. Accordingly, early diagnosis of ICAD may improve the therapeutic strategy, while the disease is still asymptomatic. However, the natural history of asymptomatic ICAD is not fully known, especially in Caucasians [3].

The natural history of asymptomatic versus symptomatic ICAD differs from that of extracranial carotid disease (ECAD). Patients with symptomatic ICAD have a low risk of stroke in the stenotic arterial territory, compared to patients with asymptomatic ECAD, while patients with symptomatic ICAD have a higher risk, especially those with clinically significant hemodynamic stenosis, early after stroke [13]. Therefore, recent studies suggest that the annual risk of stroke in asymptomatic patients with at least 50% stenosis of a major intracranial artery is less than 10% [14]. Furthermore, patients with severe intracranial stenosis (70–99%) have a higher risk of stroke than do patients with moderate intracranial stenosis (50–69%) [14].

Arenillas designed a population-based study [3], which comes to clarify the natural history and the prevalence of asymptomatic ICAD in Caucasians. Study subjects (1503) were randomly selected from a population of 600 000 inhabitants, from March 2007 until June 2010. The primary enrollment criteria were: age over 50 years, no past history of cerebrovascular or ischemic heart disease, and moderate-to-high vascular risk. Presence and severity of ICAS were determined through the medium of transcranial color-coded duplex (TCCS) and subsequent MR angiography (MRA) confirmation. Preliminary results showed a prevalence of asymptomatic ICAD of 9% in the first 157 studied subjects [3].

Several transcranial Doppler (TCD) studies in an asymptomatic Asian population have also been conducted. They have come to the conclusion that the prevalence of asymptomatic ICAS ranged from 5.9 to 24.5% [15].

## **1.3 Risk factors for intracranial atherosclerotic disease (ICAD)**

Oh Young Bang reported various conditions and risk factors for ICAD, from risk factors associated with asymptomatic ICAD to risk factors for stroke recurrence [16]. ICAD risk could not be fully related to conventional risk factors for stroke; therefore, specialists are still investigating specific risk factors for ICAD [3].

## **2. The mechanisms of ischemia in intracranial atherosclerotic disease (ICAD)**

According to Arenillas [3], our traditional understanding of ICAD is based on the detection of hemodynamically relevant intracranial arterial stenosis (ICAS).

The main limitations of this classical approach are as follows:

1. It may be restricted to the most advanced stage of ICAD alone [3].
2. It is unable to differentiate atherosclerosis from stenosis caused by other entities. The etiological differential diagnosis of the arterial stenosis includes atherosclerotic disease, embolus with partial recanalization, arterial dissection, vasculitis, and vasospasm. Thus, it is important to note that while anatomic diagnosis of arterial narrowing can be made with appropriate accuracy using conventional imaging techniques, identifying the cause of stenosis involves iterative or multimodal imaging [3].
3. It may not be able to provide information about the histopathologic composition and activity of the intracranial atherosclerotic plaque. The importance of this last point is based on the fact that symptomatic intracranial atherosclerotic plaques are characterized not only by a higher degree of luminal stenosis but also by a richer content in lipid, intraplaque hemorrhage, and inflammatory cell infiltration, all of which are well-known determinants of plaque instability in the extracranial vasculature [3, 17].

Stroke associated with ICAD occurs in association with four mechanisms:

- a. In situ thrombotic occlusion (with impaired anterograde flow). Plaque rupture reveals its thrombogenic core to clotting factors resulting a thrombus that can locally occlude the artery or even embolize distally. The term of “vulnerable plaques” refers to those ones with a large lipid core, the presence of intraplaque hemorrhage, or a thin or ruptured fibrous cap; this kind of plaques are liable to suffer anytime a rupture. Patients with unstable intracranial plaques may show large territorial lesions via sudden thrombotic occlusion [16].
- b. Artery-to-artery embolism. This mechanism commonly causes multiple cortico-subcortical infarcts [16].
- c. Hemodynamic insufficiency/failure (with impaired collateral flow and cerebrovascular reserve). Severe narrowing or occlusion of the lumen may lead to hypoperfusion of the distal brain territory, especially in patients with inadequate collateral flow. The hypoperfusion through a stenotic intracranial artery causes watershed or border-zone strokes [16].
- d. Branch occlusion disease (BOD) is one of the main stroke mechanisms of ICAD. This mechanism, specific to ICAD, consists in growing of the plaque over the ostia of penetrating arteries. It is defined by a milder degree of stenosis and comma-shaped infarcts extending to the basal surface of the parent artery. BOD has been related to cryptogenic strokes [16, 18].

Thus, even mild stenosis of intracranial atherosclerotic arteries (<50%) may be clinically relevant, and high-resolution magnetic resonance imaging (HR-MRI)

studies are needed to identify and determine the degree and location of stenosis in this patient group [19]. Oh Young Bang and others asserted that these mechanisms can coexist and interact in the same patient [16, 18, 20, 21].

## **2.1 Clinical recurrence rate**

As we mentioned before, the annual recurrence rates for any ischemic stroke reported in the WASID trial were as high as 15 and 14% in the aspirin and warfarin arms, respectively [16].

It has been shown that symptomatic ICAD is particularly burdened with a high clinical recurrence rate [3]. Moreover, Famakin and coworkers reported that most subsequent strokes in patients with symptomatic ICAS occurred in the same arterial territory were nonlacunar, and nearly half of them were disabling [19]. Their results were similar to the findings in NASCET, which showed that 95% of strokes were ipsilateral in patients with 70–99% carotid stenosis, and 71% of strokes were ipsilateral in patients with 50–69% carotid stenosis [22].

It is also important to mention that Famakin and coworkers observed that patients with ICAS have a propensity for atherosclerotic stenosis at different sites within the intracranial circulation [19]. Supporting this idea, they reported that among the 27% of the strokes occurring outside the territory of the symptomatic intracranial artery, almost half (48%) could have been caused by previously asymptomatic or newly developed ICAS in a different vascular territory. However, in the same study, it was suggested that it is also possible that some of these strokes may have been caused by an embolus which partially recanalized leaving a residual stenosis [19]. Supporting this theory is data from another WASID analysis, which showed that asymptomatic ICAS that was present at study entry (coexistent with the symptomatic stenosis) was associated with a low rate of stroke (3.5% after 1 year of follow-up) [23].

Identifying whether ICAS is actually the cause of the present stroke (determining whether the stenosis is symptomatic or asymptomatic), it is however still a challenge, knowing that, according to Famakin, in up to 20% of the patients with stroke and ICAS, there is another cause for its occurrence (extracranial large artery stenosis, cardiac embolism, and small artery occlusion can co-exist with ICAS) [19]. Nowadays, different noninvasive imaging techniques can provide physiological data on the mechanisms associated with ICAD-linked stroke and their forms of coexistence, including markers of anterograde and collateral flow, dynamic cerebrovascular reserve, static tissue perfusion, characteristics and morphological details of plaques with embolic potential, etc. [16, 18, 24].

All these data may improve stroke risk stratification, adding to clinical and anatomic (i.e., percent stenosis) predictors of stroke risk, developing mechanism-specific prevention and treatment strategies, and also serve in patients' selection for endovascular therapies [16, 18, 24].

## **3. Catheter-based digital subtraction angiography (DSA)—diagnostic test for intracranial arterial stenosis (ICAS)**

Catheter-based digital subtraction angiography (DSA) is the gold standard in the diagnosis of ICAS. ICAS is considered as symptomatic, if there are obvious radiological signs of acute ischemia in the supplying vascular area and if no other obvious cause (e.g., acute occlusion) is present.

