The Intracranial Vertebral Artery: A Neglected Species

The Johann Jacob Wepfer Award 2012

Louis R. Caplan

Beth Israel Deaconess Medical Center, Boston, Mass., USA

THE JOHANN JACOB WEPFER AWARD

THE JOHANN JACOB WEPFER AWARD
OF THE
EUROPEAN STROKE CONFERENCE
2012

IS DEDICATED TO

PROF. LOUIS CAPLAN, MD
BOSTON, MASS. (USA)

FOR OUTSTANDING WORK IN
THE FIELD OF CLINICAL RESEARCH
OF STROKE MECHANISMS,
DIAGNOSIS AND TREATMENT

LISBON, MAY 23RD, 2012

J. M. FERRO
CHAIR SCIENTIFIC COMMITTEE

M. G. HENNERICI
CHAIR PROGRAMME COMMITTEE

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

© 2012 S. Karger AG, Basel
1015–9770/12/0341–0020\$38.00/0

Accessible online at:
www.karger.com/ced

Prof. Louis R. Caplan, MD
Beth Israel Deaconess Medical Center
330 Brookline Ave., Boston, MA 02215 (USA)
Tel. +1 617 632 8911
E-Mail lcaplan@bidmc.harvard.edu

Key Words

Vertebral artery • Medullary infarction • Cerebellar infarction

Abstract

Among posterior circulation arteries, the intracranial vertebral artery (ICVA) has been given the least attention, especially concerning treatment of occlusive lesions. Early clinicopathological studies showed that the ICVA was often occluded in patients with lateral medullary and posterior inferior cerebellar infarcts. Severe stenosis or occlusion of the ICVA was the most common arterial lesion among the 408 patients in the New England Medical Center Posterior Circulation Registry (NEMC-PCR). In this registry, the distal portion of the artery was most often involved, sometimes with spread into the basilar artery. ICVA occlusive lesions were often bilateral and very often accompanied by basilar and cervical vertebral artery occlusive lesions. Patients with bilateral ICVA occlusions often had attacks of dizziness, blurred vision, and ataxia during months and years but rarely later developed disabling infarction. Most posterior circulation infarcts in patients with ICVA occlusive lesions were located in the middle and distal posterior circulation territories and were rostral to the medulla and inferior cerebellum. Although diagnostic techniques now image the ICVA and its lesions well, the optimal treatment of patients with various ICVA occlusive lesions has very rarely been analyzed or reported. The therapeutics of patients with ICVA disease is uncharted territory and begs for attention and clarification.

Copyright © 2012 S. Karger AG, Basel

During the past quarter century there has been a quantum increase in interest in stroke. New stroke-related journals have appeared and three times as many cerebrovascular disease articles were published compared to the preceding 25 years. The bulk of reports about lesions in arteries that supply the brain concern neck arteries. Disease of the internal carotid artery (ICA) in the neck has been by far the commonest topic. Disease of the vertebral artery (VA) in the neck is the next most frequent vascular topic. Among intracranial arteries the middle cerebral artery (MCA) and basilar artery (BA) are the topic of most reports. The least popular large artery topic is the intracranial vertebral artery (ICVA) (fig. 1). In this Wepfer lecture, after very brief historical comments, I review what is known about disease of the ICVA and what is not known and often has not been studied.

Fig. 1. Results of a PubMed search for the presence of various brain-supplying arteries contained in the titles of articles published during the past 50 years. The graph represents the relative frequencies of the arteries cited.

Abbreviated Historical Background

Wepfer

Johan Jacob Wepfer followed the example of Vesalius and performed meticulous necropsy examinations. He described the results of his dissections in his magnum opus on apoplexy published in 1658 [1]. He described the appearance and the course of the intracranial arteries and recognized blockage of the carotid and vertebral arteries caused by disease of the arterial walls as a cause of apoplexy, the obstruction preventing entry of sufficient blood into a portion of the brain. Wepfer distinguished two types of apoplexy: in one form, the supply of blood to the brain was obstructed or precluded, and in the other, animal spirits escaped and hemorrhage occurred.

He described the anatomy of the ICVA as follows [2]: 'As regards the vertebral arteries, they emerge from the nearest foramen, that great orifice through which the spinal marrow descends. They advance to the sides of the medulla oblongata... When they reach that place where the sixth pair of nerves (IX, X, XI, XII) arises, the right and left branches are joined and form a single channel (basilar artery) and remain united along the whole marrow tract.'

Lateral Medullary Infarction

Very little was written about the ICVA until the time of Wallenberg. Although he was not the first physician to describe the occurrence and signs, his name is probably permanently linked to lateral medullary infarction.

Adolph Wallenberg was a physician who practiced in Danzig, Poland, and also performed neuroanatomical research. His expert knowledge of anatomy, based in part on his own original observations, allowed him to predict the location of his original patient's brain lesion. Wallenberg wrote four papers on lateral medullary infarcts [3]. The initial publication was a detailed analysis of the clinical findings in a single patient [4], and the second report described the necropsy findings in this patient [5]. Wallenberg knew the original patient, a 38-year-old rope maker from prior personal medical encounters. He had first seen the patient in 1889 for appendicitis and later examined him several times for cardiovascular symptoms, namely tachycardia, dyspnea, and pounding pulse, that Wallenberg attributed to 'fatty degeneration of the heart' [3, 4]. Recall that blood pressure measurement was not available at that time. The patient drank alcohol and smoked heavily. At autopsy, he had a very large heart and extensive atherosclerosis. Hypertension and premature atherosclerosis had undoubtedly been present for years.

