Cognitive and Physical Performance in Patients with Asymptomatic Carotid Artery Stenosis and Occlusion

by

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Abstract

Cognitive and Physical Performance in Patients with Asymptomatic Carotid Artery Stenosis and Occlusion.

This dissertation project presents a review of the anatomy and functional relationships of the circulatory territory of the internal carotid artery, and considers the functional changes that can occur when there is disease within this system. The project has two specific aims which are addressed in two articles. The first specific aim is to determine if persons with asymptomatic carotid artery disease (high moderate stenosis through occlusion) demonstrate deficits in cognition and on physical performance measures. The second specific aim is to determine if there is a correlation between the cognitive measures and the instrumental activities of daily living in these asymptomatic patients.

In the first article, the purpose of the study was to determine if patients with asymptomatic carotid artery stenosis and occlusion demonstrate deficits in cognitive and physical performance. The relationship between cognitive measures and performance of instrumental activities of daily living was examined. Thirty-nine patients with asymptomatic carotid artery stenosis of moderate and severe degrees, or occlusion were tested. Cognition was assessed via the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and the Executive Interview (EXIT). Physical performance was assessed via the Physical Performance Test (PPT), and the Lawton Instrumental Activities of Daily Living. Deficits in cognitive function were found on the RBANS for all levels of stenosis and occluded subgroups in the domains of visuospatial/constructional and delayed memory, in the moderate stenosis subgroup in immediate memory, attention and visuospatial/constructional, and in the severe subgroup in all domains

except language. There were no significant findings on the EXIT. Decreased performance on the PPT was identified in all 3 subgroups. The Lawton IADL did not identify any decrease in IADL performance.

The second article included a more definitive examination of physical performance. Physical performance was assessed via the 9-item and 7-item Physical Performance Test (PPT). Individual tasks were also timed. Patients with asymptomatic carotid artery stenosis and occlusion demonstrated less than optimal performance on the PPT (9-item, 27/36; 7-item 21/28). Simulated eating was the slowest task to perform for the patients with moderate stenosis.

Deficits in cognitive function were found in this observational study of patients with asymptomatic carotid artery stenosis and occlusion. Additionally, patients exhibited changes in function as indicated by their performance on the PPT. This may be indicative of preclinical disability, and a potential symptomatic status of the patient. Both articles demonstrate that asymptomatic patients may not be truly asymptomatic. This potential change in status needs to be considered as patients are being evaluated for interventions to manage their carotid artery disease.

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My victory is not behind me
I keep on pressing forward to my goal
Your Word is always right here to remind me
To keep on pressing forward to my goal.
Be strong, Be courageous
For the Lord has won the victory

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Table of Contents

List of Tables

List of Figures

I. Introduction

Stroke is a major health care problem in the United States with an annual incidence of more than 700,000, and is the leading cause of adult disability amongst Americans.[1,2] Stroke prevention has become a major concern in health care. One population that has been identified as persons at possible risk for stroke is persons with carotid artery disease, stenosis and occlusion. Persons with carotid artery disease are described as being symptomatic or asymptomatic. However, in the case of asymptomatic persons, the question has been raised as to whether persons with asymptomatic carotid artery stenosis and occlusion truly are asymptomatic. Often discovered as an incidental finding, persons with carotid artery disease who claim to be asymptomatic may actually be unaware of or in denial of their possible symptoms. This problem has led to the question that is the focus of this dissertation project, which is to determine if asymptomatic persons with stenotic or occluded carotid arteries are truly asymptomatic.

After observing patients with carotid artery disease in the neurosurgery clinic at the University of Pittsburgh over the last two years, it has been noted that many patients with carotid artery stenosis and occlusion have impairments. Significant others of the person and clinical examination have revealed that the persons with symptomatic and asymptomatic carotid artery disease are experiencing symptoms which may serve as warning signs of a potential stroke, such as brief periods of confusion, word-finding difficulties, and forgetfulness. There is some controversy about the neurosurgical management of at least a subgroup of these symptomatic occluded persons, who are believed to have hemodynamically compromised cerebral blood flow depending upon the physiology of their carotid artery occlusion.[3-6]

In this project, in asymptomatic moderately and severely stenotic, and occluded persons, an attempt will be made to take a detailed look at the person's function in both the cognitive and the physical domains. Some of the subtle changes that may be occurring in persons with carotid artery disease may be detected through inexpensive and noninvasive assessments of cognitive and physical functioning. Also, the relationship between the patient's cognitive performance and ability to complete instrumental activities of daily living will be examined. Data about the persons cognition and physical functioning will aid in planning future care of the patient based on the presence of any impairments noted that might be influencing the person's quality of life.