Regarding the advantages of DSA, it allows [12]: the visualization of vessel contour—at a high resolution (microns); the localization of stenosis; and the

estimation of degree and length of stenosis (DSA measures stenosis precisely); 3D reconstruction provides even greater detail, highlighting of collateral circulation (measure anterograde and collateral flow). Prabhakaran and coworkers suggested that DSA can identify the mechanisms of stroke in symptomatic ICAS by using surrogate imaging markers of stroke risk [12]: for the mechanism of *decreased antegrade flow*—the surrogate imaging marker of TICI (thrombolysis in cerebral infarction) flow grade; for the mechanism of *progression of stenosis*—the surrogate imaging marker of TICI (thrombolysis in cerebral infarction) flow grade; and for the mechanism of *poor collateral flow*—the surrogate imaging marker of collateral flow grade. However, being an invasive method that can generate periprocedural complications (periprocedural neurologic injury, access site injury, radiation risks, contrast risks, low availability, and great costs), DSA cannot be used in everyday routine clinical practice, in all patients [25].

### **3.1 DSA allows an excellent visualization of intracranial arterial contour, at a high resolution (microns)**

Monitoring the natural history of stenosis due to ICAD may be a useful method in finding new possible treatments. Long-term angiographic progress of ICAS has not received much attention before WASID trial; Bauer et al. [26] reported the progression of atherosclerotic stenoses by location, including extracranial and intracranial sites. Overall, 35.3% of intracranial sites progressed. Craig et al. [27] noted that intracranial ICA stenoses progressed in 5 of 5 patients on follow-up angiography. Akins and coworkers retrospectively reviewed records over a 7-year period to identify patients with ICAS and serial angiograms. The most common location for an ICAS of 50% or greater was the intracranial portion of the ICA (49% of lesions), followed by the MCA (20%), PCA (11%), distal VA and BA (11%), and ACA (9%) [28].

Angiography is an excellent method for monitoring intracranial atherosclerosis, but this method defines the vessel lumen only; the disease process leading to luminal narrowing being inferred [28]. If the patient has widespread atherosclerosis, the stenosis is usually ascribed to this. The arterial narrowing is generally caused by local atherosclerosis, but associated thrombus may also contribute. Emboli also cause luminal narrowing. In this situation, the follow-up study may show the complete resolution of the stenosis due to spontaneous clot lysis. This pattern was encountered in 3 of the 45 sites studied by Akins. He noted that there are also other pathological conditions that can cause vessel narrowing, such as vasculitis, vasospasm, or malignancies. He concluded that ICAS is dynamic lesions [28].

### **3.2 DSA allows an excellent localization and evaluation of the degree and length of intracranial arterial stenosis (ICAS)**

Angiographic measurement methods are routinely used nowadays in clinical practice to identify patients who may benefit from carotid endarterectomy [29]. Samuels affirmed that the established methods for measuring extracranial ICA stenosis are unsuitable for measuring the stenosis of a major intracranial artery because the intracranial arteries are often tortuous, have several branches, and are narrowing gradually in their distal portions [29].

If the prognosis of ICAS and the choice of therapy for these patients was clearly shown by WASID trial [2] to be based on the severity of ICAS, a repeatable method for measuring percent stenosis of the major intracranial arteries was required: standard WASID criteria for grading of ICAS [29].

All patients enrolled in the WASID trial have been subjected to DSA, to confirm a symptomatic ICAS (50–99%) of the ICA, MCA, VA, or BA. All major intracranial vessels were screened for stenosis stratified into three categories of lumen reduction (30–50, 50–70, and >70%). The percentage of stenosis of an intracranial artery was defined by Samuels [29].

$$\text{WASID method } [1 - (D_{\text{stenosis}}/D_{\text{normal}})] \times 100 = \% \text{ Stenosis.} \quad (1)$$

Rules applied for measuring a stenosis of the carotid siphon and basilar artery.  $D_{\text{stenosis}}$  is the residual diameter of the artery at the site of the most severe stenosis, and  $D_{\text{normal}}$  is the diameter of the proximal normal artery.

- If the proximal segment is diseased, contingency sites are chosen to measure  $D_{\text{normal}}$ : distal artery (second choice) or feeding artery (third choice).
- If tandem intracranial lesions are present (e.g., distal vertebral and mid-basilar), percent stenosis of both sites is measured and the more severe stenosis is selected.

When a “gap sign” is present (i.e., the lumen of the vessel cannot be visualized at the site of severe stenosis),  $D_{\text{stenosis}}$  cannot be measured with calipers. In these cases, percent stenosis is defined as 99% luminal stenosis [29].

### **3.3 DSA is an excellent assessor of collateral intracranial arterial circulation**

Cerebral collateral circulation is a supplementary vascular channels network that plays an important role in stabilizing the cerebral blood flow when the main arterial supplying systems fail (Liebeskind and coworkers) [30, 31]. Arterial insufficiency due to thromboembolism, hemodynamic compromise, or a combination of these factors may lead to the recruitment of collaterals [30, 31].

Impaired cerebral hemodynamics is a well-established predictor in large artery stroke [32]. Cerebral perfusion pressure distal to a high-grade stenosis or occlusion depends on collateral sources of blood flow. The anterior and posterior communicating arteries (ACoA, PCoA) provide most collateral flow in ICA and BA stenosis (primary collaterals), while distal pial and leptomeningeal anastomoses (secondary collaterals) are important in MCA stenosis [32]. DSA is the most valuable investigation that provides the assessment of collateral cerebral flow; Liebeskind and coworkers reporting that collateral flow on DSA was found to be absent in 69% of patients with symptomatic ICAS and it was also considered an independent predictor of recurrent ipsilateral stroke [30, 31].

Stroke risk, due to ICAD, increases with the arterial stenosis degree. Liebeskind and coworkers conducted a retrospective analysis of the baseline DSA acquired in the WASID trial, and they provided the first comprehensive evaluation of collaterals in modifying stroke risk in patients diagnosed with ICAD and its impact on subsequent stroke characteristics. They observed that the collateral circulation was adequately available for analysis in 287/569 patients from WASID (50%) subjects with proximal arterial stenoses ranging from 50 to 99% [30, 31].

According to Liebeskind, collateral brain circulation is one of the most significant factors that mediates the potentially devastating effects of cerebral ischemia. He asserted that patho-physiological recruitment of these collateral vessels (potential anastomotic connections) depends on the temporal course of numerous compensatory (hemodynamic, metabolic, and neural) mechanisms and on the caliber and patency of primary pathways that may rapidly compensate for decreased

blood flow and the adequacy of secondary collateral routes [30, 31]. He asserted that collaterals maintain perfusion downstream from arterial occlusions in acute stroke, determining the hemodynamic characteristics of the ischemic penumbra, the evolution of infarct, and susceptibility for hemorrhagic transformation [30]. He suggested that focal neurologic symptoms manifest only when collaterals fail. Regarding the therapeutic point of view, robust collaterals are an effective predictor of arterial recanalization and good clinical outcomes in acute stroke [31]. It is also well known that arterial occlusion secondary to progressive atherosclerotic stenosis of an intracranial segment allows the development of robust collaterals over time, unlike the cardioembolic or abrupt thrombotic occlusion. Collaterals and functional demonstration of flow impairment may be more informative than isolated anatomic measures of maximal stenosis or length [30].

