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Review Article

A review of the diagnosis and management of vertebral basilar (posterior) circulation disease

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Abstract

We have reviewed the English literature published in the last 70 years on Diseases of the Vertebral Basilar Circulation, or Posterior Circulation Disease (PCD). We have found that errors have been made in the conduct and interpretation of these studies that have led to incorrect approaches to the management of PCD. Because of the difficulty in evaluating the PC, the management of PCD has been incorrectly applied from anterior circulation disease (ACD) experience to PCD. PCD is a common form of stroke affecting 20-40% patients with stroke. Yet, the evidence is strong that the Anterior Circulation (AC) and Posterior Circulations (PC) differ in their pathology, in their clinical presentations, in the rapidity of development of symptoms, in optimal imaging methods, and in available treatments.

There appears to be two categories of patients who present with PCD. The first, acute basilar artery occlusion has a more rapid onset. The diagnosis must be made quickly and if imaging proves a diagnosis of Basilar Artery Occlusion (BAO), the treatment of choice is Interventional removal of the basilar artery thrombosis or embolus. The second category of PCD and the most commonly seen PCD disease process presents with non-specific symptoms and early warnings of PCD that now can be related to ischemic events in the entire PC vessels. These warning symptoms and signs occur much earlier than those in the AC.

IA angiography is still the gold standard of diagnosis and is superior in definition to MR and CT angiography which are commonly used as a convenient screening imaging tool to evaluate PCD but are both inferior to IA angiography in definition

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for lesions below 3-4 mm. In at least two reported studies 7T MR angiography appears superior to other imaging modalities and will become the gold standard of imaging of PCD in the future. Medical treatments applied to the ACD have not been proven of value in specific forms of PCD. Interventional therapy was promising but of unproven value in Randomized Controlled Trials (RCT) except for the treatment of Basilar Artery Occlusion (BAO).

Surgical revascularization has been proved to be highly successful in patients, who are refractory to medical therapy. These studies have been ignored by the scientific community basically because of an incorrect interpretation of the flawed EC-IC Bypass Trial in 1985 as applying to all stroke patients. Moreover, the EC-IC Bypass Study did not include PCD patients in their study population, but the study results were extrapolated to patients with PCD without any scientific basis. This experience led clinicians to an incorrect bias that surgical treatments are of no value in PCD. Thus, incorrectly, surgical treatments of PCD have not been considered among the therapeutic possibilities for PCD.

QMRA is a new quantitative MR technique that measures specific blood flow in extra and intracranial vessels. QMRA has been used to select those patients who may benefit from medical, or interventional, or surgical treatment for PCD based on flow determinations with a high success rate. QMRA accurately predicts the flows in many large and small vessels in the PC and AC and clearly indicates that both circulations are intimately related.

From medical and surgical studies, the longer one waits for surgical treatment the higher the risk of a poor outcome results. This observation becomes obvious when the rapidity of development of PCD is compared with ACD. Recent advances in endovascular therapy in the treatment of acute basilar thrombosis is a clear sign that early diagnosis and treatment of PCD will reduce the morbidity and mortality of these diseases.

In this review it is evident that there are multiple medical and surgical treatments for PCD depending upon the location of the lesion(s) and the collateral circulation demonstrated. It is clear that the AC and PC have significant differences. With the exception of the large population studies from Oxford England, the reported studies on the management of PCD in the literature represent small selected subsets of the universe of PC diseases, the information from which is not generalizable to the universe of PCD patients. At this point in the history of PCD, there are not large enough databases of similar patients to provide a basis for valid randomized studies, with the exception of the surgical studies. Thus, a high index of suspicion of the early warning symptoms of PCD should lead to a rapid individual clinical assessment of patients selecting those with PCD. Medical, interventional, and/or surgical treatments should be chosen based on knowledge presented in this review. Recording the results in a national Registry on a continuing basis will provide the data that may help advance the management of PCD based on larger data bases of well documented patient information to guide the selection of future therapies for PCD treatments. It is also clear that the management of patients within the complex of diseases that comprise PCD should be performed in centers with expertise in the imaging, medical, interventional and surgical approaches to diseases of the PCD.

Key Words: Posterior circulation, stroke, vertebral basilar insufficiency

OPENING STATEMENT

A number of previous reviews of vertebral basilar circulation or posterior circulation disease have been written over the past 35 years[11,29,37,85,109] but none have covered the distinct differences that have emerged over the years between the vertebral basilar system (VBS) or posterior circulation (PC) and the anterior circulation (AC) over the 70 years in which these two circulations have been studied. This review was compiled from a review of papers cited using the PubMed database and searching for the terms – Vertebral basilar Insufficiency, Basilar

Artery thrombosis, Posterior Circulation Disease, Anterior Circulation Disease, Interventional Therapy, IVtPA, or any other terms used in the Abbreviations listed previously. The search extended from 1946 to 2017.

INTRODUCTION - SHORT SUMMARY OF THIS PAPER FOR THE READER, WITH KEY REFERENCES

Because the anatomical location of the vertebral basilar vessels is not easily accessible for pathological, imaging, clinical, or management studies, it has taken 70 years of publications to begin to understand the differences between the PCD and ACD.

Key studies by decade relating the AC to the PC and PCD

Postmortem anatomical studies have shown that 65% of the brains studied have an incomplete Circle of Willis with up to 50% with absent or hypoplastic posterior communicating arteries. Thus, the anatomical connection between the AC and PC is impaired in half of the patients presenting with PCD.[71]

The seminal paper by Kubik and Adams in 1946[80] first described the correlation of the clinical symptomatology with the postmortem pathological changes in the intracranial vertebral and basilar circulations. They described two types of presentation of patient with PCD – one with a rapid onset of symptoms and signs as in acute basilar artery occlusion, and second, with a more slowly developing ischemia in the PC leading to various lesions in the vertabral basilar system. In 1955 in a clinical study, Milliken and SIekert introduced the term known as "vertebral basilar insufficiency," to describe the progressive occlusion basilar and distal vertebral vessels. Without imaging, they successfully treated this progressing clinical disease with Coumadin as the first major drug treatment for CVD and PCD.[89,90,112] In studies of atherothrombotic lesions from the subclavian origins of the extracranial vertebral arteries to the intracranial vertebral and basilar arteries and its branches in the 1950s and 1960s, several authors demonstrated the differences between the AC and the PC pathologically.[36,51,58,75,111] In 1961, Reivich *et al*. correlated the clinical symptoms of subclavian artery stenosis or occlusion in patients with measured changes in flow made in the extracranial vertebral and carotid arteries in 2 patients and in an animal model with an occluded subclavian artery. The authors found that measured disturbances in flow in vertebral arteries can occur with either subclavian stenosis or AC occlusions, demonstrating for the first time that flow deficits in the PC can likely produce symptoms of PCD.[2,101] Yet, no advances in medical or surgical treatment of PCD occurred after this study until the 1980s.[27] Up to this time, treatment of PCD was extrapolated from experience with ACD.

In the 1980s, the introduction of new detailed subtraction angiography showed the anterior and posterior circulations better than any known imaging modality at that time. With the addition of digital subtraction, four-vessel angiography became, and still is, the "gold standard" for evaluating AC and PC disease.[23,34,78,105,109] At the same time, the development of EC–IC bypass microneurosurgery permitted surgical reconstruction of the PC vessels, which was performed successfully with excellent outcomes in several centers.[14,18,74,115] Only those patients who had failed maximal medical therapy were referred for PC reconstructive surgery. In numerous reports of patients who had failed maximal medical therapy, PC reconstruction was successfully performed with low mortality and morbidity for lesions from the origin of the vertebral arteries to the basilar and its branches.[14,18,74,115]

The publication of the first randomized surgical trial of the best medical vs EC–IC bypass surgical treatments was published as the EC–IC bypass trial in 1985. EC–IC bypass was not found of value in the treatment of ACD.[1] However, this study was criticized because only 20% of the eligible patients were entered into the study, and the reporting by the principal investigators could not be verified.[12,64,114] Two more RCT of medical vs. EC–IC bypass therapy for "misery perfusion" also showed no differences in therapies, but these studies also were criticized on technical bases.[35,69] No properly performed RCT has ever evaluated the efficacy of reconstruction of the PC in a RCT in which patients subjected to surgery had failed medical management even though the reported clinical results were excellent in patients who had exhausted medical management. PCD reconstructive surgery was mostly ignored without justifiable reasons until the present time, and this denial was based on conclusions from AC studies in a RCT that was seriously flawed.