II. Statement of the Problem

There is one study available that reports cognitive function only,[7] and no study that reports physical function of asymptomatic patients with carotid artery stenosis and occlusion. In asymptomatic patients with stenosis, the stroke risk has been observed to be relatively low.[8,9] However, there is an increase in the risk of stroke when the degree of stenosis is more severe.[10] Additionally, it is controversial as to whether asymptomatic patients with carotid artery occlusion are at risk for stroke.[11-15] However, if there is reason to believe that asymptomatic patients are really not asymptomatic, then a low stroke risk may not be an accurate prediction for some patients. In a related patient population who are considered at risk for stroke (patients with asymptomatic cerebral aneurysms) Weibers et.al. identifies that asymptomatic patients demonstrate impaired mental status on a Mini-Mental State Examination or a Telephone Interview for Cognitive Status, both of which indicated a serious cognitive abnormality at 30 day and one year follow-ups.[16] This was the first time that deficits with supposedly asymptomatic patients with aneurysms were documented. It is suspected that patients with asymptomatic carotid artery disease may show a similar presence of undetected deficits. Therefore the purpose of this research project is to perform a more detailed assessment of cognitive and physical functional abilities in the patient with asymptomatic moderate or severe carotid artery stenosis and occlusion. The second part of the project will consider the relationship between the patients' cognitive function and their ability to perform instrumental activities of daily living. Cognitive skills from six cognitive domains and physical functional performance will be assessed.

The following sections will describe: 1) the carotid circulation to the brain and its branches, 2) the relationships of the circulation to the anatomy of the brain and the functions associated with these regions, 3) the pathology of carotid artery disease including both carotid artery stenosis and occlusion, 4) the characteristics of patients with asymptomatic and symptomatic carotid artery stenosis and occlusion and their risk for stroke, and 5) the assessment tools chosen to use for the evaluation of cognitive and physical function in patients with asymptomatic carotid artery stenosis and occlusion.

2.1. The Circulation of the Carotid Artery System

The circulation to the brain consists of a network of arteries developed to feed the anterior and the posterior portions of the brain. The internal carotid artery (ICA) is the primary blood supply to the anterior brain circulation. (Figure 1)

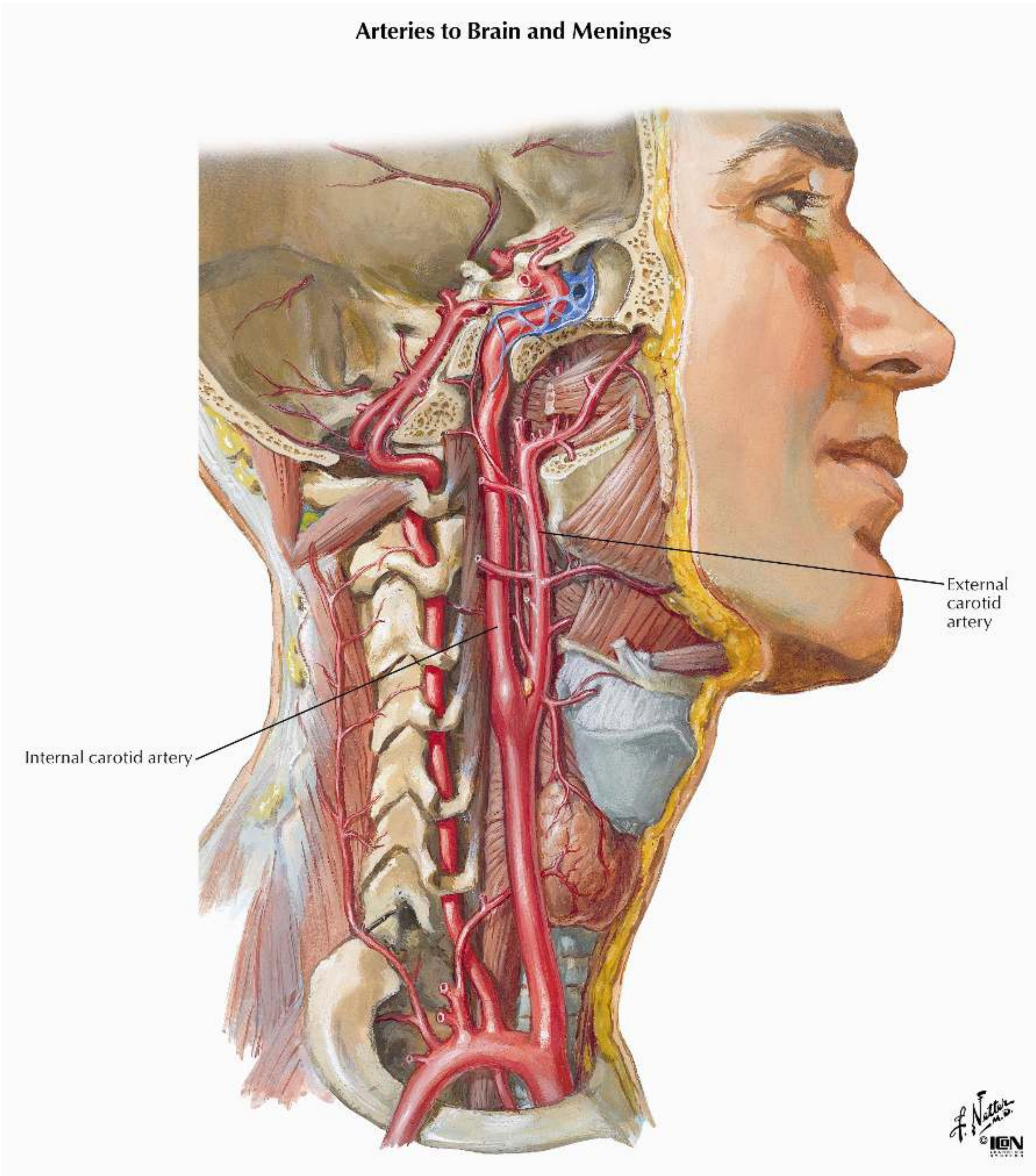

Figure 1: Circulation of the Internal Carotid Artery.