On the evening of September 9, 1893, the patient suddenly developed vertigo and intense pain in the left eye which spread to the entire left side of the face. Although the vertigo subsided, he found that he could not swallow and his voice was hoarse. Wallenberg examined the patient in great detail on the next day and found: (1) horizontal and vertical nystagmus, (2) hyperesthesia of the entire left face with a decreased left corneal reflex, (3) loss of pain and temperature sense on the right side of the body and the right face, (4) weakness of the left palate, (5) paralysis of the left vocal cord, and (6) left limb ataxia [3, 4]. Six years after the original stroke, the patient had several dizzy spells on two successive days and noted right-hand weakness. He did not consult a physician. As he undressed for bed, he suddenly collapsed and died. Wallenberg [5] performed the autopsy himself and reported the pathological findings in detail. The vessels at the base of the brain showed 'irregular thickened calcified areas with occasional bumpy prominences' [3, 5] (fig. 2). The ICVAs and the rostral BA were very stenotic. The left posterior inferior cerebellar artery (PICA) was very stenotic at its origin from the left ICVA, and the left PICA was occluded 2 cm after its origin. Wallenberg described the findings in sections from the upper cervical cord through the brainstem. The location and extent of the infarct in the left lateral medulla was exactly as he had predicted.

Although Wallenberg attributed the infarction to disease of the left PICA branch of the ICVA, subsequent an-

Fig. 2. Photograph of the posterior circulation arteries and brain structures in the case reported by Wallenberg [5].

atomical studies, especially those of Duvernoy [6], showed that PICA does not supply the lateral medulla; the medial branch of PICA supplies a small portion of the dorsal medulla only. Figure 3 shows the branching of the lateral medullary penetrators and PICA from the ICVA. In 1961, Fisher et al. [7] reviewed the blood supply of the lateral medulla and the causative vascular lesions found in 26 prior patient reports. The authors commented 'It is surprising to find that despite the extensive literature on the lateral medullary syndrome, in only 26 instances, usually single case reports, was the state or pattern of the arteries described'. Fisher et al. [7] described each of their 16 patients in detail. They noted the clinical signs and symptoms, and defined the localization and extent of the brain infarcts and the underlying vascular lesions. Among their 16 patients, the most common arterial lesion was occlusion of the ICVA ipsilateral to the lateral medullary infarct either alone (7 patients) or with its PICA branch (5 patients) [7].

In the 1970s, Hauw et al. [8] and Escourolle et al. [9] and their French clinical and pathology colleagues described the topography and underlying vascular lesions, mostly involving the ICVAs. Ogata et al. [10] showed that ruptured ICVA plaques often generated erythrocyte-rich thrombi within the artery that could propagate or embolize. A recent review of subsequent reports by Kim [11] established that occlusion of the ICVA is the most common underlying pathology in patients with lateral medullary infarcts. A minority are related to intrinsic disease of lateral medullary penetrators that arise directly from the ICVA.

Fig. 3. Photo of a dissection of the right lateral medullary fossa that shows the ICVA with its PICA and lateral medullary penetrators. From Duvernoy [6], with permission. 11 = ICVA; 12 = PICA; B = branches from the VA to the lateral medulla that course through the lateral medullary fossa; A = a branch to the medulla from the PICA.

Cerebellar Infarction

The second common syndrome that was attributed to occlusive disease of the ICVAs was cerebellar infarction in the territory of PICA. In 1975, George Sybert, a neurosurgeon, and Bud Alvord, a neuropathologist, wrote the first detailed and systematic clinicopathological study of cerebellar infarction [12]. They reviewed the neuropathology files of the University of Washington School of Medicine for cases of cerebellar vascular lesions studied during the years 1963–1973. The Sybert and Alvord report consisted of an analysis of the 28 acute cerebellar infarcts and the 24 old cerebellar infarcts discovered at necropsy.

Among the acute fatal cerebellar infarcts, 26 were located in PICA distribution (3 bilateral, 23 unilateral). Cardiac disease was very common in this series. The heart was enlarged in 22 of 28 patients and old myocardial infarcts were present in 4 patients. At necropsy, recent arterial occlusions involved the ICVA in 18 patients (1 bilateral) and PICA in 10 patients. The authors attributed most of the ICVA and PICA occlusions to embolism from the heart.

Fig. 4. Drawing of an ICVA dissection described in Escourolle et al. [19].

Since the lateral and medial medulla and the PICA-supplied region of the cerebellum fell within the supply zone of the ICVAs, subsequent reviews emphasize these clinical syndromes as the major lesions likely to be found in patients with intrinsic disease of the ICVAs or embolism to the ICVAs.

What Was Known about the ICVAs circa 1990?