Computed tomography (CT) and magnetic resonance (MR) imaging and angiography was introduced in the 1980s and 1990s and used as a basis of clinical trials of various medcial therapies, even though the imaging studies were not able to demonstrate PC lesions with high accuracy, calling into question the conclusions of these studies.[23,34,78,105,109]

In the first decade of the 2000s, 60 years after the first clinical pathological study of PCD, Caplan *et al*. developed a large registry of 407 patients with PCD who were evaluated angiographically and followed clinically. Accrual of patients in this study preceded IVtPA and acute interventional approaches to treatment. Many patients were entered days after onset. Yet, as thorough as this registry was, it represented an eclectic sample of the universe of patients with PCD seen during the 1980–1996 period, as the authors admit. Only three patients had surgery and five interventional treatment, indicating

a further treatment bias of the study. There were no patients described who were refractory to medical therapy as in the surgical studies.[30,33,34,97]

Although intravenous thrombolytic therapy was used in patients with PCD, most studies reported a mixture of patients with ACD and PCD. Two studies on non-angiogrammed patients with PCD reported favorable results after IVtPA.[82,107]

It was not until the 2010 decade that significant advances in the diagnosis and treatment of PCD were reported. (1) There were reports of the successful use of stent retrieval systems to remove a basilar artery thrombosis, a subset of the universe of PCD.[21,45,53,60,67,83,91,96,110,116,118,122]

(2) Using QMRA, Charbel *et al*. were able to differentiate patients with symptomatic PCD with low posterior circulation blood flows from those with normal flows to reveal another subset of patients with PCD. Those with normal flows had a much higher stroke-free survival than those with low PC flows. This latter category of patients was amenable to reconstructive PC techniques and then resumed a postoperative stroke-free course that paralleled those who had normal PC flows.[6,7] These studies represent a major advance in the diagnosis and treatment of PCD, as patients with flow deficits are separated into categories in which various therapies can be studied.

(3) In a third major advance since 2010, studies using 7T MR angiography were able to delineate the PCD in far better detail than angiography. This imaging modality available in limited centers represents another diagnostic method of evaluation with QMRA.[46]

(4) Finally, in a large population study from Oxford England, Paul *et al*.[97] determined that the presenting symptoms of PCD occur initially with relatively nonspecific symptoms and progress more rapidly than that of ACD to produce the onset of stroke. Marquardt *et al*. studying the same population found that there was a 46% recurrent transient ischemic attack (TIA) or stroke rate in the PCD patients within 90 days of presentation.[86] Both of these population studies highlight the differences in the course of PCD compared with a more benign and prolonged presentation of ACD.[86,97] These large population studies appear to provide a larger universe of PCD than previously reported studies in the literature. The authors' observations seriously question the standard evaluation of PCD symptoms and indicate that a higher index of suspicion of nonspecific symptoms be used to lead to more rapid triage of these patients for diagnosis and management.

In an observation from a human surgical study, when both ends of the basilar artery were occluded, and the basilar artery incised to remove an atherosclerotic plaque, blood was seen coming into the basilar artery from the paramedian vessels indicating that there was collateral circulation in the brainstem in vessels formerly believed to be end arteries. This observation explains the reason for the survival of patients with BAO with minimal deficits.

Lastly, after a review of the conclusions from the voluminous studies over the 70-year period by decade, indicating the distinct differences between the AC and PC in pathology, clinical presentations, imaging, and management strategies, it is obvious that these reports came from separate subset samples of the universe of patients with PCD and are not generalizable, making most of the literature on PCD difficult to assess and use in analyzing treatment of PCD. Yet, this conclusion is important in that it suggests along with the other studies cited, that PCD is composed of a number of different subsets of pathology that will require individual types of treatments first described by Caplan in 1975.[32] Thus, the literature on PCD is filled with observations on number of patients who represent selected undefined subsets of the universe of patients with PCD explaining the slow rate of progress in 70 years in PCD, diseases that represent over 20% of all stroke patients. Suggestions are made for future studies to better define the characteristics of patients with PCD and thus, treatment options.

EPIDEMIOLOGY

Diseases of the vertebral basilar circulation (VBC) represent 20–40% of all the strokes in a year.[7,8,24,37,59,85,99] Caplan has referred to diseases of the VBC as posterior circulation disease (PCD).[109]

Anatomy of the circle of Willis and brainstem

Sixty-five percent of the people have abnormalities or anomalies in their Circle of Willis and 18–32% have one hypoplastic and 24–49% have bilateral hypoplastic posterior communicating arteries.[71] The anatomy of the brainstem vessels has been reviewed by others.[80] Those authors describe the anatomical clinical correlation in the vascular anatomy of the brainstem and related perforating branches. Simply described, the median arteries off the midline basilar artery bifurcation and the paramedian arteries, which, respectively, supply the medial portion of the tegmentum and the posterior diencephalon and the midline brain stem structures down through the medulla; the short circumferential arteries supply the lateral 3/5 of the pons; and finally, the long circumferential arteries (superior, anterior, inferior, cerebellar arteries) supply the cerebellum and lateral tegmentum and tectum with other arteries. There is an overlap of the supply of the vessels from the injection techniques used.[80]

Observation #1: Two-thirds (66%) of the population have variations in their circle of Willis that can affect the collateral circulation between the AC and the PC

SPECIFIC BRAINSTEM VASCULAR SYNDROMES

This review will not cover the specific syndromes of vascular occlusion of the basilar artery branches that has been reviewed in other publications.[32,34]

CHRONOLOGICAL REVIEW OF PCD LITERATURE

1940s

Basilar artery thrombosis

While there was literature on the vascular syndromes of the brainstem reported previously, the symptoms of basilar artery thrombosis had not been established. In 1946, Kubik and Adams reported a detailed clinical and autopsy study of 18 patients with basilar artery thrombosis.[80] Among the 18 cases, 11 were caused by thrombosis of the basilar artery with or without vertebral or posterior cerebral involvement. Many of these eleven patients had nonspecific symptoms preceding the symptoms and signs of axial nervous system involvement. Those nonspecific symptoms occurring singly or in combination were headache (frontal or occipital), dizziness, vertigo, nausea vomiting, tinnitus, and confusion. These symptoms preceded the thrombosis from days to weeks to years. Others over the following 70 years reported similar observations.[42,79,81,89,97,112] As the patients' clinical picture progressed to basilar artery thrombosis, in some cases no pathological lesions fully explained the clinical signs. The authors opined that collateral circulation was sufficient to produce cellular malfunction without producing cell death, a hypoperfusion state. These observations will also be reported by others over the ensuing decades, as will be discussed in this review. Obviously, the time to completed basilar thrombosis of 2 days to 35 days today would allow an opportunity for interventional management of progressing clot in some patients.

The brainstem and cerebral symptoms and signs in all cases of basilar thrombosis were progressive over days to include a combination of motor sensory loss of the face and 1–4 extremities, cranial nerve dysfunction, dysarthria, cerebellar signs, nystagmus, and incontinence.[80]

There were 7 cases of embolism to the basilar artery all of whom presented with sudden or rapidly progressing coma. One had a rare tumor embolus to the basilar artery, 3 others had a cardiac murmur, and 2 had atrial fibrillation. in these patients, death occurred in 2–35 days.[80] The authors did not report if the autopsy examinations included the entire vertebral basilar circulation from the aortic arch to the intracranial vertebral arteries. Likely, that examination was not made; so, no definitive conclusions can be made on the origin of the emboli.

Forty-six years later, in 1990, Morgan *et al*. reported a case of rapidly progressing basilar artery thrombosis with a deteriorating level of consciousness dysarthria, dysphagia, and periods of apnea. Angiography demonstrated an occluded basilar artery, patent vertebral arteries, with collateral filling of the basilar tip but no posterior communicating vessels. The patient was treated with intra-arterial thrombolytic agents given directly at the site of occlusion to lyse the clot and restore the patient to a normal clinical state. An atheroma at the mid basilar artery was found and a superficial temporal artery (STA) to superior cerebellar artery (SCA) bypass was performed insuring the competency of the distal basilar artery circulation. The patient recovered. This report provides an example of what can be done in the 21st century for this dreaded disease with rapid diagnosis and treatment.[92] By 2009, clot removal technology had been developed to remove basilar artery thromboemboli and to establish reperfusion of the basilar artery by interventional approaches.[110]

1950s

Early reports on diagnosis and treatment of PCD

In 1955 Millikan and Siekert performed a less detailed study of patients with basilar artery occlusion. Seventy percent of Millikan and Siekert's patients developed symptoms before occlusion. Early in the course of the disease, the symptoms and signs were difficult to localize to the brainstem and alone were "non-specific," but as the course of the disease progressed the involvement of the basilar artery became apparent. In many cases, the early symptoms and signs were transitory leading them to describe the syndrome as "intermittent insufficiency of the basilar arterial system," or as is commonly used, vertebral basilar insufficiency (VBI).[89,112] During autopsy in 3 of their 10 patients, they found basilar artery thrombosis in two patients, and one had a basilar aneurysm lined with a laminated thrombus. They only viewed the distal vertebral arteries removed at autopsy, as did Kubik and Adams. Both studies incompletely evaluated the entire vertebral basilar circulation, pathologically.[89]

Seeing laminations in the basilar thrombus, they believed that the occlusion occurred progressively and started Coumadin therapy empirically to stop that progression, which appeared successful in their initial 10 patients.[89,90,112] There was no angiographic confirmation of the vascular lesion, and the diagnosis was made on a clinical basis. Twenty-one patients with presumed impending basilar occlusion were treated with intravenous anticoagulants. The mortality decreased from 43% in a previously untreated group to 14% in the newly treated group.[112] This report established anticoagulation as a treatment for a devastating clinical problem. In the late 1950s and 60s there were other reports of "unequivocal VBI" that were studied.[11] "However, no uniform criteria for the diagnosis were used, angiography was not performed to prove the diagnosis, and, so, the clinical diagnosis was never confirmed."[11]