Modified from: [Netter FH: Atlas of Human Anatomy, 2nd ed., East Hanover, New Jersey, 1997, Novartis, Netter illustrations used with permission from Icon Learning Systems, a division of MediMedia USA, Inc. All rights reserved.]

The internal carotid artery and the external carotid artery branch off from the common carotid artery in the neck. This artery enters the brain through the carotid canal in the petrous portion of the temporal bone in the bottom of the skull. The cerebral segment of the ICA terminates into the middle cerebral artery (MCA) and the anterior cerebral artery (ACA), and also gives off the major branches of the opthalmic artery, superior hypophysial artery, the posterior communicating artery and the anterior choriodal artery.[17] (Figure 1)

In some situations, the posterior cerebral artery will be derived from the ICA, coming off an enlarged posterior communicating artery, however this is not typical.[18] The branching arteries and corresponding areas of the brain that receive blood supply from these main ICA branches (Figure 2) include the:

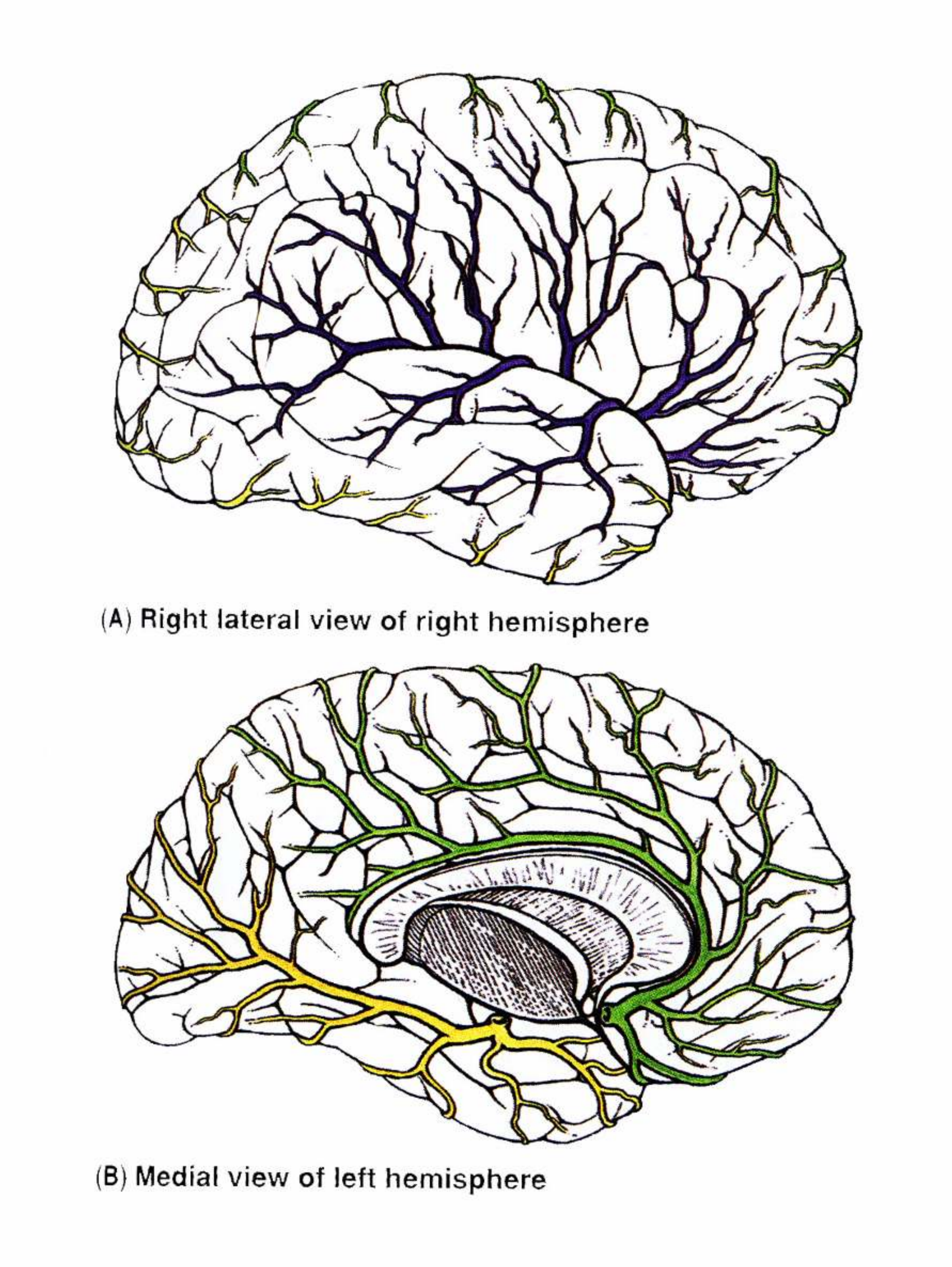

Figure 2: Portions of the Brain Supplied by the Anterior, Middle and Posterior Cerebral Arteries.