Liebeskind concluded that collateral circulation is a powerful determinant of stroke risk in ICAD, demonstrating a protective role with severe stenoses and perhaps distinguishing milder stenoses that are relatively unstable [30, 31].

#### **4. Transcranial Doppler (TCD) and transcranial color—coded sonography (TCCS)—diagnostic tests for intracranial arterial stenosis (ICAS)**

Intracranial circulation can be examined by transcranial Doppler ultrasonography (TCD) or transcranial color-coded duplex sonography (TCCS) through different bone windows (transtemporal, transforaminal, and transorbital). The signal can be enhanced by using ultrasound contrast agents [33–38]. TCD combines in real-time intracranial blood flow patterns and velocities modifications with arterial diameter in the stenotic vessels. The most important data are: depth, blood flow direction, different velocities (peak systolic-PSV, end diastolic-EDV, and mean blood flow velocity-MFV), pulsatility index-PI, and resistance index-RI. The physiological data assessed from TCD are complementary to the anatomical data analyzed from other neuroimaging techniques (DSA, CTA, and MRA) [33–38].

TCD has some advantages: inexpensive, noninvasive, portable test than can be performed bedside, serial examination, emboli detection, and vasomotor reactivity testing. TCD has high specificity, sensitivity, and negative predictive value (NPV) [33–38]. In the same time, TCD has some disadvantages: low reliability, technical limits (inadequate or absent windows, the tortuous course of the basilar artery, etc.), and operator-dependent results. TCD presents a modest positive predictive value (PPV) (36–75%). Therefore, it is useful to exclude significant ICAS with high certainty but requires confirmation by other imaging methods when stenosis is suggested [33–41]. The circle of Willis is complete in only 20% of cases; in other cases, one or several vascular segments may be hypoplastic or aplastic. Visualization of the intracranial vessels and assessment of cerebral hemodynamics are only possible with TCCS, but this technique still requires further certification in larger studies [33–41].

Prabhakaran and coworkers suggested that TCD can specify the mechanisms of stroke in symptomatic ICAS by using surrogate imaging markers of stroke risk: for the mechanism of decreased antegrade flow—the surrogate imaging marker of flow velocity; for the progression of stenosis—the flow velocity; for the poor collateral flow—the circle of Willis collaterals; for the artery-to-artery embolism—the microembolic signal; and for the impaired vasomotor reactivity—the cerebrovascular reactivity [33–41]. Serial monitoring of flow velocities by TCD can detect the evolution of ICAS and therapeutic effects [22, 41].



Transcranial ultrasound is used for multiple aims: TCD/TCCS can detect, localize, and grade the severity of ICAS; can detect and localize the intracranial arterial occlusion; can realize the real-time monitoring of recanalization in patients treated with systemic thrombolysis and of rescue reperfusion techniques (identification of reocclusion, hyper-perfusion syndrome, etc.); can detect clinically silent emboli: microembolic signals (MES), which recognizes patients at higher risk of embolic stroke; can recognize patients with extracranial internal carotid artery (ICA) stenosis at a higher stroke risk; can assess both collateral pathways and the vasomotor reactivity (VMR), which detects the risk stratification of hemodynamic stroke [22, 33, 37, 41]; and can identify intracranial arterial blood flow steals.

#### 4.1 TCD/TCCS can detect, localize, and grade the severity of ICAS

In clinical practice, interpretation of TCD data should be individualized, with various parameters (velocities values, spectrum, waveform patterns, flow pulsatility, collateral flows, status of extracranial arteries, systemic conditions: anemia, etc.) (Tables 1 and 2) [35]. TCD presents higher precision for identification of ICAS in the MCA and BA than in other intracranial arteries, due to the tortuosity in the latter [33].

ICAS criteria are direct and indirect.

Artery	Stenosis >50% (MFV, SPR)	Stenosis >70% (MFV, SPR)	Diffuse disease or near occlusion (MFV, SPR)
MCA	>100 cm/s, >2	>120 cm/s, >3	<30 cm/s, <1
ACA	>80 cm/s, >2	n.a., >3	<30 cm/s, <1
PCA	>80 cm/s, >2	n.a., >3	<30 cm/s, <1
BA	>90 cm/s, >2	>110 cm/s, >3	<20 cm/s, <1
VA	>90 cm/s, >2	>110 cm/s, >3	<20 cm/s, <1

*MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; BA, basilar artery; VA, vertebral artery; MFV, mean flow velocity; n.a., not available; and SPR, stenotic/prestenotic MFV ratio.*

**Table 1.**  
TCD criteria for intracranial stenosis (ICAS) [33].

Artery	Mild stenosis	Moderate stenosis	Severe stenosis
	Stenosis <50% (PSV)	Stenosis >50% (PSV)	Stenosis >80%
MCA	>155 cm/s	>220 cm/s	+Indirect signs
ACA	>120 cm/s	>155 cm/s	+Indirect signs
PCA	>100 cm/s	>145 cm/s	+Indirect signs
BA	>100 cm/s	>140 cm/s	+Indirect signs
VA	>90 cm/s	>120 cm/s	+Indirect signs

*MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; BA, basilar artery; VA, vertebral artery; and PSV, peak systolic velocity.*

**Table 2.**  
TCCS criteria for intracranial stenosis (ICAS) [42].

A. Direct criteria (modifications observed at the stenosis level) include:

- a. A color aliasing phenomenon (only in TCCS exam), which may indicate augmented flow velocities, caused by a stenosis or other etiologies (tortuosity, etc.) [35].
- b. A progressive focal increase of blood flow velocities in  $\geq 50\%$  stenosis or paradoxical velocity decrease with very severe stenosis, near-occlusion or diffuse intracranial disease (Figures 1, 2).

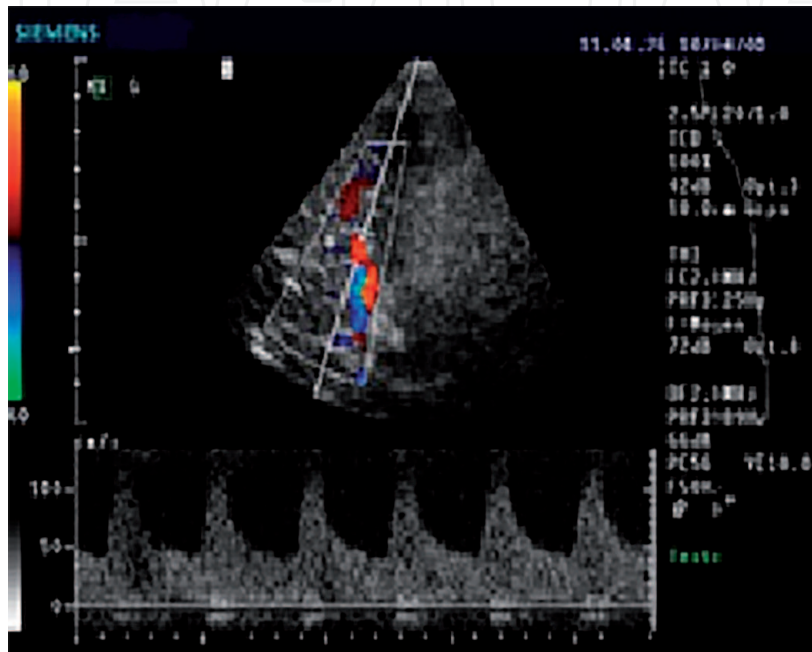


Figure 1.  
TCDS, transtemporal approach, axial midbrain plane, color mode (left M1 higher grade stenosis).