Early angiography

Direct vertebral angiography by vertebral artery puncture of the vertebral basilar system was introduced in 1949 but had a risk of 25%, which made it impractical for clinical use.[11] Retrograde brachial[68] and supraclavicular subclavian artery arterial angiographic injections[11] were introduced the late 1950s and used in the early 1960s.[11] Transfemoral cerebral angiography was introduced in 1956, and its risk fell to less than 1% over several decades making it the diagnostic procedure of choice. Angiographic studies of large numbers of patients with PCD before the 1980s were uncommon because of that risk, and medical treatment was empirical, mostly extrapolated from anterior circulation disease.[30,34]

Observation #2: Diagnostic angiography for PC disease is more difficult to perform than for AC disease. Medical Treatment of PCD was extrapolated from studies of ACD

Anatomical divisions of the vertebral artery

To understand the pathology reports and subsequent studies on the VBC, it is important to review the anatomical vertebral artery segments. Numerous investigators have divided the vertebral artery into four segments.[37,48,49,113] The first portion, V1 extends from the subclavian artery to the entry of the vertebral artery into the cervical transverse foramen at C6. The V1 portion is the site of vertebral artery origin stenosis.[111] The second portion, V2, traverses the cervical vertebral foramen in the transverse process to the second cervical level. The V3 segment extends from point the vertebral artery exits the C1 transverse process and swings around the arch of C1 until it enters the dura of the posterior fossa. This is a common site of atherosclerosis.[4,16,17,95,111] The V4 portion extends from the vertebral artery entry into the dura to its junction with the basilar artery.

1960s

Pathology of the VB system

Because of the lack of information on the pathological changes from the vertebral origin to the intracranial VBC, papers were published in the late 1950s and early 1960s on this subject. This information provided a basis for understanding the pathological changes in the VBC.

The pathology studies examined the entire extra and intracranial vertebral basilar circulation.[36,75,111] Studies were divided into unselected autopsies[58,111] and those performed on patients selected with cerebrovascular disease.[36,51,75] Caplan *et al.* have written an excellent review of these studies.[34]

The fundamental conclusions that can be made by mixing the data from these studies are:

1. Atherosclerotic disease occurs throughout the vertebral artery[36,111]
2. Atheromas are localized at the vertebral origin, the mid vertebral artery, C3, the proximal basilar and the posterior cerebral arteries with the highest percentage at the vertebral artery origin[58,111]
3. Since the vertebral arteries are smaller than the carotids, plaques produce more stenosis in the vertebrals than in the carotids[36,111]
4. Vertebral plaques are less ulcerated than in the carotid arteries[58,111]
5. Most occlusions in the VBS occur at the vertebral artery origins or near or at the sites of stenosis[36,72]
6. The atheromas in the vertebral develop a thrombus that can embolize[36]
7. The right vertebral has more stenotic lesions (75%) than the left vertebral[111]
8. Distal V3 lesions are more symptomatic than proximal V1 stenoses[58]
9. Atheromas occur more in the proximal than distal basilar artery[58]
10. Atheromas can produce flow related symptoms in studies done with clinicopathological correlations[51,80,111]
11. Occlusion of one vertebral artery does not assure adequate circulation to the VBC[51]
12. Dissections can occur at the vertebral origins, in the mid-vertebral, C3, and basilar sites[34]
13. Atherosclerosis is the cause of basilar occlusion 94% of the time[36]
14. Atherosclerotic occlusions of the posterior cerebral arteries in a small series of 16 patients occurred in 63% of the cases; antegrade thrombus produces occlusion in 5/16 (31%) and cardiac embolus occluded the posterior cerebral arteries 1/16 cases (6%); 1/3 (33%) of posterior cerebral artery occlusions were bilateral[36]
15. In some patients over 75 years with PCD, there were no lesions in the VBC[111]
16. The total cerebral circulation is important to understand in evaluating the adequacy of perfusion in the VBC[111]
17. Narrowing of one of the four carotid or vertebral vessels means a high probability of narrowing in others[111]
18. More recent studies by Caplan *et al.*[34] show that Asians, Blacks, and women have more predominantly intracranial occlusive lesions, whereas white men have more extracranial (VA origin) lesions.

Observation #3: Studies of the pathology of atherosclerosis in the VBC establish significant differences in the types of and locations of cerebrovascular pathology between the PC and the AC

While these pathology studies were being reported, some important information was emerging that suggested that hemodynamic and blood follow changes can account for symptoms in the VBC.

Subclavian steal

In 1961, Reivich *et al*. reported the first cases of subclavian steal syndrome (SSS), an excellent example of the flow-related (hemodynamic) production of symptoms in the posterior circulation.[101] In this condition, there is blockage with atheromatous occlusion or stenosis of the proximal subclavian artery before the take-off of the vertebral artery. As a result, blood supply to the affected arm was reduced and the blood pressure in that arm was much less than in the unaffected opposite arm. In patients with this arterial blockage, blood flows up the unaffected vertebral artery then down the other vertebral artery on the opposite side past the subclavian stenosis or occlusion into the arm. Subclavian steal can occur in either subclavian artery.[56] Essentially, blood is being stolen from the posterior circulation to supply the arm. Supporting animal studies and measurements of flow change in humans were reported in the same paper. The anterior circulation was also shown to contribute this steal through the posterior communicating arteries.[101]

In a laudatory editorial on the Reivich *et al*. report of SSS in the NEJM, Fisher reported that transient spells of cerebral ischemia had been noted in clinical pathological reports in the past 10 years but not understood.[1] In the first patient in Reivich *et al*. report, symptoms included suboccipital headache on the side of the SSS, worse with exercise, and episodes of flaccid paralysis of the left arm. In a second case, transient visual blurring, precipitated also by head turning to the left, an episode of aphasia, and paresis of the right hand occurred. In both patients, blood pressure was reduced in the left arm compared with the right. The second patient had reduced retinal artery pressures, but his left internal carotid was also occluded. In the first patient, carotid compression with EEG monitoring produced bilateral slowing on the EEG and one episode of temporary loss of consciousness indicating the both carotid arteries were necessary for adequate cerebral blood flow. Further, in the second patient, an EEG with right carotid compression revealed slowing with the development of clonic movements of the right arm and then loss of consciousness, again indicating the importance of the carotids for cerebral blood flow. The first patient had stenosis of the left subclavian artery while in the second the subclavian was occluded proximal to the origin of the vertebral.

Studies were performed in four dogs with both carotids and vertebrals exposed and flows recorded extravascularly. With occlusion of the left subclavian artery there was a reversal of flow in the left vertebral artery that almost equaled its antegrade flow before occlusion. Right vertebral flow increased by 78% as did flow in each common carotid artery by 22% and 23%. The calculated reduction in total cerebral blood flow was 41%.[101]

Observation #4: The discovery of the subclavian steal syndrome, with a stenosis or occlusion in a vessel far removed from the brain but yet producing vertebral basilar symptoms described by numerous clinical and pathology investigators previously, establishes flow deficits in the AC and PC as a cause of vertebral basilar vascular symptoms and signs in PCD[2]

1970s

Multi-institutional angiographic study to determine efficacy of surgery in accessible lesions of the carotid and vertebral arteries

By the 1970s, disease of the VBC was known clinically and pathologically but could not be definitively diagnosed angiographically. There were no surgical treatments for disease beyond the origins of the vertebral arteries. Angiography had become safer and more widely used.[32,72] Hass and Fields began a large multi-institutional study on the evaluation of cerebrovascular disease by cerebral angiography using different methods of angiography. The goal of the study was "to determine the efficacy of surgical treatment of cerebrovascular disease secondary to surgically accessible lesions in the neck and upper portion of the thorax."[55] They accumulated a large body of data on 4748 patients, 80% of whom had complete angiography. The "grave complication rate" (0.7% mortality and 0.5% morbidity) in their study was 1.2%. The most common sites of stenosis or occlusion were in the carotid bifurcations or the origins of the vertebral arteries. However, their studies were limited to revealing lesions that were surgically correctible at the time that only included vertebral origin stenosis or occlusion. Forty one percent (41%) of the lesions found in their studies were surgically accessible at that time. However, since that study, lesions throughout the PC became amenable to interventional and surgical treatments. Thus, their landmark study is only of questionable value today. Their reports suggested that carotid endarterectomy was significantly better than medical treatment.[54] The treatments for subclavian steal were successful but had significant risks associated with the procedures.[56]

Other important studies at the time

Others[10,61] reported studies on selected samples of patients with PCD who were studied clinically and angiographically. Caplan found patients with vertebral or basilar occlusions, who had a benign poststroke course. Sixty percent of his patients had TIAs, usually multiple, within one month of their stroke.[28] Archer and Hornstein found that those with basilar occlusion had a high mortality.[10] Thus, vertebral or basilar occlusions can occur with or without clinical deficits. Caplan *et al*.[32] stated that advances in angiography and imaging provided greater detail in analyzing the PC so that a definitive diagnosis can be made, sometimes finding a normal study that suggests other medical diagnoses or treatments.

Caplan *et al*. stated[32] "thus, it must be clear that vertebrobasilar disease is not a homogenous entity; some

clinical subgroups have relatively better prognosis than others."