(Anterior – Green, Middle – Purple, Posterior – Yellow) [From Moore KL, Dalley AF: clinically oriented Anatomy 4th ed., Baltimore, 1999, Lippincott Williams and Wilkens, with permission]

- Anterior Cerebral Artery (ACA) – The medial surface of the cerebrum, superior border of the frontal and parietal lobes.
- Middle Cerebral Artery (MCA) – Most of the lateral surface of the cerebral hemispheres including the lateral frontal lobe, temporal lobe – superior and lateral portions, and the deep structures of the frontal and parietal lobes.
- Posterior Cerebral Artery (PCA) (not typically) – The occipital lobe and inferior and medial portions of the temporal lobe.

Also important to the blood supply to the brain are the lenticulostriate arteries, which are penetrating branches from the larger cerebral arteries, and supply the basal ganglion and internal capsule.[18] The perforating branches of the posterior cerebral artery supply the thalamus.[18]

2.2. Anatomic and Functional Relationships

There has been evidence accumulating in the cerebrovascular literature that in patients with carotid artery disease, a transient ischemic attack (TIA) or a stroke can occur. In cases of carotid artery stenosis and occlusion, this may be due to either 1) an embolus formation in an artery that would disrupt blood flow in the distal artery, or 2) compromised hemodynamic cerebral blood flow.[3-6,19-24] Currently, these investigations are being preformed from a physiologic perspective with the evaluation and measurement of cerebral blood flow through technology such as positron emission tomography (PET), single-photon emission CT, transcranial doppler studies, or stable Xenon CT.[22] The outcome measures in many of these studies consist solely of the occurrence of a TIA or a stroke.[3,5,21,25,26] At the present time there is one article in the literature that addresses how patients with asymptomatic carotid artery disease function from a cognitive perspective.[7] The researchers concluded that cognitive dysfunction is more common in patients with severe stenosis affecting the left carotid artery.[7] No documentation of function of asymptomatic persons with carotid artery disease from the physical perspective has been found. It is important to relate the areas of the brain that may be demonstrating a disruption of blood flow due to the carotid artery disease, and the functional attributes of these areas, with the patient's actual functional performance. Figure 3 describes these relationships:

Figure 3: Relationships of Blood Supply, Brain Area and Function[17]

ARTERY	BRAIN TISSUE SUPPLIED	FUNCTION OF THIS AREA
ANTERIOR CEREBRAL ARTERY	Medial surface of the cerebrum	Frontal lobe- Discrete lower extremity movements, gross movements, emotions Parietal lobe – Somatosensory localization lower extremity Temporal lobe-Fear/anxiety; short-term memory Occipital Lobe – Contralateral visual field
	Superior border of the parietal and frontal lobes	Proximal lower extremity and trunk voluntary movements and sensation
MIDDLE CEREBRAL ARTERY	Lateral frontal and temporal lobes	Frontal lobe – Discrete voluntary movements, eye movements, motivation, planning, judgement Temporal lobe – Long term memory
	Superior temporal lobe	Bilateral hearing and possibly new memory
	Deep frontal and parietal lobe	Language production, taste, discrete voluntary movements of the jaw, mouth and tongue, somesthetic sensations
POSTERIOR CEREBRAL ARTERY	Occipital lobe	Vision and visual association
	Inferior and medial temporal lobe	Emotions, behavior and memory

Clearly cognitive function and motor and sensory physical function may be in jeopardy in patients that have jeopardized cerebral circulation from carotid artery disease. It is the intent of this dissertation project to evaluate patients with asymptomatic carotid artery moderate and severe stenosis and occlusion based on their functional abilities with respect to the cortical areas served by the main internal carotid artery branches, in particular, the anterior cerebral artery and the middle cerebral artery. Therefore cognitive measures that will screen patients for deficits in the domains of short-term memory, long term memory, attention, language, problem-solving, and association functions of visuospatial/constructional nature are included in the screening. This project will determine if these functions are intact or if there are deficits. If there are identified deficits, then to determine if there is a relationship between the deficit and the amount of carotid artery disease (moderate stenosis, severe stenosis, or occlusion) is of interest. Additionally, a relationship between the side of the carotid artery disease and the domain of cognitive deficit is of interest, since some of the cognitive functions are attributed to one side of the brain more than the other.[27] For example, language is primarily mediated via the left cerebral hemisphere, and attention and visuospatial/ constructional functions are more attributed to the right hemisphere.[27] Additionally, physical measures that parallel activities that are important in daily life will be tested to assess physical function. Also, performance on the instrumental activities of daily living, such as taking medications, meal preparation, and answering the phone will be compared to the individual's cognitive function.