The two most frequent pathological lesions known to involve the ICVA are atherosclerosis and dissections. Post-mortem studies of atherosclerosis during the 1960s and 1970s showed that atherosclerotic occlusive lesions most often involved the ICVAs shortly after they penetrated the dura to enter the posterior fossa, or at the distal end of the artery [13–16]. Thrombi formed within the ICVA could propagate and embolize [10]. Arterial dis-

sections often began in the distal portion of the extracranial vertebral artery (ECVA) and spread into the proximal ICVA or began within the ICVA and often spread into the BA [17–19]. Figure 4 shows a dissection that spread from one ICVA into the BA [19]. The ICVA is known to be a donor source and a recipient site for brain embolism [20]. Emboli to the ICVAs most often arise from the ECVAs but less often from the heart or aorta.

Before 1990, most information about the arteries that supplied the posterior circulation came from catheter-based cerebral angiography, but this was often performed only in selected circumstances only in patients with severe neurological deficits [21]. The advent and increasing availability of MRI and MRA especially in academic medical centers during the 1990s made it possible to study the brain structures and blood vessels within the vertebrobasilar arterial supply safely and quickly during life and dramatically improved knowledge.

The New England Medical Center Posterior Circulation Registry (NEMC-PCR) and Knowledge Derived from It about the ICVAs

In order to understand the relationship of brain lesions to the ICVA lesions, I must first review the method of characterizing posterior circulation territories and vascular lesions used in the NEMC-PCR. In the registry, we categorized brain and vascular lesions as proximal, middle, and distal. The proximal intracranial posterior circulation territory (IPCT) included regions supplied by the ICVAs, the medulla oblongata and the PICA-supplied region of the cerebellum. The middle IPCT included the portion of the brain supplied by the BA up to its superior cerebellar artery (SCA) branches, the pons and the anterior inferior cerebellar artery (AICA)-supplied portions of the cerebellum. The distal IPCT included all of the territory supplied by the rostral BA and its SCA, posterior cerebral artery (PCA) and their penetrating artery branches, midbrain, thalamus, SCA-supplied cerebellum, and PCA territories. This distribution is shown diagrammatically in figure 5. Lesions within the intracranial arteries were also designated by location. Within the ICVA, occlusive lesions from dural penetration to PICA were called proximal, those that involved the middle third of the artery beyond PICA were called middle, while those involving the distal third up to the ICVA/BA junction were called distal ICVA [22–27].

Fig. 5. Drawing of the anterior surface of the brainstem showing the BA, VAs, and their major branches. The region is divided into the distal, middle, and proximal intracranial territories. From Searls et al. [44], with permission.

Frequency and Locations of ICVA Lesions in the NEMC-PCR

Tables 1 and 2 show the frequencies of severe occlusive vascular lesions in the registry. Occlusive lesions of >50% stenosis were present in 132 patients. Seven had ICVA dissections, 1 bilateral. The remainder were atherosclerotic. Among multiple vascular occlusive lesions, the ICVA was the most commonly affected artery. Considering patients in whom only 1 artery was severely involved, isolated ICVA lesions were more common than the BA lesions but less common than cervical VA origin occlusive lesions. Within the ICVA, the distal-most portion of the artery was most involved (66%), while the proximal portion was affected in 24%, and the entire artery was occluded in 28%.

An unexpected and important finding in patients with occlusive ICVA disease was the very frequent involve-

Table 1. Vascular lesions with >50% luminal stenosis in the NEMC-PCR

Artery	Number
Innominate	2
Subclavian	5
Vertebral artery origin (VAO)	131 (29 bilateral)
Intracranial vertebral artery (ICVA)	132 (36 bilateral)
Basilar artery (BA)	109
Posterior cerebral artery (PCA)	38 (4 bilateral)
Posterior inferior cerebellar artery (PICA)	14
Anterior inferior cerebellar artery (AICA)	2
Superior cerebellar artery (SCA)	10

Table 2. Isolated single artery involvement in the NEMC-PCR

Artery	Number
Subclavian	1
Vertebral artery origin (VAO)	52 (15 bilateral)
Intracranial vertebral artery (ICVA)	40 (12 bilateral)
Basilar artery (BA)	46
Posterior cerebral artery (PCA)	14
Posterior inferior cerebellar artery (PICA)	5
Superior cerebellar artery (SCA)	3

ment of the contralateral VA. In patients with unilateral ICVA occlusive disease, the contralateral ECVA was often stenotic or hypoplastic or the VA ended in PICA. In these patients the VA was essentially basilarized, meaning that the BA was a direct continuation of flow from one VA. Accompanying BA stenosis or occlusion was also often coexistent.

Bilateral severe ICVA atherosclerotic disease was present in 36 patients. The vascular lesions in these 36 patients are shown in table 3. Twenty patients with bilateral ICVA disease also had BA disease. Risk factors were particularly prevalent in patients with bilateral ICVA disease in whom 76% were hypertensive, 52% had elevated cholesterol, 36% were diabetic, and 36% smoked cigarettes [26].

Brain Infarcts in Patients with ICVA Disease

Relatively few NEMC-PCR ICVA disease patients had isolated lateral medullary or PICA cerebellar infarcts. Most ICVA occlusive lesions involved the distal ICVA at or near the ICVA-BA junction beyond the ICVA branches that penetrate the lateral medullary fossa and beyond

PICA. Occasional patients had thrombi originating in one distal ICVA and extended into the BA causing pontine, middle territory infarction. When an ICVA thrombus extended into the BA, the occluded ICVA was always dominant. Some patients with a single functional distal ICVA (the other ICVA being hypoplastic or ending in PICA) had middle and/or distal territory ischemia. Many patients with extensive combined bilateral ICVA and BA disease had TIAs or minor strokes within the middle and distal intracranial territories. Figure 6 shows the distribution of brain infarcts in patients with ICVA occlusive disease. Only one-fifth of patients with severe ICVA occlusive disease had infarcts limited to the proximal IPCT.