The medical treatment of cerebrovascular disease was summarized by Byer and Easton. Heparin and Coumadin were used for progressing stroke while Aspirin was useful for AC disease, but there seemed to be little further to offer the patients with PCD.[27] Caplan commented that neurologists were reluctant to order angiography to diagnose the disease because of a lack of therapeutic options.

1980s

Reconstructive surgery for PCD

With the development of microvascular surgery and small vessel anastomosis by Yasargil in the late 1970s,[121] EC–IC bypass surgery became a prevalent treatment in the 1980s by neurosurgeons. Neurosurgeons became interested in PCD as the medical treatments for PCD had reached its limits, and the full extent of the VBC became available through new surgical approaches.[11]

Neurosurgeons studied the vertebral basilar circulation from the vertebral origins to the basilar artery and its terminal branches including the posterior communicating arteries with detailed angiography and subtraction views to understand the anatomy of the obstructive lesions and plan for reconstructive vascular surgery. There are three groups who have had extensive experience with the surgical treatment of PCD, (Ausman *et al*.,[11,13,14,16-18,20,48,49,87] Sundt *et al*.,[115] and Spetzler *et al*.[73,74,100,113])

The revascularization procedures used by these investigators for the extracranial vertebral artery included vertebral to carotid transpositions, which appeared a safer procedure than removal of the vertebral origin plaque itself.[48,100,113] For lesions located further up the extracranial vertebral artery in the V2 portion, external carotid artery bypass to the patent distal segment of the vertebral artery was found successful.[4,49,113] For lesions at the V3 and V4 portions of the vertebral artery an occipital artery to posterior inferior cerebellar artery (PICA) bypass or radial artery graft from the extracranial vertebral artery to the PICA or AICA were done.[4,16,17,95] For lesions in the intracranial vertebral or basilar arteries, usually a superficial temporal artery to superior cerebellar or posterior cerebral artery bypass was done.[11,13,14,16,18,20,48,49,73,87,100] Some used vein grafts to supply high flow to the affected areas.[115]

Vertebral artery surgery

The 1980s marked the introduction of surgery on the vertebral origins[48,100,113] the mid and distal vertebral arteries[4,49,113] and the use of a variety of bypasses[14,18,20,74,113,115] to circumvent the stenoses or occlusions in the vertebral[13,16,17] and basilar arteries. These investigators, with large series of patients, reported success for the first time in treating vertebral basilar circulation problems in patients with VBI, who had failed maximum medical therapy.[18,48,49,74,113,115] Surgery for extracranial vertebral artery disease produced complete resolution of symptoms in 96–100% of the treated patients. This subset of the VBI population of patients, who were refractory to medical management, had never been reported in the literature as a selected group. This subset of patients was different from that reported later by Caplan *et al*. in his Registry of patients with PCD in 1988–1996.[30,34]

Surgery for intracranial arterial disease of the PC

Using various EC–IC bypasses to the PC, Hopkins *et al*. in their initial report of 45 cases found a 2% mortality, 0 morbidity, and 0 strokes after PC vascular reconstruction of the intracranial vessels.[74] In 77 cases, Sundt and Piepgras had excellent or good outcomes in 71%, 13% mortality, and 16% poor results.[115]

Furthermore, Ausman *et al*.[18] divided their series of 75 patients with PCD mostly located in the distal portions of the VB System and treated with EC–IC bypasses into stable and unstable subsets, referring to their symptom frequency. All had failed medical management. Patients who were unstable had a higher mortality and morbidity after surgery (15% mortality, 26% morbidity, 44% resolution of symptoms) than the stable group whose mortality was 5%, morbidity 7%, with 78% resolution of symptoms after reconstructive vascular surgery. This observation indicated that patients with PCD, who were unstable in the face of maximal medical therapy, should have undergone surgery sooner to prevent the associated complications and mortality that patients with advanced disease have when undergoing surgery late in the course of their disease. Without surgery in these unstable patients, the mortality should have been very high, but there are no comparable untreated patients like this subset in the literature. The work of Spetzler *et al*.[73,74] and Sundt *et al*.[115] reported a similar experience.

Observation #5: These surgical studies showed that diseases of the PC from the vertebral origin to the intracranial vessels could be successfully treated surgically in a selected sample of patients with PCD who had failed medical management

International EC–IC Bypass Study

As EC–IC bypass surgery became more common with successful reports in individual case studies or series for relieving symptoms of cerebral ischemia, it became important to develop a RCT of this surgery. The first RCT of a surgical therapy (EC-IC Bypass Study) versus best medical therapy for TIAs in the anterior circulation in patients with carotid occlusion was published in 1985.[1] The study conclusions stated that EC–IC bypass surgery "failed in preventing cerebral ischemia in patients with atherosclerotic disease in the carotid and middle cerebral arteries."[2] However, the conclusions of this study of

anterior circulation disease were incorrectly generalized to the Stroke Population at Large, which was not studied.[12,64,102,114] The principal investigators of the EC–IC bypass trial stated that EC–IC bypass was of "No Value for Stroke." As the first randomized study of a neurosurgical procedure, most people uncritically and erroneously accepted these conclusions.[12,103] The results of the study could not be verified by an independent group of observers who visited the principal investigating center.[64] It was found that the study was corrupted because 2572 patients had EC–IC bypass surgery outside the study compared with only 601 patients who were randomized to surgery in the study during the same time period by the participating investigators. Many operated outside of the trial were eligible for the trial. In addition, a large number of asymptomatic patients were included in the bypass study as were centers with low surgical volume.[102,114] Through Medicare the US Government stopped payment for bypass surgery for ischemia based on the EC–IC bypass results. This step was taken against the recommendations of the independent reviewers.[64] Because of these trial results, bypass surgery and other reconstructive vascular surgery for PCD was abandoned, even though patients with PCD were not included in that trial. Only medical therapy remained as a treatment for PCD.[30]

A second EC–IC bypass study was performed[69] but its patient population was diluted by the addition of centers that did not have the proper equipment to analyze misery perfusion, which was the diagnosis used to select patients for this second study.[35] Thus, both EC–IC bypass studies were seriously flawed but blindly accepted to prove that bypass surgery was of no value for cerebral ischemia.

Observation #6 Although PCD was not studied in either EC–IC bypass study, the conclusion was made that EC–IC bypass surgery for PCD was of no value as a treatment for PCD without any supporting scientific evidence from the studies performed

Results of medical and surgical management of patients with PCD refractory to maximal medical therapy similar to the surgically treated cases

There was very little information on the medical management of patients similar to those treated surgically. Likely, those who failed medical therapy, died, or developed an infract, but these patients are not reported. Jones *et al*. reported that in 37 consecutive non-angiogrammed patients with infarcts from PCD, there was a 27% mortality, 2.5-times higher than in carotid artery system disease.[76]

In a study closest to the surgical populations reported above, Moufarrij *et al*. examined 44 patients with >50% stenosis of the distal vertebral or basilar artery presenting with VB-TIA or infarction who were followed for 6.1 years.[93] Eighty percent received either coumadin, aspirin, or aspirin and dipyridamole. Their treatment course is not described. Overall, 12 of the 44 (27%) developed VB ischemia/infarction during follow-up. Five patients had a brainstem infarction and 7 TIA without infraction. "The observed 5-year survival rate on an actuarial basis was 78% compared to 90% in a matched normal population."

Observation #7: Still there is no published comparable medical study of patients who failed maximal medical therapy to the surgically treated group of patients of patients with PCD who had failed maximal medical treatment

The goal of treatment for any disease is to provide the treatment with the lowest risk and the best outcome at each stage of the disease. No treatment is also therapeutic option. That option also has risks and must be compared with the risks and benefits of other options available. Vascular reconstruction for PCD is a treatment option that has been inappropriately disregarded because neurologists and neurosurgeons worldwide accepted inaccurately analyzed data, and the investigators of those studies supported financially by the US Government have not admitted the failures and limitations of their research.[64]

From 1985 until 2011, surgery for PCD was not considered in the treatment of these patients. In the Stroke Guidelines of the American Heart Association and American Stroke Association of 2011, "for those patients with 50–99% stenosis of a major intracranial vessel EC–IC bypass surgery was not recommended." However, "for those with extracranial vertebral stenosis, surgery or endovascular treatment "should be considered for patients having symptoms despite optimal medical management."[62] The 2011 Guidelines from the specialty societies just documented some of the literature results for PCD but made no recommendations.[26]

Observation #8: Yet, in a critical analysis of the data in the literature on PCD over decades, there is excellent evidence, in critically ill patients, who had failed medical therapy, that the outcomes of surgery were superior to no therapy or medical therapy, which would have had a high mortality rate

1990s

Imaging diagnosis of PCD

Starting in the mid-1990s minimally invasive diagnostic methods were employed that included CT angiography and/or MR angiography as a replacement for intra-arterial digital angiography as screening and diagnostic tests.[106] Because surgery was no longer considered to be a treatment option by the neurologists to whom most of these patients were now referred, CTA or MRA seemed to provide the imaging of the VBC without the need for the higher risk IA digital angiography. Studies favoring the less invasive MR angiography or

CT angiography have been reported.[30,34,78,104] Other studies have indicated that CT angiography and MR angiography cannot reveal posterior circulation details as well as IA angiography, which is still believed to be the "gold standard" of diagnosis.[23,34,78,109] 7T MR angiography is superior to 1.5 and 3T MRA but is not widely available and may be better than IA angiography, but there is not enough information available to make that determination.[77]

MR angiography has been used by many investigators as a noninvasive, negligible risk, alternative to IA angiography in most studies from the late 1990s forward.[78,86] This screening evaluation is not the "gold standard' of imaging for PCD and certainly not what an interventionalist or neurosurgeon would need for an accurate picture of the PCD. Rustemi *et al*., in a study of 286 patients with 335 unruptured intracranial aneurysms, reported their study of DSA vs. MR and CT angiography for the detection of aneurysms. For aneurysms smaller than 4 mm, DSA was superior to the other modalities.[105] This work confirms that CT and MR angiography are not able to detect lesions less than 3–4 mm in size, which is the dimension of vessels found most commonly in the PC.