2.3. Carotid Artery Disease

The pathology behind carotid artery stenosis, which can lead to occlusion, is injury to the artery wall, especially the intima, due to the process of atherogenesis. During this process there is focal injury to the vessel wall with a breakdown of the connective tissue surface. This breakdown stimulates blood platelets to aggregate inside the arterial wall. During this, there is a release of certain substances including lipids that will induce endothelial cell proliferation and form a fibrous plaque that protrudes into and can completely block the blood vessel lumen. (Figure 4)

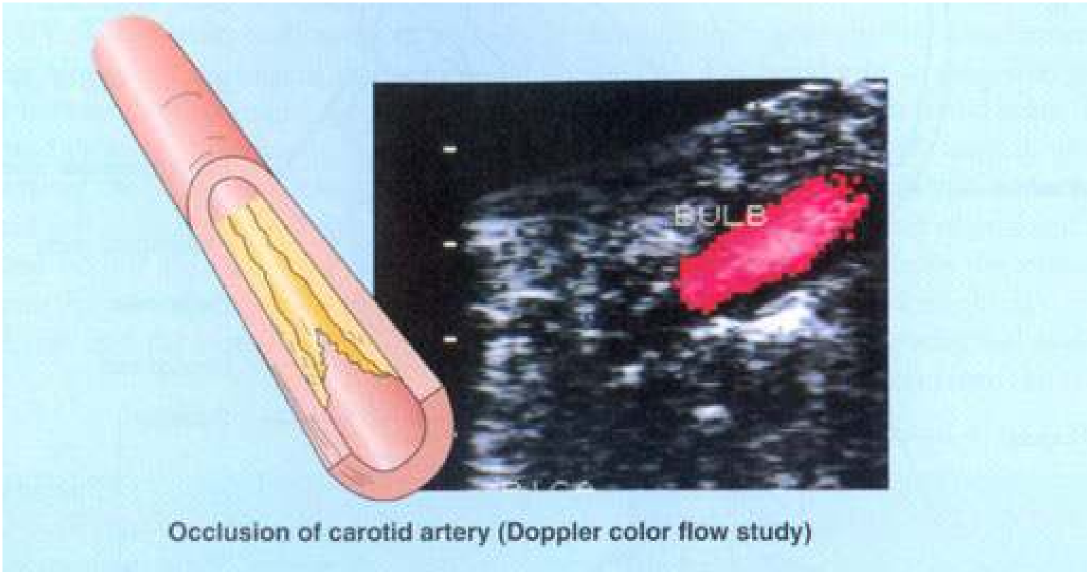

Figure 4: Occluded Carotid Artery.
[From Moore KL, Dalley AF: *clinically oriented Anatomy, 4th ed.,*Baltimore, 1999, Lippincott Williams and Wilkens, with permission]

Atherosclerotic plaque is most commonly found in the neck immediately after the bifurcation of the external and internal carotid arteries in the proximal portion of the internal carotid artery (ICA).[18] The other places where this atherosclerotic plaque is most frequently found include the proximal (near the point of exit from the ICA) middle cerebral artery, and within the vertebral and basilar arteries.[18] In arteries that are partially occluded, or stenotic, the atherosclerotic lesion can release emboli that can lodge in the distal arteries on the same side, resulting in a "carotid artery" ischemic stroke.[28] (Figure 5)

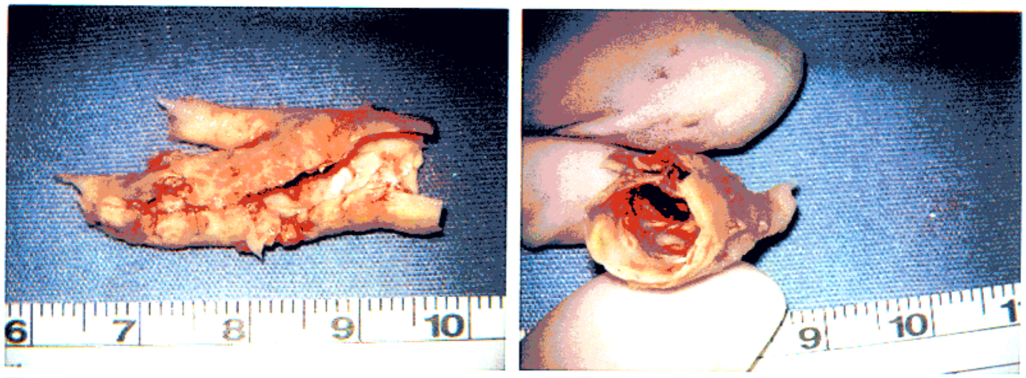

Figure 5: Ulcerated plaque removed from a patient with an asymptomatic carotid artery. [Courtesy of Dr. Howard Yonas, Department of Neurosurgery, University of Pittsburgh Medical Center, with permission]

A second complicating factor that places patients with stenosis at risk for stroke is the progression of stenosis to complete occlusion.[29] The result of decreased blood flow to brain tissue distal to this blockage in the artery can also lead to cerebral infarction by way of two proposed mechanisms; embolic sources, and hemodynamic compromise.