Figure 7 shows the distribution of brain infarcts in the proximal IPCT, the one supplied by the ICVA and its branches. Cerebellar infarcts in PICA territory were most common and were mostly caused by embolism to the ICVA from the heart or ECVA [28]. Lateral medullary infarcts were caused mostly by atherosclerotic occlusion of the ICVA or of the lateral medullary penetrating branches of the ICVA. The lateral medulla and cerebellum were infarcted concurrently in only one-eighth of the proximal territory infarcts.

Mechanisms and Patterns of Brain Ischemia in Patients with ICVA Disease

We divided ischemia patterns in patients with severe ICVA occlusive disease into six groups (table 3). The most frequent group, accounting for about half of the patients, were those with extensive occlusive disease involving the ICVAs bilaterally, sometimes with other occlusive lesions. Table 4 shows the vascular lesions in patients with bilateral ICVA disease. These included 41 patients, 36 who had bilateral ICVA occlusive disease and 5 who had unilateral severe disease and hypoplasia of the contralateral ICVA. Some patients with unilateral ICVA disease also had BA and other occlusive lesions. The commonest clinical pattern in these patients was the presence of multiple TIAs. These attacks were often provoked by standing, hypovolemia, and decreases in blood pressure. The commonest symptoms during attacks were faintness, visual blurring, visual loss often bilateral, diplopia, vertigo, and ataxia. TIAs continued to occur during months and even years. Some patients in this group had distal territory infarcts due to intra-arterial embolism or hypoperfusion. Surprisingly, patients with extensive vascular posterior circulation occlusive disease who had predominantly multiple TIAs had excellent outcomes. Few had disabling brain infarction.

Fig. 6. Distribution of locations within the proximal, middle, and distal portions of the posterior circulation in patients with vascular occlusive lesions limited to the ICVA alone and in those in whom the ICVA lesions were accompanied by other occlusive posterior circulation lesions (ICVA+) in the NEMC-PCR.

Fig. 7. Distribution of infarcts within the proximal IPCT in the NEMC-PCR.

Table 3. Subgroups of patients with ICVA severe occlusive disease

Focal hypoperfusion-related TIAs or infarcts limited to proximal territory	19%
Embolism to the ICVA	8%
ICVA/BA junction disease with middle territory infarction	8%
Widespread posterior circulation occlusive disease with multifocal hypoperfusion	52%
Distal territory infarcts due to intra-arterial embolism or hypoperfusion	32%
Infarcts likely not related to ICVA disease	4%

Table 4. Lesions among 36 patients with bilateral ICVA occlusive disease

Bilateral ICVA alone	10
Bilateral ICVA + BA	20
Bilateral ICVA + BA	12
Bilateral ICVA + BA + bilateral ECVA	2
Bilateral ICVA + BA + unilateral ECVA	2
Bilateral ICVA + BA + bilateral ICA	2
Bilateral ICVA + BA + unilateral ICA	2
Bilateral ICVA + ECVA	4
Bilateral ICVA + bilateral ECVA	1
Bilateral ICVA + unilateral ECVA	2
Bilateral ICVA + unilateral ECVA + unilateral MCA	1
Bilateral ICVA + anterior circulation	2
Bilateral ICVA + unilateral ICA	1
Bilateral ICVA + unilateral MCA	1

The next commonest subgroup of ICVA disease patients were those who presented with distal territory infarcts, accounting for about one-third of patients. Some patients in this group also had TIAs involving the vestibulo-cerebellar systems in the medulla and/or cerebellum. Proximal territory infarcts accounted for one-fifth of patients. A few patients presented with middle territory infarcts when thrombi within the distal ICVA extended into the BA, had embolism to the ICVA, or had infarcts attributable to other lesions (e.g. BA occlusion).

Among the 7 patients with ICVA dissection (1 bilateral), 4 arteries were stenotic and 4 occluded. Among the dissection patients with brain infarcts, 2 had lateral medullary infarcts and 3 had infarcts attributed to embolism to the distal territory (1 SCA cerebellum, midbrain, and thalamus, 1 PCA territory, and 1 SCA cerebellum and PCA).

Symptoms and signs in Patients with ICVA Occlusive Disease

Table 5 lists the symptoms of patients in the NEMC-PCR who had severe single artery steno-occlusive lesions of the ECVA, ICVA and BA. The only symptom that was more prevalent in patients with ICVA disease was pain or burning in the face. There were no signs that were particularly more prevalent in patients with ICVA disease (table 6).

Prognosis in the NEMC-PCR

Mortality was highest among patients who had embolism to the distal territory arising from the ICVA – one-

quarter of these patients died. The mortality and morbidity in all other groups was low. Upon hospital discharge, one-quarter of the patients had moderate or severe disability but one-half had no disability. Death or severe disability was present in 18% of patients with ICVA occlusive disease compared to 30% in those with severe BA disease [27]. At follow-up examinations 3 years after discharge, 38% had no symptoms and 78% had no or only slight disability [29, 30]. Most surprising was the relatively good outcomes in patients with bilateral ICVA disease (table 7). These patients with the most severe occlusive disease had the best outcomes, indicating the adequacy and durability of their collateral circulation.