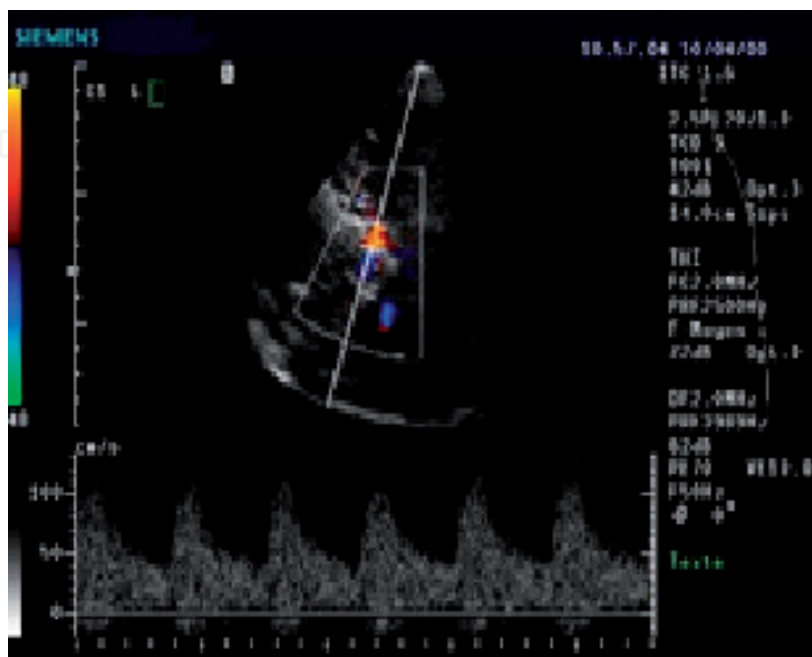


Figure 2.  
TCDS transtemporal approach, axial, midbrain plane, color mode (left C1 stenosis).

Baracchini noted that, as a rule for a vessel with straight walls, a 50% diameter reduction double the velocity, and a 70% stenosis may triple the velocity at the end of the stenosis compared with a prestenotic segment or with the contralateral non-affected side. The velocity values detected by TCCS are higher than those by TCD (due to angle correction) [35].

- c. A significant (>30%) side-to-side difference of velocity (for symmetrical vessel segments after angle correction) [35].

**B. Indirect criteria (changes observed in other arteries):**

- a. Only observed in very severe stenosis (>80%).
- b. Are the same as for occlusion—proximal or distal flow alterations: a diastolic velocity drop; high RI in the feeding vessel or in the proximal segment of the stenotic vessel; a delayed systolic flow augmentation and velocity drop downstream; and flow diversion and signs of collateralization [35, 41–43].

TCD criteria for ICAS in anterior as well as posterior circulation have been validated against DSA, MRA, and CTA, and serve as reliable tools for their diagnosis (**Table 1**) [33].

The velocity criteria for  $\geq 50\%$  ICAS were detected by Feldmann and coworkers in (SONIA) trial [39], which standardized the data of TCD, MRA, and DSA. The cut points were the measures of continuous variables such as the percentage of stenosis on MRA or velocity on TCD for each intracranial arterial vessel:

- a. MRA  $\geq 50\%$  stenosis, without occlusion, or the presence of a flow gap defined a positive test. Stenosis  $\geq 50\%$  on TCD was identified using an MFV >100 cm/s in MCA, >90 cm/s in the intracranial ICA, or >80 cm/s in the BA or VAs [39].
- b. For 80% stenosis on MRA, the SONIA TCD-MFV (cm/s) cut points for 70–99% DSA stenosis of different arteries were: MCA 240, ICA 130, BA 130, and VA 130 [39].

SONIA trial established that both TCD and MRA could reliably exclude the presence of ICAS, rather than identifying them; abnormal findings on TCD or MRA requiring a confirmatory test such as DSA to diagnose ICAS [39].

The correlation between TCD and DSA for the identification of  $\geq 50\%$  ICAS at laboratories with (SONIA) TCD scanning protocol was established by Limin Zhao and coworkers [40]. Stenosis  $\geq 50\%$  on TCD was detected using an MFV >100 cm/s in the MCA, >90 cm/s in the intracranial ICA, or >80 cm/s in the VAs/BA. For  $\geq 70\%$  ICAS, they used expanded criteria (MFV-MCA >120 cm/s, MFV-VAs/BA >110 cm/s, stenotic/prestenotic velocity/ratio-SPR  $\geq 3$ , and low velocity). These criteria demonstrated excellent-to-good sensitivity of TCD and indicated good agreement with DSA [40].

Baumgartner and coworkers conducted a TCCS study that evaluated PSV cutoff values for the assessment of >50 and <50% stenosis of the intracranial arteries (**Table 2**) [42].

#### **4.2 TCD/TCCS can detect and localize the intracranial arterial occlusion**

Intracranial occlusion can be directly or indirectly detected by ultrasound examination.

- a. Direct criteria for intracranial arterial proximal occlusion are diagnosed using the thrombolysis in brain ischemia (TIBI) flow-grading system. They include: no flow signal (TIBI 0) and minimal flow signal (TIBI 1), while blunted flow signal (TIBI 2) and dampened flow signal (TIBI 3) are criteria for distal occlusion (**Figure 3**). A missing flow signal could be occlusion or hypoplasia/aplasia (it is essential to use ultrasound contrast agents and to verify for indirect criteria of intracranial arterial occlusion) [35, 36, 43, 44].
- b. Indirect criteria for intracranial arterial occlusion comprise proximal or distal flow alterations: a diastolic velocity drop; high RI in the feeding vessel or in the proximal segment of the stenotic vessel; a delayed systolic flow augmentation and velocity drop downstream; and flow diversion and signs of collateralization (**Figure 4**) [33–38].

#### 4.3 TCD/TCCS can realize the real-time monitoring of recanalization in acute ischemic stroke patients treated with systemic thrombolysis and of rescue reperfusion techniques (identification of reocclusion, hyperperfusion syndrome, etc.)

TCD/TCCS can detect the residual flow at thrombus-blood interface.

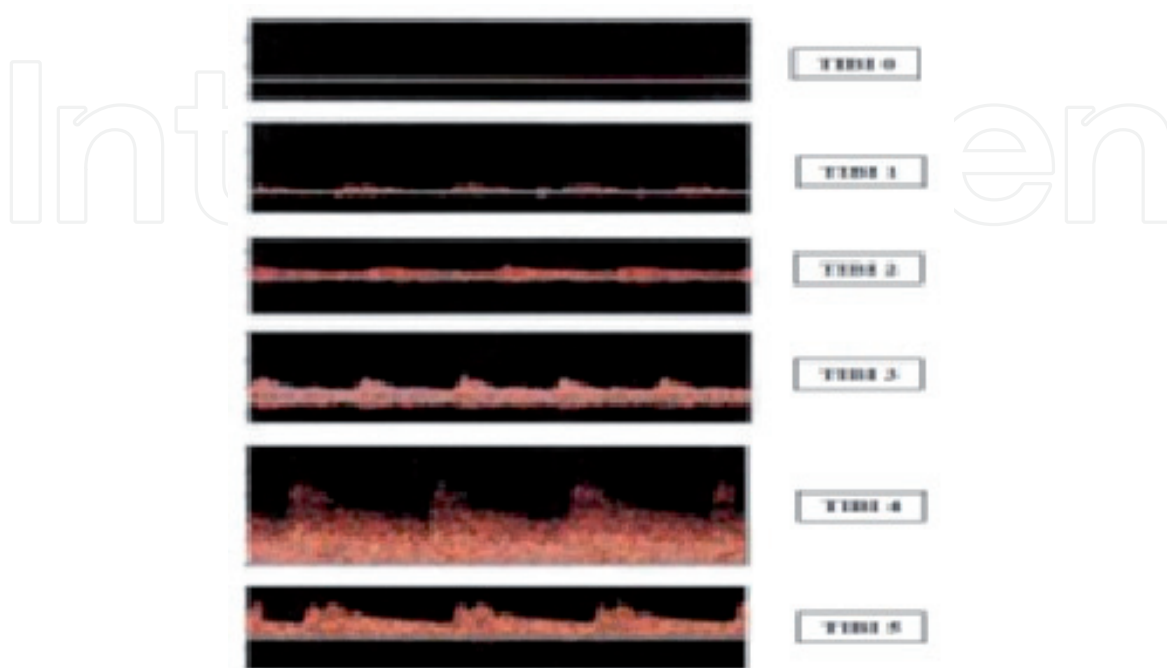
The TIBI flow grading system, TIBI: 0–5, was elaborated to identify residual flow and to monitor thrombus dissolution in real time [37, 43–45].