Observation #9: As found 40 years ago, imaging of PCD is far more difficult to perform and interpret than ACD. IA angiography is still the gold standard for the diagnosis of PCD, although it is more difficult to perform technically according to angiographic radiologists. MRA and CTA can only be regarded as screening examinations because the limit of their resolution is less than that of IA angiography. For those with symptoms and signs of PCD and with normal MRA and CTA, IA angiography should be performed. Had neurologists developed the capability to perform cerebral angiography as cardiologists did for cardiac disease, neurologists would have not been reluctant to investigate the vascular anatomy of the brain. This specialty change would have propelled a more rapid understanding of the ACD and PCD

2000–2010

NEMC-PCR

Caplan *et al*. stated, "Autopsy studies select patients who die of stroke or its complications. Angiographic studies also contain selection bias since more severely ill patients have been studied. Unfortunately, no detailed reports from large registries of posterior circulation ischemia patients define the frequency and location of vascular occlusive lesions using modern vascular imaging techniques."[34] Caplan *et al*. developed the NEMC-PCR for that reason.

Inclusion criteria were that:

- All 409 patients were examined by Drs. Caplan, Pessin or DeWitt,
- Patients must have had posterior circulation TIAs or strokes within the past 6 months. Stroke patients must have had CT or MRI documented infarction. TIAs had to be clearly vertebrobasilar and brain imaging and vascular tests must have shown vertebrobasilar territory infarction or occlusive lesions, and
- Investigations must have been adequate.[30]

By the inclusion criteria stated above this sample of patients represents a defined subset of the PCD population.

The sample of the universe of patients with PCD in their Registry, included 63% males, 37% females, with an average age of 60 years; 84% were white, 9.5% Asian, 4% Black, and 2% Hispanic.[30] Fifty-nine percent (240 patients) had stroke without TIAs, 1%[30] had strokes followed by TIAs, 16%[30] had only TIAs, and 24%[71] TIAs before stroke. "The most likely stroke mechanism was decided by consensus."[34] This group of patients is obviously not a representative sample of the USA population. The authors admit to a possible referral selection bias with the most neurologically ill patients never being admitted to their series.[30,63]

Embolism was the likeliest stroke mechanism for 40% of their cases, Cardiac embolism in 24%, artery to artery in 14%[30]. These figures are in disagreement with the published studies of other pathologists.[36,58,111] Castigne *et al*.[36] found only 9% cardiac emboli in their autopsy series.[36] However, that was not a clinical series. Furthermore as Caplan *et al*. have stated, the statistical chances of a cardiac embolus to the posterior circulation, based on the distribution of blood flow to the brain, is 1/5 for the posterior circulation vs. 4/5 for the anterior circulation.[30] The vertebral arteries of the posterior circulation are smaller than the carotids and often have a higher percentage of stenoses at the vertebral origins than in the rest of the VBC.[34,58,111] That anatomy would make it difficult for large cardiac emboli to reach the distal posterior circulation. Caplan *et al*. in their paper reported a prevalence of occlusive disease of the vertebral arteries.[34] Furthermore, from pathology studies, emboli from a thrombus associated with a vertebral atheroma would be more likely.[36] This information can only be determined by detailed examination of the vertebral origins and arteries, which is better done angiographically than with MRA or CTA. Also, it is possible to have associated cardiac abnormalities that are not the principal cause of the emboli, particularly in the PC.

The distribution of lesions was among their defined proximal, middle, and distal VB territories and was mixed with the predominant territory being distal, consistent with the predominance of embolic causes of PCD in their sample. ("The distal territory included regions supplied by the rostral BA, SCA, PCA and their penetrating artery branches-midbrain, thalamus, SCA cerebellum, and PCA territories.")[30] The authors characterize the outcomes of the different groups of patients in their sample.[30]

The 30-day mortality of the NEMC-PCR was "very low," at 3.6%. Twenty-one percent of patients in their series had died by 30 days or had a major disability, while almost 80% recovered with little or no disability.[30,63,109] These figures differ from other subsets of patients reported with PCD having a higher mortality from progressing disease, which are likely represented by the 21% who died or had a major disability when entered into the NEMC-PCR. However we do not know the medical treatment details of those who died within 30 days.[63] The authors state, "surgery was seldom pursued."[30] Only 3 patients had surgery: 1 with a vertebral artery to common carotid bypass and 2 with Occipital Artery to PICA bypasses. (Neither of the 3 procedures are the favored operations for revascularization).[18] Five patients had intracranial angioplasties, which has proven to be a treatment with a high recurrence rate.[38]

Highlights from the authors' second paper in the discussion of the 407 patients in the NEMC-PCR[34] are:

- "…Intracranial occlusive lesions are most common in blacks, individuals of Asian origins, and women…
- …necropsy studies showed that although extracranial vertebral artery lesions (ECVA) were common, most posterior circulation infarcts were attributable to intracranial occlusive disease
- …Subclavian artery disease patients often have coexistent ICA disease that is usually responsible for brain ischemia
- … The benignity of atherosclerotic vertebral artery origin (VAO) lesions was attributed to: (1) the capacity to develop collateral reconstitution of the ECVAs; (2) the usual presence of two viable arteries that join together intracranially, so that if one became compromised, the contralateral artery could compensate adequately; and (3) the slow development of luminal compromise by atherosclerotic plaques allowing time for collateral development…Infarcts in patients with VAO disease were mostly attributable to artery-to-artery embolism arising from the ECVA
- …Hypoperfusion related to VAO occlusive lesions was usually transient causing brief spells of dizziness, veering, visual blurring, and ataxia. Attacks were self-limited probably reflecting reconstitution of the ECVA distal to the occlusion
- …The closer an artery is to the brain, the more likely that occlusion will lead to brain infarction
- …The patients with severe multifocal disease most often had benign courses usually characterized by multiple TIAs but few serious strokes
- …[in basilar artery disease] Some had headache and episodic TIAs during the weeks preceding an acute stroke
- "…The case mix of our patients with BA disease likely included more patients with less severe ischemia than in other reports…We evaluated more patients with minor posterior circulation ischemia using presently available noninvasive vascular and brain imaging than was possible in the past. Undoubtedly, this imaging led to discovery of BA disease in many patients who would likely have not been exposed to catheter angiography in the past so that BA disease would have been missed…"
- …The pathology within penetrating arteries consists of lipohyalinotic disruption of the arterial lumen."

"This report documents the frequent coexistence of multiple arterial constrictive lesions, most often involving the ICVAs bilaterally, often with accompanying BA and ECVA stenosis. Prior reports contain hints of this group of patients although none describes this group in detail.[6,76] TIAs dominated the clinical findings in these NEMC-PCR patients. Few had severe strokes despite months or years of TIAs. The most frequent TIA components were dizziness, faintness, visual blurring, and ataxia."

Population studies

Marquardt *et al*. in their population study of 2009 from Oxford, England in patients with VBI imaged with 1.5 T MR angiography, found that there was a 45% risk of recurrent stroke in 90 days from presentation.[86] It is quite possible that the NEMC-PCD Registry in entering patients up to 6 months after symptoms missed these people in their cohort they studied.

Observation #10: The extensive studies by Caplan et al., of the NEMC-PCR population of patients,[30,33,34,63] have provided a treasure of information about PCD in that selected population and are a benchmark for the analysis of PCD.[30,34] As Caplan, himself, has stated, PCD represents subsets of populations with different courses of disease.[32] It is obvious that their sample of patients does not reflect the subset of patients seen by the neurosurgeons in the 1980s for vascular reconstruction of the posterior circulation in patients refractory to all medical management.[18,73,74,113,115] Caplan and his colleagues continue to write about this cohort of patients they collected. Yet, the NEMC-PCD Registry still represents a biased sample of the universe of patients with PCD

2000–2017

Randomized drug trials, IVtPA, and interventional approaches to PCD and basilar artery occlusion

Randomized drug trials

From 2000, there were a number of drug treatment studies performed using CT angiography and MR angiography to evaluate CVD. These studies were devoted principally anterior circulation disease[84] or mixed with AC and PC patients,[39,50] and some believe the treatments for the AC and PC should be the same.[109]

Observation #11: These drug studies cannot be used as definitive guides to medical therapy for PCD, specifically. Also, it is clear that many of the patients had not been on maximal medical therapy prior to enrollment and so they cannot be compared to the surgical series in which patients had become unresponsive to medical management

Intravenous tPA

In 2005[109] Savitz and Caplan wrote, "The National Institute of Neurological Disorders and Stroke (NINDS) trial showed that intravenous administration of tissue plasminogen activator (IVt-PA) enhances neurologic recovery from ischemic stroke when administered within three hours after the onset of stroke, after brain hemorrhage has been excluded on the basis of CT."