Blaser et. al followed patients with severe carotid artery stenosis who were symptomatic and scheduled for carotid endararectomy to determine parameters predictive of stroke recurrence, or carotid artery occlusion prior to the scheduled surgery.[30] They found that exhausted cerebrovascular reactivity as determined by a Doppler CO_2 test of the middle cerebral artery was predictive of disabling stroke in these patients with stenosis. Also, 12 of the 120 patients experienced progression of the stenosis to occlusion of the artery. However, in the absence of hemodynamic compromise of blood flow, occlusion was not associated with increased stroke risk.[30] Similar conclusions were drawn by Markus and Cullinane, who in patients with hemodynamic compromise, found risk for stroke in patients with carotid occlusion (6 %/year), and risk to a lesser extent in patients with severe asymptomatic carotid stenosis (1%/year).[24]

2.3.1. Symptomatic Carotid Artery Disease:

Transient Ischemic Attack (TIA) – The Common Symptom

In both disease processes of carotid artery stenosis and occlusion, a common symptom is recognized, the transient ischemic attack (TIA). The TIA, occurring in the carotid-middle cerebral artery territory, has been described with the most common symptoms of weakness, paralysis, numbness, tingling or heaviness, which tend to involve the opposite arm or leg or half of the face. It has been documented in symptomatic carotid disease that 40% of the cases will have monocular blindness.[31] Monocular blindness is described by patients as a gray-black shade or curtain that comes down over the eye, a fog, blur, or blindness in one eye.[32] The symptoms of a TIA are to last less than 24 hours and then resolve.[31] However, a revised definition has been proposed that suggests that a TIA is a brief episode of neurologic dysfunction with clinical symptoms that should last less than 1 hour with no acute infarction visible on imaging.[33]

As previously mentioned, in cases of carotid artery stenosis and occlusion the source of the TIA has been proposed to be from an embolic source, or due to hemodynamic compromise of the blood flow.[22,29,32,34-37] In a study by Pessin and others, the investigators identified that patients with both open carotid artery lumens (> 2mm) and tight carotid artery lumens (< 2mm or occluded) experience TIA's which included pure hemispheric symptoms, pure monocular blindness, or a combination of the two symptoms experienced separately from one another.[32] The mechanisms proposed by the authors for TIA's in this situation included: 1) cerebral embolism, 2) lacunar disease, and 3) transient carotid occlusion.[32] Barnett et. al. studied nine patients with carotid artery occlusion and determined that that their TIA's were a result of thromboembolism from the stump of the ipsilateral occluded carotid artery.[38] Embolic events causing symptoms have also been found in cases of carotid artery occlusion on one side and stenosis on the other side.[35] In these patients the investigators have recommended that carotid endarterectomy of the stenotic side may reduce the passage of the emboli from one cerebral hemisphere to the other and potentially reduce the risk of stroke.[35]

The hemodynamic explanation for the incidence of TIA's has also been suggested in cases of carotid artery stenosis and occlusion.[22,24,36,37,39,40] However in this situation, the symptoms have some potentially different manifestations. The most common different characteristic is described as limb shaking.[31,36,37,39,40] Limb shaking is a rhythmic involuntary movement of one or both extremities on the side opposite the pathologic carotid artery. The attacks are brief, and can resemble simpler focal motor seizures. In these patients, the compromised cerebral blood flow to the brain can be measured by positron emission tomography (PET), transcranial doppler, single-photon emission CT, or stable Xenon CT.[22,36,41-45] Klijn et.al found that venous stasis retinopathy (VSR) was another common symptom associated with a hemodynamic cause of decreased blood flow to the opthalmic artery (a branch of the internal carotid artery) in patients with symptomatic carotid artery occlusion.[46] In this study, one third of the 110 patients studied with carotid artery occlusion experienced monocular blindness. The researchers concluded that VSR is associated with an impaired blood flow state to the brain.[46]

In 1999, the American Heart Association Stroke Council published a supplement to The Guidelines for the Management of Transient Ischemic Attacks.[47] In this document, recommendations are outlined for the management of TIA's based on the latest medical evidence, with stroke prevention as the ultimate goal of the guidelines. The recommendations include: a) risk factor management, b) medical therapy, and c) surgical management. Within this document, the management of TIA's in patients with either carotid artery stenosis or carotid artery occlusion is discussed.[47]

2.3.2. Carotid Artery Stenosis - Symptomatic

Carotid endarterectomy (CEA) is now recognized as the "gold standard" for management of clinically significant carotid artery stenotic disease.[28,48,49] Clinical significance is the presence of symptoms such as the TIA previously discussed, retinal infarction, or a non-disabling ischemic stroke.[28] Clinical significance is also determined by the amount of stenosis of the internal carotid artery. In two landmark studies, the MRC European Carotid Surgery Trial, and the North American Symptomatic Carotid Endarterectomy Trial, arterial stenosis of 0-29% was considered mild, 30-49% low moderate, 50-69% high moderate and 70-99% severe.[28,49] In the case of mild and low moderate stenosis, the early risks of surgery outweighed any benefit over a 3-year follow-up, and surgical intervention is not a typically recommended course of treatment.[49] In high moderate stenosis, the recommendations have not been as clear. However, recent research on this population has shown that there is benefit of carotid endarterectomy surgery over medical management in the reduction of ipsilateral stroke rate followed for 5 years with a 22% medically managed group rate versus 16% CEA rate after 8 years of follow-up.[48,50,51] In severe stenotic cases, the risk of carotid endarterectomy surgery was significantly outweighed by the benefit of a reduced risk of stroke in the patients, a sixfold reduction in the European Carotid Surgery Trial, and a 17% risk reduction in the North American Symptomatic Carotid Endarterectomy Trial.[28,49]