Absent flow (TIBI 0): no flow signals; or lack of regular pulsatile flow signals (using lowest pulse repetition frequency-PRF and increased color-gain settings).

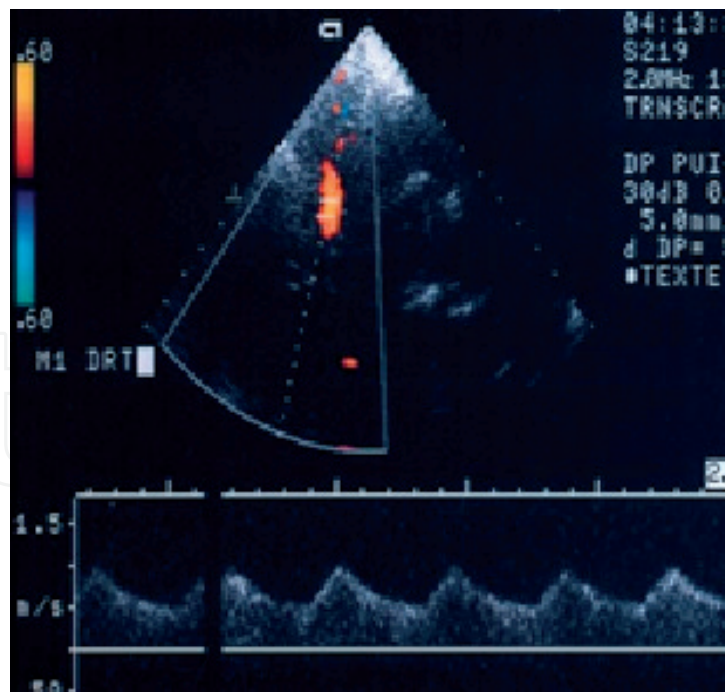
Minimal (TIBI I): systolic spikes of variable velocity and duration; and absent diastolic flow during all cardiac cycles.

Blunted (TIBI II): flattened or delayed systolic flow acceleration compared with control side; positive end-diastolic velocity (EDV); and pulsatility index (PI) <1.2.

Dampened (TIBI III): normal systolic flow acceleration; positive EDV; and >30% decrease in mean flow volume (MFV) compared with control side.



**Figure 3.**  
*Thrombolysis in brain ischemia (TIBI) flow-grading system.*



**Figure 4.** TCDS, transtemporal approach, axial midbrain plane, color mode (right proximal ICA occlusion, with right M1-MCA poststenotic flow pattern).

Stenotic (TIBI IV): MFV  $>80$  cm/s and velocity difference  $>30\%$  compared with control side; if the velocity difference is  $<30\%$ , look for additional signs of stenosis; and affected and comparison sides have MFV  $<80$ cm/s.

Normal (TIBI V):  $<30\%$  MFV difference compared with control side; and similar wave form shapes compared with control side [37, 43–45].

TIBI flow grades I–III correspond to acute proximal intracranial artery occlusion, while a TIBI flow grade of IV is an indicative of proximal artery hemodynamically significant ( $>50\%$ ) stenosis.

The assessment of the diagnostic value of transcranial power motion-mode Doppler (PMD-TCD) against computed tomography angiography (CTA) in patients with acute ischemic stroke was evaluated by Tsivgoulis and coworkers. They asserted that PMD-TCD detected a substantial proportion of ICAS or occlusions, in concordance with CTA in patients with acute ischemic stroke. PMD-TCD identified data supplementary to the CTA: collateralization of flow with extracranial ICA stenosis/occlusion; real-time embolization-MES; and arterial blood flow steal [45].

The evaluation of the diagnostic value of PMD-TCD against DSA in the detection of acute posterior circulation steno-occlusive disease was realized by Tsivgoulis and coworkers. They showed that the higher value of PMD-TCD compared with single-gate TCD may be associated with its ability to observe flow on the PMD display along tortuous and long arterial segments that may not be readily identified by sonographers during a single-gate TCD exam. In conclusion, PMD-TCD can exclude vertebro-basilar artery occlusion and can select patients for DSA and endovascular interventions if the sonographers are confirmed by DSA [46].

An acute arterial occlusion differs from chronic as it is often partial and incomplete and exhibits dynamic processes (partial obstruction to flow, thrombus propagation, reocclusion, and sometimes spontaneous recanalization). TCD can rapidly identify patients with these lesions and detect not only the flow-limiting lesion but also the ongoing embolization, the collateralization, and the failure of the vasomotor reserve [37].

#### **4.4 TCD can identify clinically silent emboli: microembolic signals (MES), which recognizes patients at higher risk of embolic stroke**

MES detection in different interventional procedures (cerebral and coronary angiography, angioplasty, carotid endarterectomy, etc.) and in patients with extra and intracranial large artery atherosclerotic stenosis is useful in risk stratification, thus enabling to select those patients who could benefit from a more aggressive treatment [33, 41, 47]. MES detection requires continuous monitoring (at least 1 hour) of the major intracranial arteries. Most MES can be detected several days after the embolic event. The origin of emboli is important; the detection of an embolic signal in the distal MCA might represent an atherosclerotic plaque in the ipsilateral MCA or ICA. On the other hand, the identification of MES in multiple bilateral arteries indicates a cardiac origin [33, 41, 47].

#### **4.5 TCD can recognize patients with extracranial ICA stenosis at a higher stroke risk, can assess both collateral pathways, and the vasomotor reactivity (VMR), which detects patients at higher risk of hemodynamic stroke**

Severe extracranial ICA stenosis may produce embolic or hemodynamic hemispheric infarct [48]. While the risk of an embolic ischemic stroke increases with the severity of ICA's stenosis, the hemodynamic risk correlates less well with the degree of stenosis because of the functional capacity of the collateral pathways [48]. A complete circle of Willis and the possibility to activate primary collaterals (anterior communicating artery-ACoA, posterior communicating artery-PCoA) or secondary collaterals (ophthalmic artery-OA, lepto-meningeal arteries) reduce the risk of hemodynamic infarct ipsilateral to the extracranial ICA disease [33, 36, 38]. In patients with collateral flow signals (reversed OA, anterior cross-filling, and PCoA flow) identified by TCD, proximal ICA occlusion is confirmed by subsequent neck CTA, MRA, or DSA [33, 36, 38].