In 2011 Report of the Specialty Societies on "Guideline on the Management of Patients With Extracranial Carotid and Vertebral Artery Disease: Executive Summary,"[26] the authors stated, "Although various medical, interventional, and surgical approaches have been developed for treatment of patients with vertebral artery disease, none have been evaluated in randomized trials. Despite the paucity of evidence applicable to patients with vertebral artery disease, we recommend that medical management follow the guidelines for those with disease of the carotid arteries."

In 2011, Sarikaya *et al*. reported that "no randomized controlled trial or Phase IV study investigated the safety and efficacy of IVT according to stroke territory and that "just 5% of patients from the National Institutes of Neurological Diseases and Stroke (NINDS) study had PCD, although approximately 20% to 25% of all ischemic strokes are localized in the posterior circulation."[107] Sarikaya *et al*. undertook a multicenter observational study to compare the safety and clinical outcome of IVT according to stroke territory.[107] Posterior circulation stroke (PCS) was defined as a symptomatic infarct in the vertebral, cerebellar, posterior cerebral or basilar arteries determined by CT or MR. No vascular imaging was done. Ninety-five patients had PCD out of 883 patients collected. Sixty-six patients with PCD had a 66% favorable outcome and 0% ICH while mortality was 9%. They showed that IV Aleptase (tPA) in acute PCS can be used with good results and low complications. Still, the vascular anatomy of the infarctions or carotid supply of the posterior circulation was not shown.

Lindley *et al*. used Aleptase (tPA) for acute ischemic stroke in the IST-3 trial and randomized 3035 patients with ACD and PCD to receive IVtPA. Only 246 patients were in the PCD category and 110 were treated with IVtPA. The authors concluded that "Among the types of patient in the Third International Stroke Trial, this secondary analysis did not identify any subgroups for whom treatment should be avoided."[82] Neither the details of the patients with posterior circulation infraction or imaging of the vascular anatomy were defined in their study. Their use of IVtPA appears generally helpful for patients presenting with PCS, but further imaging analysis of the Posterior Circulation would be necessary to define the location of the vascular pathology.

Observation #12: The evidence of the value of IVtPA for posterior circulation ischemia has been explored in limited studies and seemed to be of benefit in patient populations of PCS that were clinically but not angiographically defined. Results from the studies suggest that there is no harm to give iVtPA to patients with PCS, but no RCTs of IVtPA were reported. Given the evidence that symptoms may develop into a stroke quickly,[9,86] it is advised that a more detailed evaluation of the patient with PCD rapidly follow the IVtPA administration

Interventional treatments

At the beginning of the first decade of the 21st century there were numerous reports suggesting the promise of interventional treatments for PCD.[22,65,88,94] Also, there were a number of randomized interventional studies using stents of various types or angioplasty to treat stenoses in the vertebral basilar circulation and intracranial vessels from the vertebral origin up the VB system. Basically, the studies all showed a high recurrence of stenosis and up to a 25% procedure complication rate or other complications. The results in randomized and non-randomized trials were no better than medical management if not worse[3,26,38,43,44,47,52,57] using endovascular stenting or angioplasty vs. best medical therapy. Both approaches were used to achieve reperfusion, but neither medical or interventional approaches showed any difference in outcome. However, these studies had enrolled too few PCD patients to be of any significance and were performed early in the development of the newer more effective clot retrieval systems.[25,40]

From 2008–2014, major advances in removal of clots in large vessels of the anterior circulation were made. Badhiwala *et al*. summarized the results of "8 trials involving 2423 patients…including 1313 who underwent endovascular thrombectomy and 1110 who received standard medical care with tPA." In general, "among patients with acute ischemic stroke, endovascular therapy with mechanical thrombectomy vs. standard medical care with tPA was associated with improved functional outcomes and higher rates of angiographic revascularization, but no significant difference in symptomatic intracranial hemorrhage or all-cause mortality at 90 days."[21] This endovascular success was followed by reports of endovascular treatment of acute basilar artery occlusion (BAO).

New advances in the treatment of basilar artery occlusion

Basilar artery occlusion (BAO) was first described by Kubik and Adams in 1946.[80] Their patients presented

with rapid symptoms and signs of brain stem ischemia progressing to coma. Among all the studies reviewed in this paper BAO appears to be a separate category of PCD that new studies have shown are amenable to specific interventional treatment. During the last 6 years, interventional approaches have been used to treat basilar artery occlusions with some promising results. Shonewille *et al*.[110] wrote, "Treatment strategies for acute basilar artery occlusion (BAO) are based on case series and data that have been extrapolated from stroke intervention trials in other cerebrovascular territories, and information on the efficacy of different treatments in unselected patients with BAO is scarce." [Again, subsets of the universe of patients with PCD]. In the Basilar Artery International Cooperation Study (BASICS) which Shonewille *et al*. reported,[110] they analyzed 592 patients with BAO and treated them according to each physician's choice of either (1) antithrombotic treatment (AT) consisting of antithrombitic treatment only or systemic anticoagulation, (2) primary intravenous thrombolysis (IVT), including subsequent intra-arterial thrombolysis; 3) or intra-arterial therapy (IAT), which comprised thrombolysis, mechanical thrombectomy, stenting, or a combination of these approaches. Sixty eight percent of all the patients had a poor outcome. No treatment strategy was found to be superior to any other. The estimated time of BAO was taken as the time of onset of symptoms, which previous bypass surgical evidence[18] and recent clinical evidence[9,86] show is too late in the disease for successful treatment. For example, according to the authors, "Transient ischaemic attack (TIA) or minor stroke in the hours or days before the index event were not counted as the time of the occlusion but were recorded under the prodromal phase." In addition, "the reporting of symptomatic intracranial haemorrhage was done entirely on the basis of each investigator's judgment." The time of treatment with AT "was not recorded accurately" while those who received IVT were treated within 3 hours. The IAT group had the longest time to treatment and had the patients with the most severe deficits. Yet, "72% of patients treated with IAT had partial or complete recanalization of the basilar artery. Recanalization protected against poor outcome." There was a 67% patency rate after IVT treatment. Ninety-three (93%) of the patients who received AT treatment died or were dependent. The authors admit that the study was an observational one and that there was no protocol for all to follow. Most patients in the BASICS Registry received IAT.[110]

What the authors of this study failed to recognize is obvious from the surgical bypass studies on patients who failed medical therapy described previously.[18] (1) They achieved a high rate of recanalization with IVT or IAT. (2) As the surgical studies indicated, the later the treatment, the higher the mortality.[18] The investigators should have initiated diagnosis and aggressive treatment at the first onset of symptoms as reported subsequently by others.[91] And finally, (3) they did not recognize the success of what they had done and were overwhelmed by the bad results. Their study was an excellent start in the diagnosis and treatment of a complex condition.

Since that study, there have been other reports on successful reopening of the basilar artery or posterior cerebral arteries by endovascular thrombectomy and other treatments.[45,53,60,67,83,91,96,116,118,122] Gory *et al*.[67] reviewed the literature on all previous studies of stent retriever thrombectomy in BAO patients with stroke between November 2010 and April 2014. Including their own study of 22 patients using a stent retriever, there were 15 studies reported involving 312 subjects. The recanalization rate reached 81%, ICH 4%, favorable outcome in 42% and 30% mortality. In Gory *et al*.[67] series, all patients received IVtPA and were given endovascular treatment with the following conditions: Patients were eligible for mechanical thrombectomy (MT) if they (1) had a clinical diagnosis of acute stroke in the posterior circulation; (2) were admitted within 24-hour after onset of symptoms; (3) had a significant clinical deficit following physician evaluation (no National Institutes of Health Stroke Scale (NIHSS) limit); (4) underwent an MRI or CT before treatment (no pc-ASPECTS limit); (5) presented with acute basilar ischemia and BAO on MR or CT angiography. "In 5 out of the 6 patients [in the Gory *et al*. study] with a favorable outcome, recanalization was achieved more than 6hr after symptoms onset.

Another study reported in 2016 by Fahed *et al*.,[53] extending from 2006 and 2015, was a retrospective review that used different types of clot retrieval systems for opening acute basilar artery occlusions. "The overall successful recanalization rate… was 50% (17 of 34 patients). A good clinical outcome (mRS score 0–2 at 3-month follow-up) was achieved in 11 (32.3%) of 34 patients. The mortality rate at 3-month follow-up was 29.4% (10 of 34 patients). Patients treated with the Solitaire stent retriever and the ADAPT catheter had a higher recanalization rate (92.3% vs. 23.8% and a shorter mean …procedure duration (88 ± 31 minutes vs 126 ± 58 minutes, $P = 0.04$) than patients treated with older devices." Other devices have been tried with some success.[67]

Observation #13: So far, interventional treatments for PCD have only been successful in the removal of acute basilar artery thrombosis

2010-2017 – Recent advances in the diagnosis and treatment of PCD

Natural history of PCD-2000–2017

From the late 1990s to 2017, numerous papers reported on the natural history of subsets of patients with PCD. As expected the results vary considerably reflecting

the samples taken from the universe of patients with PCD.[59,70,99]

Given the tendency of Registries to produce selected samples of the universe of patients with PCD, there was a need for population based studies to give a more comprehensive view of patients with PCD.