2.3.3. Carotid Artery Stenosis – Asymptomatic

In asymptomatic carotid artery stenosis, the stroke risk has been found to be relatively low, and related to the degree of carotid artery stenosis.[8,10] Autret et.al. followed 242 patients with no neurological symptoms and carotid stenosis for an average of 29.4 months using an occurrence of a TIA or a stroke as the endpoint. The researchers concluded that patients with 0-50% stenosis had a crude annual stroke risk of .23%, in patients with 50-75% stenosis the crude annual stroke risk was 2.48%, and in patients with 75-99% stenosis, the risk was 1.71%. The researchers did not consider any of these findings to delineate a group of asymptomatic stenotic patients to have a major risk of stroke.[8] Norris et.al. also identified stroke risk in asymptomatic patients with varying degrees of carotid stenosis. In patients with stenosis ≤ 75%, the researchers concluded that risk was negligible (1.3%), and in patients with > 75% stenosis, there was an ipsilateral stroke risk of 2.5%.[10] In the patients with the more severe stenosis, the researchers recommended that consideration of a carotid endarterectomy for stroke prevention be considered.[10]

More recent research by Benevente et.al. has concluded that in asymptomatic carotid artery stenosis the reduction of ipsilateral stroke risk via CEA still occurs, however the risk reduction is relatively small.[52] The authors of the Asymptomatic Carotid Artery Study (ACAS) do, however, conclude that in asymptomatic carotid artery disease of 60% stenosis or more, that carotid endarterectomy surgery in patients with good general health can help to decrease a 5-year risk of ipsilateral stroke by 53%.[19] In asymptomatic patients with carotid artery stenosis, the physician needs to consider a myriad of factors in weighing the benefit of surgical treatment versus medical intervention. These factors include the patient’s age, gender, general health, and degree of stenosis. In high grade (>90%) asymptomatic carotid artery stenosis, the procedure of a carotid endarterectomy has been the intervention of choice.[53] This may be due to the increased risk of stroke as stenosis progresses to occlusion.

In 1995, the American Heart Association published a Medical/ Scientific Statement as a Special Report: Guidelines for Carotid Endarterectomy; A Multidisciplinary Consensus Statement From the Ad Hoc Committee, American Heart Association.[54] In this statement, the indications for carotid endarterectomy in symptomatic good-risk patients, and asymptomatic good-risk patients are enumerated.[54] It is advised that this statement be a driving force in the clinical decision making of the physician regarding patients with carotid artery stenosis considering carotid endarterectomy as a possible intervention for management.

2.3.4. Carotid Artery Occlusion - Symptomatic

The incidence of stroke in a patient with symptomatic carotid artery occlusion has been documented in the literature. In a summary of twelve prospective follow-up studies of symptomatic patients with carotid artery occlusion, Hankey and Warlow documented an overall subsequent stroke risk of 7% per year, and a 6% risk of stroke on the ipsilateral side of the occluded carotid artery.[55] The risk of stroke persists despite medical treatment with platelet-inhibiting and anticoagulation medications that are the attention of current medical and neurosurgical research.[23] There has also been the resurgence of the question of the viability of extracranial-intracranial (EC/IC) arterial bypass surgery for the prevention of stroke.[23] Extracranial-intracranial bypass surgery had been the standard of care in patients with symptomatic carotid artery occlusion until 1985, when an international multi-center study concluded that the bypass of the superficial temporal artery to the middle cerebral artery was not effective in subsequent stroke prevention in these patients.[56]

Over the last decade or so, there has been ongoing discussion as to the appropriateness of this decision to abandon the EC/IC arterial bypass surgery. There has been the identification of a subgroup of patients with carotid artery occlusion who may be viable candidates to benefit from this surgery for the prevention of a subsequent stroke.[4,22,57] However, it is yet unproven as to the long term outcomes of using impaired cerebral hemodynamics to identify this subgroup and select possible candidates for this procedure.[23] One of the first identifying factors of a patient who belongs in this subgroup of patients with hemodynamic compromise comes from the history and clinical examination. There are a characteristic set of symptoms that describes these patients with symptomatic carotid artery occlusion who may fall into this subgroup with reduced cerebral blood flow.[36,37,39,40] One distinguishing symptom is "limb-shaking" which typically occurs with a change in position toward upright; this causing a drop in blood pressure.[37,39,40] Other findings are typically described as a transient ischemic attack (TIA) and may include transient monocular blindness (blindness in one or both eyes described as a shade coming down over the eyes), weakness of an arm or leg, numbness of an arm or leg, slurred speech, and possibly aphasia.[31,32,39] Appropriately, these symptoms are related to the functional areas of the brain which receive their blood supply from the major branches of the internal carotid artery already discussed.