Vasomotor reactivity (VMR) defines the autoregulatory vasodilation of cerebral vessels in response to a vasodilatory challenge, such as hypercapnia or acetazolamide (apnea test, breath-holding test, and Diamox test). VMR represents a measure of dynamic cerebrovascular reserve capacity. Its study recognizes patients at higher risk of hemodynamic stroke, in both intra and extracranial large vessel disease, thus allowing to select those patients who could benefit from a more aggressive treatment [38, 48]. According to Prabhakaran, the presence of MES, poor collateral flow, and impaired VMR predict the high risk of recurrence in intracranial atherosclerosis [41].

TCD can identify intracranial arterial blood flow steals (reversed Robin Hood syndrome).

Intracranial arterial blood flow steals can be detected in chronic disease (e.g., subclavian artery stenoses, arterio-venous malformations, and fistulas) but also in patients with acute ischemic stroke. Flow diversion is the hallmark of a steal and can appear at any level of the intracranial arteries (large proximal vessels and small distal vessels) [33–35].

### **5. Magnetic resonance angiography (MRA) and high-resolution magnetic resonance imaging (HR-MRI) for the diagnosis of intracranial atherosclerotic disease (ICAD)**

ICAD includes two major features: (a) atherosclerosis caused by lipid deposits in the intima of the arteries and inflammation; and (b) sclerosis, as a result of endothelial dysfunction, leading to arterial stiffness [49].

Strokes associated with ICAD occur in association with four major stroke mechanisms: in situ thrombotic occlusion; branch occlusion; artery-to-artery embolism; and hemodynamic insufficiency [50, 51]. Unstable intracranial plaques can suddenly lead to thrombotic occlusion. Using transcranial duplex monitoring, artery-to-artery embolism can be discovered, which commonly causes multiple cortico-subcortical infarcts. Branch occlusive disease (BOD) is one of the main stroke mechanisms of ICAD, which can be characterized by a milder degree of stenosis [19] and comma-shaped infarcts extending to the basal surface of the parent artery [52].

The first two mechanisms are the consequences of plaque rupture, which reveals the thrombogenic core to clotting factors, resulting a thrombus that occludes the artery locally or embolizes distally [50].

The third mechanism, specific to ICAD, is the growth of plaque over the ostia of penetrating arteries resulting in occlusion, which was described by Caplan [53] as branch atheromatous disease. Lastly, high-grade narrowing or occlusion of the lumen may lead to the fourth mechanism: hypoperfusion of the distal brain territory, particularly in cases with inadequate collateral flow [31, 50].

MRA, CTA, DSA, TCD, and TCCS can detect ICAS of different histopathological nature (including partially recanalized emboli) and can assess ICAS progression and in-stent restenosis. Unfortunately, these methods are unable to directly examine plaque instability, with the exception of microembolic signals (MES) detection by TCD as a surrogate marker [3].

Arenillas suggested that for the detection of intracranial plaque morphology, the imaging techniques used include high-resolution MRI (HR-MRI), high magnetic field (3T) preferable, and intravascular ultrasound. This new concept allows the detection and characterization of nonstenotic intracranial atheroma, establishing its role in stroke of undetermined origin, and may have the power to confirm the atherosclerotic nature of ICAS [3].

### **5.1 Magnetic resonance angiography (MRA)**

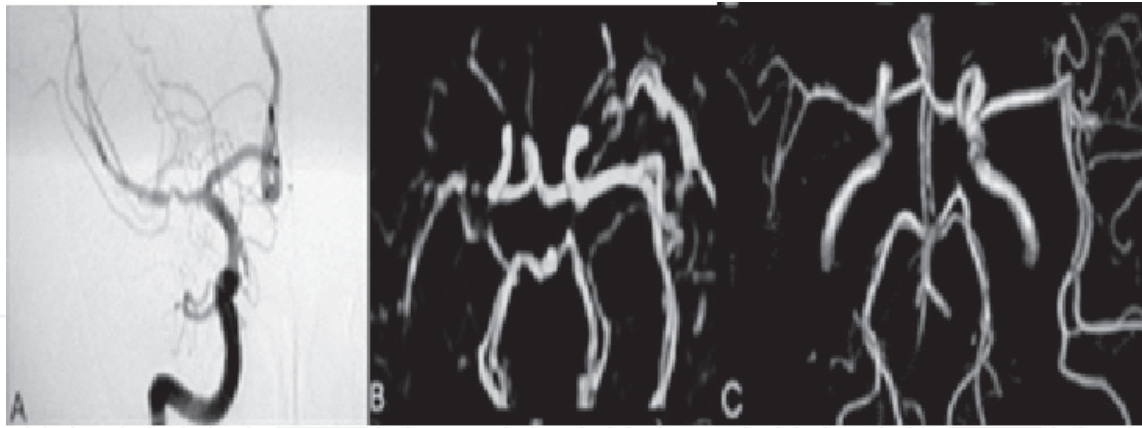
Degnana noted that 3D time-of-flight (TOF)-MRA is a imaging technique that noninvasively explores the intracranial arteries. It takes the advantage of the contrast between nonsaturated spins in the blood entering the imaging plane and the stationary adjacent tissue, which remains saturated. 3D TOF-MRA allows the visualization of any variation in blood flow. It provides detailed information about the lumen status of the intracranial vessels (**Figure 5**) [54].

The following arterial segments are assessed: bilateral intracranial ICA, ACA-A1/A2, MCA-M1/M2, PCA-P1/P2, BA, and VA. According to the severity of stenosis, there are four groups in which patients are classified: <50% or no stenosis, 50–69% stenosis, 70–99% stenosis, and occlusion groups. Focal flow void found on MRA with distal filling is considered as severe stenosis (70–99%) [55].

Other MR sequences, such as T2-/T1-weighted imaging, fluid-attenuated inversion recovery sequences, and diffusion-weighted imaging (DWI), are also performed on a conventional MRI on a 3.0 or 1.5T MR scanner [56].

Degnana asserted that MRA offers good equivalency with DSA for the detection of >50% stenosis with the reported sensitivity, specificity, and accuracy of 92, 91, and 91%, respectively [54].

Higher field strength scanners may carry additional benefits in improving signal intensity-to-noise ratio and background suppression; other sequences, such as novel sensitivity encoding (SENSE) TOF-MRA protocols, also have substantially abbreviated acquisition times [57].



**Figure 5.** Comprehensive imaging of a patient with recent stroke depicting left MCA stenosis. A–C, DSA (A) confirms stenosis, but contrast – enhanced MRA (B) and volume-reduced TOF MRA (C) overestimate the degree of stenosis in this particular case [54].

MRA has some advantages: noninvasive, no radiation, low cost, and widely available, but for the detection of ICAS requires confirmation by another imaging modality [51, 54]. The main disadvantage is that it overestimates stenosis. MRA can render ambiguous or erroneous results. The inability to distinguish between high-grade stenosis and occlusion is another major disadvantage [58].

In addition, MRA has magnet contraindications: limited to no use in morbidly obese and claustrophobic patients and those with implanted metallic objects [51]. Although CTA performs better overall compared with MRA for the purpose of determining the degree of stenosis (CTA can better visualize high-grade stenoses than MRA since the latter tends to overestimate the degree of stenosis), MRA is better than CTA at evaluating the petrous and cavernous ICA as bony artifacts affect CTA [51, 54].