Population Studies-Comparison of PC and AC of PCD

In 2009, Marquardt *et al*. collected patients with VBI from a population of 91,000 around the city of Oxford, England.[86] This population study more closely approaches an unbiased sample of the PCD universe of patients. They stated, "There have been no population–based studies of unselected patients with posterior circulation stroke, and there are no published data on patients with [PC] TIA". In their study of this large unselected population of patients they chose those patients with VBS and carotid stenosis (CS) who had a greater than 50% stenosis in their respective circulations using MRA imaging for the VBS patients and ultrasound for the CS patients to determine the percentage stenosis in the two populations. Twenty-six percent of the VBS patients presented with TIAs or mild stroke whereas 11.5% of the CS group were symptomatic. "In patients with posterior circulation events, 50% vertebral and basilar artery stenosis was associated with multiple transient ishaemic attacks at presentation (22% for VBS versus 3% for CS)… and with a significantly higher 90-day risk of recurrent events…reaching 22% for stroke and 46% for transient ischaemic attack and stroke in the VBS patients."[86] "The prevalence of symptomatic 50% vertebral and basilar artery stenosis is greater than that symptoms in the 50% Carotid Stenosis group and is associated with multiple transient ischemic attacks on presentation and high early risk of recurrent stroke.[86]

Multiple TIAs with stroke were higher with VBS than with CS, and those with VBS >50%, had a high early recurrent TIA and Stroke rate of 46% in 90 days after presentation. Others note a recurrence rate of 10–15% per year.[8] Marquardt *et al*. stated that…all the previous (reported) imaging studies on VB stenosis were done in selected cohorts, and none report data on prognosis."[86] They also noted that there is very limited data on the optimal management of large artery atherosclerosis in posterior circulation stroke.[86]

Observation #14: It appears that not only does the PC differ pathologically from the AC, but the diagnosis of its abnormalities is more difficult, interventional treatments are not successful with the exception of BAO, while surgery for those who fail medical management remains as a successful alternative that has been ignored. In addition, the clinical presentation of PCD symptoms is higher and develops faster into a stroke than of ACD stenosis

Thus, by 2010, after 70 years of studying PCD, we have multiple papers analyzing subsets of a universe of patients with PCD, which all have different natural histories evaluated by different methodologies. Regardless of all of this information about posterior circulation disease, about which far less is known that that of the anterior circulation,[30,59] it is apparent that each patient must be evaluated individually and completely, and then open-minded decisions need to be made from limited data accumulated over 70 years on what is the best management. It is obvious that these reported samples of patients do not reflect the subset of patients seen by neurosurgeons in the 1980s for vascular reconstruction of the posterior circulation in patients refractory to all medical management.[18,73,74,113,115] It is also apparent that PCD includes subsets of patients with disease courses that differ and require specific treatments as first described by Caplan in 1975.[32]

Quantitative measurement of flow in the posterior cerebral circulation and its relation to symptoms of PCD

Charbel *et al*. published several studies showing a highly accurate estimate of the blood flow in large and small cerebral vessels including the posterior circulation.[9,123,124] "Preliminary studies indicate that stroke risk in VBD is strongly related to hemodynamic compromise, which can be measured noninvasively using Quantitative Magnetic Resonance Angiography, (QMRA)."[8] Caplan has hypothesized that cerebral hypoperfusion in the PC occurred in patients with large vessel stenosis or occlusion.[119] Emboli from washout of the distal circulation has been also been hypothesized as a proposed mechanism of producing stroke in this compromised circulation.[31] Hypoperfusion increased the occurrence of thrombi and decreased the washout of emboli. Hypoperfusion at embolization occurred together and complimented each other.[119]

A pilot study of management was performed to determine if a sample of symptomatic patients with VBD can be selected for different treatment options based on QMRA evaluations of cerebral blood flow.[6] MR and IA cerebral angiography was performed in all patients. Forty-seven patients with >50% vessel stenosis were selected for the study. QMRA was performed in all patients. The basilar and posterior cerebral arteries were selected for measurement of flows. Those with normal flows were treated medically. Those with less than 20% of normal flows were determined to have low flow and treated with medical, interventional, or surgical therapy. Thirty-one patients had normal flows and had 100% stroke free survivals or 97% stroke/TIA free rate per person per year. Among those 16 patients with low flows who had medical treatment, they had a 71% event free stroke survival and a 53% stroke/TIA ischemic event free survival, a significantly higher risk rate than the medically treated "normal flow" group. Of the remaining 12 patients with low flow who underwent interventional treatment, or

surgery, 3 had endovascular treatment, either angioplasty or stenting. The other 9 patients underwent reconstructive cerebrovascular surgery, consisting of bypasses or vertebral carotid transpositions. This group had an 82% event free survival rate.[6] In patients identified with low flows in the VBC, their course could be altered if invasive treatments were instituted to normalize their flows.

In a subsequent multi-institutional blinded RCT of medical management only,[7] the results at 12 and 24 months were tabulated among 72 participants with recent VB TIA or stroke and 50% or more occlusion in the vertebral and or basilar arteries. All patients had IA angiograms. Patients with unilateral vertebral stenosis or occlusion were excluded from the study. Eighteen of 72 (18/72) or 25%[7] had a low flow status and had a risk of future stroke of 22% to 30% at 12 and 24 months. For the normal flow group, the 12 and 24-month risk of stroke was 4% and 13%, respectively.[7] "The primary end point for the study was fatal and nonfatal ischemic stroke in the VB territory, defined as new neurologic symptoms or signs localizing to an area of the brain supplied by the VB arterial system lasting at least 24 hours or lasting less than 24 hours but associated with a new infarct on computed tomography or magnetic resonance imaging." During follow-up, the primary end-point occurred in 5 of 18 patients (28%) with low distal flow status and 5 of 54 patients (9%) with normal distal flow status. This result translated into a significantly higher risk of subsequent stroke in the low distal flow status group.

Observation #15: This RCT provides data on the natural history of a selected group of patients with VBI evaluated with QMRA. The results show that those with low flows in the PC have a significantly higher risk of stroke than those with normal flows.

A recent publication from the same group indicates that the blood flow in cerebral vessels decreases with age adding another factor to the anatomical variants in the Circle of Willis, and the pathological changes that develop in these vessels that can contribute to PCD.[5] For the first time since the report of Reivich *et al*. in 1961 of the subclavian steal syndrome that measured blood flow in the vertebral artery of symptomatic patients, we now have a means of assessing posterior circulation cerebral blood flow and translating that data into management decisions.[2,101]

On the contrary, Savitz and Caplan "in the NEMC-PCR, 13 of 407 (3%) patients had hemodynamically sensitive ischemia, most commonly caused by bilateral intra-cranial vertebral-artery occlusive disease, and they had multiple brief episodes of dizziness, veering, perioral paresthesias, and diplopia."[109] Weren't these patients who needed reconstructive vascular surgery? What was their long-term outcome? We do not know. [In a personal communication to Dr. Ausman, Caplan stated, "in those whose symptoms lasted > 6 months without a stroke, none developed a stroke later. Many were followed for 10 years and none had a disabling stroke."]

Observation #16: Thus, a diagnostic test now exists that can help select patients for medical or surgical treatments for PCD

Early symptoms to recognize PCD

Throughout the 70 years, which this review covers, many studies have reported that patients with PCD can present with symptoms that do not fit the classic pattern of symptoms or signs involving the brain stem. Recent studies show that vertigo or hearing loss alone can be early symptoms of PCD.[42,79,81]

Paul *et al*. from the Oxford group prospectively studied a series of 275 patients from a population based group with vertebral basilar territory stroke to learn the symptoms they had 90 days preceding their stroke.[97] The authors worked under the hypothesis that "Transient isolated brainstem symptoms (e.g., isolated vertigo, dysarthria, diplopia) are not consistently classified as transient ischaemic attacks (TIAs) and data for prognosis are limited. If some of these transient neurological attacks (TNAs) are due to vertebrobasilar ischemia, then they should be common during the days and weeks preceding posterior circulation strokes. We aimed to assess the frequency of TNAs before vertebrobasilar ischaemic stroke."[92]

Those symptoms included (1) isolated vertigo, (2) vertigo with nonfocal symptoms, (3) isolated double vision, (4) transient generalized weakness, (5) binocular visual disturbance as transient neurological attacks (TNA) in the vertebrobasilar territory. They also compared this population with 759 patients with carotid territory strokes. "Of all, 59 TNAs preceded (median 4 days, range: 1–90 days) vertebrobasilar stroke, only five (8%) fulfilled the National Institute of Neurological Disorders and Stroke (NINDS) criteria for PC TIA. The other 54 cases were isolated vertigo (n = 23), non-NINDS binocular visual disturbance (n = 9), vertigo with other non-focal symptoms (n = 10), isolated slurred speech, hemisensory tingling, or diplopia (n = 8), and non-focal events (n = 4). Only 10 (22%) of the 45 patients with isolated brainstem TNAs sought medical attention before the stroke and a vascular cause was suspected by their physician in only one of these cases.