What Has Been Learned since the NEMC-PCR about ICVA Disease?

Diagnosis

The gold standard for diagnosis of ICVA occlusive disease is digital catheter angiography. More recent analysis of the accuracy of MRA and TCD in the Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis Trial [31] showed that MRA was slightly superior to TCD in recognizing >50% stenosis of the ICVA but was not especially good at distinguishing >50% from >70% stenosis (table 8). The negative predictive value of TCD at recognizing both >50% stenosis and >70% stenosis was higher than the positive predictive value so that a negative TCD was quite good at excluding severe ICVA disease (table 8). The advent of Power-Motion Mode TCD has improved the ability to insonate and image the posterior circulation large arteries and provides additional data to that derived from standard single-gate TCD spectral findings [32]. This technique is very reliable and useful in excluding important intracranial occlusive lesions. Power-Motion Mode TCD shows flow changes that are complimentary to those found using single-gate TCD spectra [32]. CTA is likely more sensitive than MRA in detecting severe ICVA disease. When CTA, MRA and digital subtraction catheter angiography were compared among 28 patients who had 115 diseased intracranial vascular segments, CTA had a higher sensitivity for intracranial artery stenosis than MRA (98 vs. 70%) and for occlusion (100 vs. 87%) [33].

Treatment

Antithrombotics

There are very few studies of the effects of various treatments in patients with severe ICVA disease. None

Table 5. Symptoms in patients with single artery location involvement

Symptoms	ECVA alone (n = 52)	ICVA alone (n = 40)	BA alone (n = 46)
Dysphagia	4 (8%)	4 (10%)	2 (4%)
Dysarthria	12 (23%)	8 (20%)	26 (57%)
Motor (all)	13 (25%)	13 (33%)	27 (59%)
Nausea, vomiting	16 (31%)	11 (28%)	12 (26%)
Dizzy, lightheaded	32 (62%)	17 (43%)	22 (48%)
Hearing loss	1 (2%)	0	1 (2%)
Diplopia	9 (17%)	4 (10%)	11 (24%)
Blurred vision	14 (27%)	5 (13%)	8 (17%)
Cranial nerve V	5 (10%)	9 (23%)	7 (15%)
Limb sensory	6 (12%)	3 (8%)	9 (20%)
Headache	18 (35%)	11 (28%)	15 (33%)
Loss of consciousness	1 (2%)	1 (3%)	1 (2%)

Table 6. Signs in patients with single artery location lesions

Signs	ECVA (n = 52)	ICVA (n = 40)	BA (n = 46)
Motor (all)	16 (31%)	16 (40%)	34 (74%)
Ataxia (all)	20 (38%)	14 (35%)	16 (35%)
Cranial nerve VII	7 (13%)	10 (25%)	20 (43%)
Dysarthria	10 (19%)	11 (28%)	24 (52%)
Nystagmus	19 (37%)	10 (25%)	12 (26%)
Visual field loss	11 (21%)	8 (20%)	8 (17%)
Limb sensory	11 (21%)	8 (20%)	8 (17%)
Cranial nerve V	4 (8%)	4 (10%)	7 (15%)
Lethargy	2 (4%)	5 (13%)	4 (9%)
Horner's syndrome	6 (12%)	4 (10%)	4 (9%)
Oculomotor	8 (15%)	6 (15%)	16 (35%)

Table 7. Modified Rankin Scale score at discharge and at follow-up among 41 patients with severe ICVA occlusive disease

Modified Rankin Scale	At hospital discharge	At follow-up
0 No symptoms	14 (34%)	13 (32%)
1 No significant disability	11 (27%)	10 (24%)
2 Slight disability	11 (27%)	8 (20%)
3 Moderate disability	1 (2%)	1 (2%)
4 Moderate to severe disability	3 (7%)	2 (5%)
5 Severe disability	1 (2%)	0
6 Dead	0	7 (17%)

Table 8. Accuracy of transcranial Doppler (TCD) and magnetic resonance angiography (MRA) diagnosis of occlusive ICVA disease (adapted from Feldmann et al. [31])

>50% stenosis by catheter angiography		>70% stenosis by catheter angiography	
<i>TCD</i>			
>80 cm/s ² *	PPV 67% (95% CI 41–87) NPV 85% (95% CI 75–92)	>120 cm/s ² *	PPV 40% (95% CI 5–85) NPV 89% (95% CI 81–94)
<i>MRA</i>			
>80% or flow gap	PPV 100% (95% CI 69–100) NPV 85% (95% CI 79–90)	>80% or flow gap	PPV 88% (95% CI 47–99) NPV 94% (95% CI 88–97)

* Criterion for abnormality ('cut point') – these have been retrospectively identified from the SONIA dataset and represent mean velocity.

of the large trial of antiplatelets analyzed treatment by individual arteries. The European Stroke Prevention Study (ESPS1) compared the effectiveness of aspirin (330 mg t.i.d.) with dipyridamole (75 mg t.i.d.) versus placebo in the prevention of stroke and stroke and death end-points among 2,500 patients with TIAs or strokes among whom 711 had 'vertebrobasilar involvement' [34, 35]. The aspirin + dipyridamole treatment was more effective than placebo in both the carotid and vertebrobasilar territories. The reduction in the end-point of stroke in the aspirin + dipyridamole-treated patients was more significant in patients with vertebrobasilar ischemia than in carotid ischemia (66 vs. 40% reduction, $p = 0.005$) [35]. No vascular imaging was mandated or reported and so results according to individual arteries were not possible.