Degnana noted that MRA can be superior in the evaluation of MCA stenosis compared with DSA but still only provides information about vessel patency alone. MRA can be an effective screening technique for patients with suspected MCA syndromes to detect stenosis within the intracranial vessels and to indicate the need for HR-MRI to accurately image the stenotic region [54, 59].

## 5.2 Contrast-enhanced (CE) MRA

It provides better anatomic visualization, particularly in the regions of changing blood flow directions; however, the visualization of smaller arteries remains limited [54, 60].

## 5.3 Quantitative MRA (QMRA)

Prabhakaran noted that QMRA, utilizing phase-contrast techniques, quantifies antegrade blood flow at distal site of stenosis; it exploits the phase shift in the signal of flowing blood, which is proportional to flow velocity, to quantify flow rate in medium and large vessels [51].

## 5.4 High-resolution MRI (HR-MRI)

The conventional imaging such as DSA, MRA, CTA, and TCD fall short in characterizing the presence of no occlusive atherosclerotic disease, because it focuses on the vessel lumen estimate luminal stenosis by measuring blood flow velocity [2, 54].



HR-MRI can be used to assess intracranial arterial disease, both atherosclerotic and nonatherosclerotic [50].

According to Bodle, HR-MRI represents MR acquisitions using clinically available 1.5–3.0 Tesla magnetic field strength targeted to intracranial arterial pathology that are of sufficient quality to visualize the arterial wall, separate from the lumen of the proximal circle of Willis vessels. HR-MRI can be accomplished at 1.5 T by limiting the field of view to focus on a single vessel or point of interest, but higher field strength at 3 T has many advantages over conventional MRI (1.5 T). Image quality in MRI depends on several factors (e.g., slice thickness, field of view, signal-to-noise ratio, matrix size, and magnetic field strength) [50, 61]. Image acquisition is faster and there are increased signal-to-noise and contrast-to-noise ratios, with better image quality for black-blood imaging. The increased signal and contrast that 3 T provides improves the detection of complex atherosclerotic plaque and can identify plaque components in larger arteries [50, 62].

HR-MRI allows the direct assessment of intracranial atherosclerotic plaques; it is capable of characterizing plaque location, severity, and morphology, and discriminating from other nonatherosclerotic etiologies [3, 50, 51].

Bodle also suggested that an intracranial plaque with HR-MRI features of intraplaque hemorrhage and a ruptured fibrous cap in a patient with downstream ischemia is likely associated with artery-to-artery embolism, whereas a stable plaque with a large amount of fibrous tissue and small lipid core resulting in high-grade stenosis may cause hypoperfusion [50]. Thus, HR-MRI may directly determine stroke mechanism and play a role in selecting secondary prevention therapies (e.g., patients with hypoperfusion may benefit from intracranial revascularization procedures that patients with artery-to-artery embolism may not benefit) [50].

The simplest use of HR-MRI of the MCA is the calculation of the degree of MCA stenosis, which may be stated as:

$$\% \text{Stenosis} = (1 - \text{Lumen area} / \text{Reference lumen area}) \times 100, \quad (2)$$

where the reference lumen area is the area of the nonoccluded lumen, preferably at a proximal segment [2].

Bodle mentioned that ICAS can be caused by diverse pathologies (e.g., atherosclerosis, inflammation, and vasospasm), with diverse treatment implications. HR-MRI may noninvasively differentiate between the etiologies of ICAS by identifying plaque components or unique enhancement patterns [50].

Patients with symptomatic (versus asymptomatic) and non-BOD type (versus BOD) ICAD had characteristic changes in: (a) the wall area (larger plaques); (b) plaque signals (eco-centric enhancement and heterogeneous signal intensity suggesting unstable plaque); and (c) remodeling patterns (positive remodeling suggesting outward expansion of the vessel wall) [63].

On the contrary, superiorly located MCA plaques (near to the orifices of penetrating arteries) are associated with BOD-type ICAD [64].

Bodle asserted that, in other vascular beds, the determination of atherosclerotic plaque constituents has helped in risk-stratify patients and select treatments. Using clinical, imaging, and pathological correlations, studies of coronary and carotid artery disease have detected characteristics that indicate plaque vulnerability: lipid core size, intraplaque hemorrhage, and fibrous cap thickness. These vulnerable plaque characteristics are also present in ICAD [50, 65] but are less well studied (**Table 3**). Bodle also noted that intraplaque hemorrhage (IPH) from rupture of plaque microvessels causing the accumulation of erythrocyte membranes, deposition of cholesterol, macrophage infiltration and enlargement of the necrotic core

Plaque characteristic	TOF-MRA	T1-weighted	PD-weighted	T2-weighted
Fibrous cap	Isointense/ hypointense	Isointense	Isointense/ hyperintense	Hyperintense
Lipid-rich necrotic core	Isointense	Isointense/ hyperintense	Hyperintense	Hypointense
Hemorrhage	Hyperintense	Hyperintense to hypointense (with age of hemorrhage)	Hypointense to hyperintense	Hypointense to hyperintense
Calcification	Hypointense	Hypointense	Hypointense	Hypointense

**Table 3.**  
*Plaque characteristics on multiple contrast weightings based on carotid imaging literature [50, 65]*

results in atheroma growth, and plaque destabilization. A large amount of lipid within the necrotic core of a plaque is another sign of plaque vulnerability HR-MRI measurement of lipid-necrotic core area in extracranial ICA plaques correlates well with pathology [50].

HR-MRI can identify fibrous cap characteristics (thin, thick, or ruptured) in extracranial ICAs. The fibrous cap is a layer of connective tissue covering the lipid-necrotic core. Thick fibrous caps are less prone to rupture [50].

HR-MRI is noninvasive, but less available, still with limited clinical value, requiring extensive postprocessing. Bodle asserted that imaging characteristics in ICAD have not yet been correlated with pathological specimens because, while the HR-MRI of the extracranial ICAs can be correlated with endarterectomy specimens, intracranial vessels are not accessible to pathology sampling in live patients. Therefore, the signal characteristics of intracranial plaque components can only be extrapolated from extracranial ICAs HR-MRI [50].

Another disadvantage is the small size (2.0–5.0 mm) and the depth of the intracranial vessels, which require relatively long acquisition times, making HR-MRI imaging difficult because of patient motion artifact and limitations in resolution.

According to Bodle, HR-MRI can help to identify stroke mechanisms, determine the degree and etiology of stenoses, identify nonstenotic plaques, and identify potentially high-risk plaque components. These plaque characteristics are not visualized with conventional luminal imaging and may be important predictors of stroke [50].

## **6. Multidetector computed tomography and multidetector computed tomography angiography for the diagnosis of intracranial atherosclerotic disease (ICAS)**

### **6.1 Nonenhanced multidetector computed tomography (MDCT)**

The study of the prevalence, and of the risk factors for intracranial internal carotid artery calcification (ICAC), as a marker of intracranial atherosclerosis was determined by Bos and coworkers. They assessed a white population (2495 persons) from the population-based Rotterdam Study with a no enhanced multidetector (16-slice or 64-slice) computed tomography (MDCT) of the intracranial ICAs. A calcified plaque had >130 Hounsfield units. They concluded that ICAC was highly prevalent and occurred in over 80% of older, white persons [66].

## **6.2 Multidetector computed tomography angiography (MCTA)**

A comprehensive high-resolution intracranial vessel assessment is possible by the introducing of multislice CT (MSCT: multiple row scanning: 4, 16, 64, up to 320 rows, associated with an increased rotational speed: 0.5 s/rotation). MSCT represents the first-line imaging modality in stroke patients [67]. CTA calculates the degree of stenosis using the published method for the Warfarin-Aspirin Symptomatic Intracranial Disease Study (WASID) (*vide supra*) [2].