Some reported symptoms as long as days, weeks, months, and years before their infarct and that their symptoms gradually progressed into PCD.[2,80] Others had shorter pre-stroke times of weeks.[97] These symptoms were 15 times more frequent in the posterior circulation than the anterior circulation.[97]

Savitz and Caplan found less than 1% of their patients in the NEMC-PCD Registry had only one presenting symptom or sign[109] perhaps reflecting a different patient population selection.

Observation #17: These observations of the early appearance of the pre-VBS symptoms are troubling and mean that PCD symptoms can occur singly and very early in the presentation of PCD. Neurologists need to see these patients early to prevent PCD. Education of emergency room physicians and neurologists about the early symptoms of PCD is important to implement prevention of PCD stroke. Again, a significant difference was found between the AC and the PCD in the variable types of presenting symptoms and the rapidity of onset of stroke in the VBC compared with the AC

NEW IDEAS IN THE FUTURE FOR PCD

New ideas and personal observations-7T MR Angiography

In another study published in 2014 in Japan, Sato *et al.*[108] used the 7.0T magnet and 7.0T MRA to demonstrate a small tentorial artery feeding a proximally occluded basilar artery in a patient with PC infarcts, VBI and orthostatic dizziness. The detail shown by the 7.0T MRA was superior to that of an intra-arterial digital angiogram. The patient then had a STA to PCA bypass and his symptoms resolved. "Angiography demonstrated that the entire posterior circulation was perfused via an anastomosed STA-PCA."[108] Other studies support the value of 7T MRA in visualizing the cerebral circulation.[46]

Collateral circulation to the brainstem

In unpublished observations on direct surgery in a patient with an atheroma of the basilar artery, Ausman and his colleagues in unpublished observations found on isolating the diseased basilar artery with temporary clips, that upon removal of the atheroma, blood flowed from the small perforators from the brainstem into the endarterectomized basilar artery. This observation is the opposite of what we have been taught for decades that the perforators off the basilar artery are end arteries. From this observation in a live patient, that conclusion is incorrect. The observation explains why people with extensive occlusion of the basilar artery can survive with minimal or no symptoms because of the collateral circulation through and around the brain stem. Detailed cerebral angiography and even 7T MRA will become necessary standard to evaluate patients with PCD.

Arterial spin labelling in neuroimaging for blood flow determination

"Arterial spin labeling (ASL) is a magnetic resonance imaging technique for measuring tissue perfusion using a freely diffusible intrinsic tracer. As compared with other perfusion techniques, ASL offers several advantages and is now available for routine clinical practice in many institutions. Its noninvasive nature and ability to quantitatively measure tissue perfusion make ASL ideal for research and clinical studies. Recent technical advances have increased its sensitivity and also extended its potential applications."[98] Specific arterial distributions and collateral flow can be imaged.[117,120]

Intracranial vertebral endarterectomy

In another study, Uschold *et al.* performed an endarterectomy of the vertebral artery at C1 extending intradurally. They could not remove the plaque but applied a patch graft to enlarge the artery lumen and then treated the patient with antiplatelet agents.[95] Ausman *et al.* reported 6 patients in which a vertebral artery V3 portion was endarterectomized and only 2/6 patients maintained a patent artery.[17] (The patch angioplasty with intense antiplatelet treatment post operatively appears to be a procedure worth further study.)

Vertebral carotid transposition: A new series 2015

In 2015 Rangel-Castilla *et al.* reported a series of 22 patients who were refractory to medical management and who were treated for proximal vertebral artery stenosis with a vertebral carotid transposition procedure from 2005–2013. They reported a 4.5% complication rate and 4.5% restenosis rate in 9-month follow up. They state, "Despite the optimization of medical therapies and lifestyle modifications, a select subset of patients with posterior vascular circulation insufficiency remains," echoing the theme of this review. They point out the failure of endovascular treatment in this location.[100]

EDAS for cerebral ischemia

In another promising area of study, Gonzalez has used the EDAS procedure laying the STA on the cerebral cortex to supply circulation to the brain in patients with MCA Stenosis or occlusion. So far his results have been very positive in showing that this therapy is superior to medical management.[66] Reconstruction of the posterior circulation vessels has been described by Ausman *et al.*[13,15,19,20]

Etiologic causes and recommendations for the diagnosis of PCD

From the pathology studies reviewed above, the causes of VBI or PCD were atheroma and stenosis limiting flow,[32,36] arterial clot and arterial to arterial embolization,[32,36] cardiac emboli in 9% of the patients,[36] branch occlusions by atheroma,[32] and hemodynamic vascular insufficiency as speculated in the pathology reports[32,51,80,111] and proven by the subclavian steal discovery and measurements.[101] Caplan stated that the critical period for deficit acquisition is at the time of the occlusion and depends upon the collateral circulation and presence of distal embolization.[28] The stage was set for new surgical advances in the treatment of cerebrovascular disease.

The conclusions that can be drawn from these studies are:

- Detailed angiography or imaging is needed to show the lesions in the VBC,[32]
- Artery to artery emboli are more common than cardiac emboli,[36]

- Angiography must show entire cerebrovascular circulation in all 4-vessel systems and the collateral circulation to the VBC[10,28,32,111]
- There are flow related causes of PCD[32,51,80,111] and
- This information should provide an opportunity for different therapeutic options in the treatment of PCD.[32]

To complicate the picture of the cause of symptoms of PCD, Caplan hypothesized that atheromas obstructing major vessel branches occurred.[32] In addition Voetsch *et al*. postulate that the low flow in the compromised VB system prevents the washout of emboli.[119] Cloud and Markus[41] using a Doppler sonography found that many presumed micoemboli were released distal to an occlusion, which may account for additional symptoms. Yet, there is no proof that these sonographic changes are diagnostic of emboli. Surgical studies on patients who failed medical therapy do not report continuing symptoms after successful bypass surgery casting doubt on the microemboli hypothesis.[18,74,115]

RECOMMENDATIONS FOR FURTHER STUDY OF PCD

A. It must be recognized that PCD differs from ACD
   a. First emergency room physicians and neurologists should be aware of the early non-specific symptomatology of PCD, which leads to a more rapid development of stroke than ACD.
   b. All such patients should be referred to neurologists with these symptoms so that a full neurological assessment can be done knowing that PCD can have rapid and devastating outcomes.
   c. Should the MRA and CTA screening test be inadequate or show stenosis of the VBC, IA angiography should be performed.
B. All such patients should be added to a National Registry and followed.
C. Patients who are not responsive to medical management should be referred to centers where vertebral artery surgery or posterior circulation revascularization can be performed. Since neurosurgeons with these skills are diminishing in numbers, which would mean that these patients should go to selected Comprehensive Stroke Centers.
D. Centers with QMRA imaging should be among those where patients with PCD are referred.
E. Patients with loss of one vertebral artery from trauma, dissection, or other causes should be studied as a subset with QMRA on a regular long-term basis to determine long-term risks of loss of one vertebral artery. It is important to remember that 65% of people have abnormalities in their circle of Willis.
F. Patients with BAO should be considered for endovascular thrombectomy if the expertise is available and studies show its value.
G. Since there is little evidence on the natural history of patients with PCD, precision personalized therapeutic decisions should be made on each patient and their course followed.
H. Those patients, who are refractory to maximal medical therapy, should be referred for consideration of surgical treatment as a subset to PCD at high risk for stroke.
I. It is hoped that from the Registry that subsets of patients can be followed and defined therapies established.

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ABBREVIATIONS

AC- Anterior Circulation
AICA-Anterior Inferior Cerebellar Artery
ASL- Arterial Spin Labeling
AT- Antithrombic therapy
BAO- Basilar Artery Occlusion
CVD- Cerebrovascular Disease
DSA- Digital Subtraction Angiography
EC-IC- ExtraCranial- Intracranial
ECVA- Extracranial Vertebral Artery
EDAS- Encephaloduroarteriosynangiosis
IA- Intra-arterial
ICH Intracerebral Hemorrhage
IVT- Intravenous Therapy
IVtPA- Intravenous Tissue Plasminogen Activator
mRS- Modified Rankin Score
MT- Mechanical Thrombectomy
NINDS- National Institute of Neurological Disorders and Stroke
NEMC-PCR- New England Medical Center Posterior Circulation Registry
PC- Posterior Circulation
PCA- Posterior Cerebral Artery
PCD- Posterior Circulation Disease
PICA-Posterior Inferior Cerebellar Artery
QMRA- Quantative Magnetic Resonance Angiography
RCT- Randomized Controlled Trial
SCA- Superior Cerebellar Artery
STA- Superficial Temporal Artery
TIA-Transient Ischemic Attacks
TNA- Transient Neurological Attacks
VAO-Vertebral Artery Occlusion
VBD- Vertebral Basilar Disease