The effectiveness of aspirin versus warfarin anticoagulation in patients with posterior circulation disease was analyzed in two studies. A retrospective trial in which treatment was decided by the investigators without randomization included 68 patients with severe posterior circulation occlusive disease as measured by catheter angiography among whom were 31 with disease limited to the ICVA [36]. Among these 68 patients, strokes in the same vascular territory during follow-up developed in 6/26 patients (23%) treated with aspirin versus 4/42 treated with warfarin [36]. A subsequent prospective randomized trial (WASID) that compared the effectiveness of aspirin (1,300 mg/day) versus warfarin (INR target 2–3) included 569 patients with angiographically confirmed severe (50–99%) intracranial arterial stenosis among whom 107 had ICVA stenosis [37, 38]. Among these 107 patients, 8/53 (15%) treated with aspirin had the end-point of stroke in the same or another vascular territory,

brain hemorrhage, and death compared to 15/54 (28%) treated with warfarin [38].

Thrombolytics

There are no therapeutic trials of either intravenous or intra-arterial thrombolysis in patients with ICVA occlusive disease. There are many reports of thrombolysis in patients with BA occlusions, but there are only rare and anecdotal reports of intra-arterial thrombolysis in patients with ICVA occlusions. Becker et al. [39] reported the results of intra-arterial thrombolysis in 9 patients treated at Johns Hopkins who had bilateral ICVA occlusions, 1 of whom also had a BA occlusion. Six patients had one hypoplastic VA. These patients were treated with urokinase an average of 19.5 h (range 1–48 h) after presentation. Two were comatose, 1 was sleepy, and the remainder were alert when they presented. Seven of the 9 patients had recanalization and 7 died. Re-thrombosis was common. Complications included 2 fatal hemorrhages – 1 subdural and the other intraparenchymal and intraventricular.

Nakayama et al. [40] reported a single patient who arrived comatose to the hospital with bilateral cerebellar infarcts attributed to an occluded ICVA and a contralateral ICVA that ended in PICA. He was treated with intra-arterial urokinase followed by angioplasty of the now patent but stenotic ICVA. He survived with minimal cerebellar ataxia as the only abnormality.

At the Xan Wu Hospital in Beijing China, among 98 patients with acute brain ischemia treated with intra-arterial thrombolysis and angioplasty/stenting, 12 patients had ICVA occlusions [41]. After ICVA thrombolysis and stenting treatment, 8 of the 12 had TIMI grade 3 flow. Two treatments were complicated by dissec-

tions. Outcomes included 7 patients who had modified Rankin Scores of ≤ 2 , 2 had scores of 3, and 2 patients died [41].

Angioplasty and Stenting

Although there are many reports of BA angioplasty and stenting there are few reports, mostly anecdotal of ICVA treatment. In 1997, my colleagues and I at the New England Medical Center reported the results of angioplasty of one ICVA in 4 patients with bilateral ICVA compromise [41]. Three of the patients had had multiple TIAs and the other a brainstem stroke. In 1 patient, angioplasty was unsuccessful. Vasoconstriction developed after dilatation in 2 of the other patients and the angioplasty caused an arterial dissection in the other. Despite these complications, all 4 patients did well [42].

At the Xan Wu Hospital in Beijing, China, between 2001 and 2012, 228 ICVA stents were placed in 215 patients [Dr. Z. Miao, Xuan Wu Hospital, Beijing, unpubl. data]. Three-quarters of the patients had had TIAs and one-quarter strokes. The vascular lesions were: 27% unilateral ICVA stenosis; 55% ICVA stenosis with contralateral ICVA occlusion; 18% bilateral severe stenosis. BA stenosis was also noted in 13.5% of these ICVA-treated patients. The technical success rate was 97%. TIA or stroke recurrence developed during the first 30 days after treatment in 7.9% of the patients stented [Dr. Z. Miao, unpubl. data].

In the Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis (SAMPRIS) trial, among 213 patients treated with intracranial stenting, the ICVA was the intracranial artery stented in 36 [43, and Dr. Chimowitz, with permission of the SAMPRIS Investigators, unpubl. data]. The study was stopped prematurely because aggressive medical therapy proved superior to stenting in preventing the primary end-point, stroke or death within 30 days after enrollment or after a revascularization procedure for the qualifying lesion during the follow-up period or stroke in the territory of the qualifying artery beyond 30 days. Three of the ICVA-stented patients had ischemic events and 3 had hemorrhagic events within 30 days of enrollment. Slightly more patients with ICVA stenting had an ischemic complication (8.3%) compared to those who had intracranial ICA (7.5%) or MCA (5.6%) stenting. However, BA stenting was followed by far more ischemic complications (10/48, 20.8%). Hemorrhagic complications were most common in the ICVA stenting group [Dr. Z. Miao, unpubl. data].