According to Arenillas, CTA detects the degree of stenosis for each of 15 large intracranial arterial segments assessed: bilateral supraclinoid ICAs, A1-ACA, M1-ACM, M2-ACM, P1-PCA, proximal, mid, and distal BA, and intracranial VA. CTA identifies and characterizes the ICAS of different histopathological nature (including partially recanalized emboli), being unable to directly assess plaque instability. It allows the examination of ICAS progression and in-stent restenosis [3, 68]. The stenotic lesions are considered to be atherosclerotic in nature, if no cases with subarachnoid hemorrhage or intracerebral hemorrhage are detected by CT head (in consequence, vasospasm is unlikely the cause of these ICAS). Arterial segments are excluded from the analyses of stenosis, if they are identified to be congenitally hypoplastic or seen only through collaterals or cross-filling [69].

The prevalence, distribution, calcification, and the risk factors predisposing ICAS in a white stroke population were investigated by Homburg and coworkers. All patients underwent MDCT of the brain and MDCTA (with a 16-slice MDCT scanner or a 64-slice MDCT scanner with a standardized protocol) of the extracranial and intracranial arteries in a single session [70]. They concluded that the majority of ICAS was observed in the posterior circulation. ICAS in the proximal intracranial arteries was mainly classified, but in distal arteries, it was frequently nonclassified, indicating a different pathophysiology of atherosclerotic disease in the two segments. The absence of calcification on CT of the brain does not exclude the presence of ICAS in the distal arteries. Association of nonclassified ICAS and ESR may indicate a prominent role for inflammatory factors in intracranial arteries disease (ICAD) [71].

## **6.3 CTA versus DSA**

CTA was compared with DSA for the detection and measurement of stenosis/occlusions in large intracranial arteries by Nguyen and coworkers [69]. They reported high sensitivity and a high PPV for CTA for the detection of occlusion and stenosis of greater than 50%. CTA has relatively fewer risks, costs less, is more readily available, and appears to have the same accuracy as DSA, to identify the exact site of arterial occlusion in acute ischemic stroke. Maximum intensity projections and volume rendering can help to quickly identify the occlusion. On the other hand, CTA does not appear to be as reliable as DSA for determining the presence of stenosis in small arteries distal to the first 1 cm of the artery [72].

## **6.4 CTA versus MRA**

CTA has several advantages compared with MRA: better anatomic visualization of the circle of Willis and of the state of the arteries [73] and quite accurate in the evaluation of stenosis, since the latter tends to overestimate high-grade stenosis attributable to turbulent flow; CTA is more accurate for identifying occlusion (sensitivity, 100%; specificity, 99.4–100%) than for measuring the degree of stenosis [68]. CTA is minimally invasive, performed quickly, modest cost, scanner availability 24/7, operator-independent, less susceptible to motion artifacts than MRA, and less dependent on hemodynamic effects compared with MRA [68, 69, 74, 75].

Its disadvantages, besides radiation risk exposure, are patient movement, contrast risk reactions (allergy to iodine contrast agents), different contraindications (nephron-toxicity-serum creatinine levels >1.2 mg/dL, etc.), and difficult evaluation of arteries within bone canals (particularly of the carotid siphon) due to bone artifacts. However, intracranial, with the proper examination and postprocessing techniques, is possible to use CTA to assess the petrous and cavernous portions of the ICA. Multiplanar reformation (MPR) can display 2D images in various planes without any loss of information. Maximum intensity projection (MIP) enhances high attenuation contrast tissues, including bone, wall calcification, or blood vessels. Since calcifications can interfere with the evaluation of the degree of stenosis, bone elimination is done during postprocessing [68, 69].

### **6.5 CTA versus 3D-TOF-MRA and DSA**

Bash et al. [76] retrospectively examined 28 subjects with ischemic stroke or TIA comparing CTA and MRA using DSA as the gold standard, among intracranial arteries with stenosis >30% (anterior circulation vessels 42 versus 58% posterior circulation arteries). They concluded that CTA demonstrated a higher sensitivity, specificity, and PPV than those of MRA for the evaluation of stenotic and occluded intracranial vessel segments. CTA has a high interoperator reliability for the quantitation of stenotic lesions when expert readers are used. Helical CTA is superior to DSA in the demonstration of arterial patency in posterior circulation arteries when very low- or balanced flow states are present due to a severe stenosis [76]. In the era of the mechanical thrombectomy with stent-retriever, when faster puncture time to endovascular therapy became very important, CTA became essential due to its shorter scan time and the evaluations of collaterals on multiphase imaging, which can contribute to faster recanalization and better evolution [68].

### **6.6 CTA versus DSA versus TCCS**

Roubec and coworkers compared ICAS in 67 patients with stroke using three different methods: TCCS, CTA, and DSA in a common clinical practice. They found substantial agreement between CTA and DSA, and moderate agreement between TCCS and DSA as well as CTA and TCCS, for the evaluation of ICAS [77].

### **6.7 Intracranial nonocclusive thrombosis (iNOT)**

The frequency and clinical course of patients with acute ischemic stroke or TIA who had intracranial nonocclusive thrombus (iNOT) on CTA of the circle of Willis were assessed by Puez and coworkers [78]. Before CTA, a noncontrast CT (NCCT) was accomplished in all cases. iNOT has been described first on DSA or MRA [79, 80]. Criteria to diagnose iNOT rather than occlusive thrombus or atherosclerotic stenosis were: (1) residual lumen present and eccentric; (2) nontapering thrombus; (3) smooth and well-defined thrombus margins; and (4) absence of vessel wall calcification [78]. Puez concluded that iNOT was relatively uncommon. Probably, iNOT may be more frequently diagnosed when performing early CTA in such patients. The majority of patients had a good clinical outcome. Clinical deterioration was associated with unchanged or enlarged iNOT in repeated vascular studies, whereas diminished or resolved iNOT was associated with a benign clinical course. Particularly, in patients with minor symptoms, iNOT may indicate increased risk for clinical deterioration. Puez's study supported the importance of urgent vascular imaging in these patients [78].

Clot length can be examined by thin-sliced noncontrast CT and CTA. A better visualization of collateral circulation (which is an important prognostic factor for favorable outcome) can be realized with multiphase CTA [81, 82].

## **7. Conclusions**

This chapter focuses on key findings and recent approaches in diagnosis of intracranial arterial atherosclerotic stenosis (ICAS), with an emphasis on novel procedures to define the underlying mechanisms of stroke in intracranial atherosclerotic disease (ICAD). The importance of ICAS as a principal cause of ischemic stroke in Caucasians is undervalued as compared to that of extracranial atherosclerotic stenosis (ECAS) and nonvalvular atrial fibrillation (NVAF). On the other hand, intracranial arterial calcifications, stenosis, and occlusions represent the most frequent disturbance observed in intracranial arteries [83].

Intracranial arterial stenosis is caused by an atherosclerotic plaque in more than 90% of cases (ICAS). Intracranial atherosclerotic stroke differs from extracranial atherosclerotic stroke in many aspects, including risk factors and stroke patterns. Unlike in patients with ECAS or NVAF, stroke correlated to ICAD occurs in association with various stroke mechanisms such as in situ thrombotic occlusion, artery-to-artery embolism, branch occlusion, and hemodynamic insufficiency [83].

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