Conclusions

To conclude: (1) ICVA occlusive disease is very common and is more common than BA disease which has been more extensively reported and studied. (2) The most common pathological processes are atherosclerosis, often with superimposed thrombosis, and dissection. (3) Occlusive atherosclerotic lesions within the ICVA most often develop at the distal end of the artery and may extend into the proximal BA. (4) ICVA occlusive lesions are often bilateral and accompanying occlusive lesions of the proximal ECVA and the BA are very common. (5) The ICVA is an important recipient site and donor source of emboli. (6) Only about 1 in 5 patients with severe ICVA occlusive disease have infarcts limited to the proximal IPCT – that supplied directly by the ICVA – the medulla and PICA-supplied cerebellum. (7) Infarcts within the middle and distal IPCTs are quite common in patients with ICVA disease. (8) Few clinical symptoms and signs are reliably predictive of occlusive ICVA disease. (9) Patients with bilateral severe ICVA occlusive disease may survive with a syndrome of repeated transient attacks of dizziness, blurred vision, and ataxia related to hypoperfusion in the posterior circulation. (10) Modern brain and vascular imaging can reliably detect and quantify ICVA disease and accompanying regions of brain infarction. (11) Very few reports describe the results of treatment of patients with ICVA occlusive disease and, as a result, very little is known about the optimal treatment of patients with ICVA occlusive disease who have various clinical presentations and findings.

References

- 1 Wepfer, Johan Jacob: *Observationes anatomicae ex cadaveribus eorum, quos sustulit apoplexia, cum exercitatione de ejus loco affecto*. J Caspari Suteri, Schaffhausen, 1658.
- 2 Clarke E, O'Malley CD: *The Human Brain and Spinal Cord. A Historical Study*. Berkeley, University of California Press, 1968, pp 774–775.
- 3 Wolf M: Wallenberg's syndrome; in Wolf M (ed): *The Classical Brain Stem Syndromes*. Springfield, Thomas, 1971, pp 113–136.
- 4 Wallenberg A: Acute Bulbaraffection (Embolie der Art. cerebellar post. inf. sinistra?). *Arch Psychiatr Nervenkr* 1895;27:504–540.
- 5 Wallenberg A: Anatomischer Befund in einem als 'acute Bulbaraffection (Embolie der Art. cerebellar post. inf. sinistra?)' beschriebenen Falle. *Arch Psychiatr Nervenkr* 1901;34:923–959.
- 6 Duvernoy HM: *Human Brainstem Vessels*, ed 2. Berlin, Springer, 1999.

- 7 Fisher CM, Karnes W, Kubik CS: Lateral medullary infarction. The pattern of vascular occlusion. *J Neuropath Exp Neurol* 1961; 20:323–379.
- 8 Hauw J-J, Der Agopian P, Trelles R, Escourolle R: Les infarctus bulbaires. Etude systématique de la topographie lésionnelle dans 49 cas. *J Neurol Sci* 1976;28:83–102.
- 9 Escourolle R, Hauw JJ, Der Agopian P, Trelles L: Les infarctus bulbaires. Etude des lésions vasculaires dans 26 observations. *J Neurol Sci* 1976;28:103–113.
- 10 Ogata J, Masuda J, Yutani C, Yamaguchi T: Mechanisms of cerebral artery thrombosis: a histopathological analysis on eight necropsy cases. *J Neurol Neurosurg Psychiatry* 1994; 57:17–21.
- 11 Kim JS: Medullary infarcts and hemorrhages; in Caplan LR, Van Gijn J (eds): *Stroke Syndromes*, ed 3. Cambridge, Cambridge University Press, 2012.
- 12 Sybert GW, Alvord EC: Cerebellar infarction: a clinicopathological study. *Arch Neurol* 1975;32:357–363.
- 13 Schwartz CJ, Mitchell JRA: Atheroma of the carotid and vertebral arterial systems. *Br Med J* 1961;ii:1057–1063.
- 14 Fisher CM, Gore I, Okabe N, White PD: Atherosclerosis of the carotid and vertebral arteries – extracranial and intracranial. *J Neuropathol Exp Neurol* 1965;24:455–476.
- 15 Moosy J: Morphology, sites, and epidemiology of cerebral atherosclerosis in research publications. *Assoc Res Nerv Ment Dis* 1966; 51:1–22.
- 16 Castaigne P, Lhermitte F, Gautier JC, et al: Arterial occlusions in the vertebro-basilar system. A study of 44 patients with post-mortem data. *Brain* 1973;96:133–154.
- 17 Caplan LR, Baquis GD, Pessin MS, D'Alton J, Adelman LS, DeWitt LD, Ho K, Izukawa D, Kwan ES: Dissection of the intracranial vertebral artery. *Neurology* 1988;38:868–877.
- 18 Estol C, Caplan LR: Intracranial dissections; in Caplan LR, Van Gijn J (eds): *Stroke Syndromes*, ed 3. Cambridge, Cambridge University Press, 2012.
- 19 Escourolle R, Gautier J-C, Rosa A, der Agopian P, Lhermitte F: Aneurysme disséquant vertébro-basilaire. *Rev Neurol* 1972;128:95–104.
- 20 Koroshetz WJ, Ropper AH: Artery-to-artery embolism causing stroke in the posterior circulation. *Neurology* 1987;37:292–296.
- 21 Caplan LR, Rosenbaum A: The role of cerebral angiography in vertebro-basilar occlusive disease. *J Neurol Neurosurg Psychiatry* 1975;38:601–612.
- 22 Caplan LR: *Posterior Circulation Disease. Clinical Findings, Diagnosis, and Treatment*. Boston, Blackwell Science, 1996.
- 23 Caplan LR, Wityk RJ, Glass TA, et al: New England Medical Center Posterior Circulation Registry. *Ann Neurol* 2004;56:389–398.
- 24 Savitz S, Caplan LR: Vertebrobasilar disease. *N Engl J Med* 2005;352:2618–2626.
- 25 Caplan LR, Chung CS, Wityk RJ, et al: New England Medical Center Posterior Circulation Stroke Registry. I. Methods, database, distribution of brain lesions, stroke mechanisms and outcomes. *J Clin Neurol* 2005;1: 14–30.
- 26 Caplan LR, Wityk RJ, Pazdera L, Chang HM, Pessin MS, Dewitt LD: New England Medical Center Posterior Circulation Stroke Registry. II. Vascular Lesions. *J Clin Neurol* 2005;1:31–49.
- 27 Glass TA, Hennessy PM, Pazdera L, et al: Outcome at 30 days in the New England Medical Center Posterior Circulation Registry. *Arch Neurol* 2002;59:369–376.
- 28 Graf KJ, Pessin MS, DeWitt LD, Caplan LR: Proximal intracranial territory posterior circulation infarcts in the New England Medical Center Posterior Circulation Registry. *Eur Neurol* 1997;37:157–168.
- 29 Muller-Kupfers M, Graf KJ, Pessin MS, DeWitt LD, Caplan LR: Intracranial vertebral artery disease in the New England Medical Center Posterior Circulation Registry. *Eur Neurol* 1997;37:146–156.
- 30 Shin HK, Yoo KM, Chang HM, Caplan LR: Bilateral intracranial vertebral artery disease in the New England Medical Center Posterior Circulation Registry. *Arch Neurol* 1999;56:1353–1358.
- 31 Feldmann E, Wilterdink JL, Kosinski A, et al, for the Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis Trial Investigators: The Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) Trial. *Neurology* 2007;68:2099–2106.
- 32 Tsvigoulis G, Sharma VK, Hoover SL, et al: Applications and advantages of power motion-mode Doppler in acute posterior circulation cerebral ischemia. *Stroke* 2008;39: 1197–1204.
- 33 Bash S, Villablanca JP, Duckwiler G, Tillis M, Kidwell C: Intracranial vascular stenosis and occlusive disease. Evaluation with CT angiography, MR angiography, and digital subtraction angiography. *AJNR Am J Neuroradiol* 2005;26:1012–1021.
- 34 European Stroke Prevention Study Group: European Stroke Prevention Study: principal end-points. *Lancet* 1987;iii:1351–1354.
- 35 Sivenius J, Riekkinen PJ, Smets P, Laakso M, Lowenthal A: The European Stroke Prevention Study (ESPS): results by arterial distribution. *Ann Neurol* 1991;29:596–600.
- 36 Chimowitz M, Kokkinos ChB, Strong J, et al, for the Warfarin-Aspirin Symptomatic Intracranial Disease Study Group: The warfarin-aspirin symptomatic intracranial disease study. *Neurology* 1995;45:1488–1493.
- 37 Chimowitz MI, Lynn MJ, Howlett-Smith H, et al, for the Warfarin-Aspirin Symptomatic Intracranial Disease Trial Investigators: Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med* 2005;352:1305–1316.
- 38 Kasner SE, Lynn MJ, Chimowitz MI, et al, for the Warfarin-Aspirin Symptomatic Intracranial Disease Trial Investigators: Warfarin vs. aspirin for symptomatic intracranial stenosis: subgroup analysis of WASID. *Neurology* 2006;67:1275–1278.
- 39 Becker KJ, Monsein LH, Ulatowski J, Williams M, Hanley DF: Intraarterial thrombolysis in vertebro basilar occlusion. *AJNR Am J Neuroradiol* 1996;17:255–262.
- 40 Nakayama T, Tanaka K, Kaneko M, Yokoyama T, Uemura K: Thrombolysis and angioplasty for acute occlusion of intracranial vertebrobasilar arteries. *J Neurosurg* 1998;88: 919–922.
- 41 Wang Bin, Wang Yabing, Li Shenmao, et al: Intra-arterial thrombolysis combined with angioplasty for treatment of acute ischemic cerebral infarction. *Chin J Cerebrovasc Dis* 2011;8:65–69.
- 42 Takis C, Kwan E, Pessin MS, Jacobs D, Caplan LR: Intracranial angioplasty: experience and complications. *AJNR Am J Neuroradiol* 1997;18:1661–1668.
- 43 Chimowitz MI, Lynn MJ, Derdeyn CP, et al, for the SAMPRIS Investigators: Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med* 2011;365: 993–1003.
- 44 Searls DE, Pazdera L, Korbel E, Vysata O, Caplan LR: Symptoms and signs of posterior circulation ischemia in the New England Medical Center Posterior Circulation Registry. *Arch Neurol* 2012;69:346–351.