2.3.5. Carotid Artery Occlusion - Asymptomatic

The prognosis of a patient with asymptomatic (never symptomatic) carotid artery occlusion remains controversial in the literature. Hennerici et al. prospectively followed 49 patients with carotid artery occlusion for an average of 31.2 months. These patients were asymptomatic without any neurological signs or symptoms. The outcome measures of death, recurrent TIA, and stroke when assessed revealed a 16% stroke rate, 10% TIA rate, and 47 % death rate during follow up. Death was primarily due to coronary artery disease. The authors concluded that patients with asymptomatic carotid artery occlusion are at considerable risk to experience a stroke.[11] Nicholls and colleagues found a 31% stroke risk in patients with asymptomatic carotid artery occlusion within the first year after the occlusion.[14]

In contrast, Bornstein and Norris followed 40 patients with unilateral carotid occlusion for two years.[12] None of the patients with an occluded carotid artery experienced a stroke. The authors concluded that the asymptomatic patients with carotid artery occlusion have a benign outcome. It was suggested that collateral blood supply is adequate to substitute for the occluded carotid artery.[12] This collateral blood supply comes from the opposite carotid artery by way of the circle of Willis, through retrograde flow of the ipsilateral opthalmic artery, and through leptomeningeal collaterals.[4,22,23]

In a later study of 30 never symptomatic and 81 symptomatic patients with carotid artery occlusion, it was concluded that the never symptomatic carotid occlusion group carried an inappreciable stroke risk.[13] One of the 30 asymptomatic patients experienced an ischemic stroke (3%). The rationale offered for the benign prognosis of these patients is the low incidence of cerebral hemodynamic compromise due to collateral blood supply.[13] This low incidence of hemodynamic compromise was documented in symptomatic and asymptomatic patients by Derdeyn et al. in a study measuring the oxygen extraction fraction (OEF), or “misery perfusion” in patients with carotid occlusion.[4] In this study five of thirty-six asymptomatic patients demonstrated an increased OEF (14 %), while thirty-nine of eighty-one (48 %) symptomatic patients demonstrated an increased OEF.[4] While this difference was significant between the two groups, and the asymptomatic group appears much less likely to demonstrate misery perfusion, it seems as though the 14% of asymptomatic patients that were found to demonstrate cerebral hemodynamic compromise still deserve attention for stroke prevention.

An asymptomatic patient is often discovered as an incidental finding due to other medical procedures or work-up. Therefore, some of the people with an occluded carotid artery may proceed to having a potentially preventable stroke if there was a mechanism to identify this problem beforehand. There may be subtle changes in function not recognized by the patient in the areas of thinking, memory, language, and motor skill that actually may declare the patient symptomatic, but go unreported. Some of the possible symptoms that have not been well documented thus far relate to the frontal and temporal lobe functions in the brain that also receive blood supply from the major ICA branches. These functions (physical, emotional and cognitive in nature) seem to escape being communicated in the clinical history and examination of the patient.[58] Yet, when specifically addressed in the clinical examination, there often is acknowledgement of forgetfulness, decreased ability to communicate in a swift and accurate manner, thought disorganization, and an overall feeling of "just not being myself" by the patient (personal observation). Specific testing of these functions would provide symptomatic information about the patient that might be overlooked or missed entirely in the neurologic examination. Deficits identified in these areas may help the physician to decide further medical management and diagnostic work-up to determine if the patient may actually have significant carotid artery disease and be in need of possible cerebral hemodynamic assessment.

2.4. Assessment Measures of Cognitive and Physical Function

There has not been identified any specific cognitive or physical function assessment tools that are acceptable and standard to test this population of patients with symptomatic and asymptomatic carotid artery disease. In most of the studies that investigated these patient groups to assess interventions and medical care, the outcome measures are primarily a transient ischemic attack, stroke or death.[5,14,24,25,57]

In only a few studies reviewed thus far, has there been any specific assessment tools used to evaluate cognition and/or physical ability in patients with carotid artery stenosis or occlusion. Cognitive function has been addressed in a few studies examining atherosclerosis of the common carotid and internal carotid arteries.[59-61] Auperin et. al considered middle-aged adults (45-71 years old) and measured atherosclerosis of the common carotid artery alone.[61] Cerhan et. al. considered middle-aged adults (45-71 years old) and averaged the measurement between the common carotid and internal carotid artery areas of atherosclerosis.[59] Both studies identified an association between presence of atherosclerosis and cognitive decline. Auperin et. al found this to be a moderate association more prevalent in men.[61] Cerhan found that a greater carotid intima-media wall thickness (averaged measurement) was associated with lower cognitive scores, and this was not gender specific. Breteler et. al. researched cardiovascular disease and cognitive function in the elderly (55-94 years old), and concluded that atherosclerotic disease of the peripheral or carotid arteries accounts for considerable cognitive impairment in these individuals.[60] However, what was not clear in these studies is the amount of atherosclerosis, and the symptomatic or asymptomatic status of the participants. In one recent study of patients 65 years and older with symptomatic carotid artery stenosis of 75% or greater, neuropsychological function was the main outcome measure considered. The researchers concluded that despite the small sample size of the study, there was some evidence for an association between severe carotid artery stenosis and impaired neuropsychological function.[62] The only study identified that has dealt with patients with asymptomatic carotid artery disease and cognitive impairment, demonstrated that cognitive impairment and decline are associated with severe carotid artery stenosis (> 75%) of the left internal carotid artery primarily.[7] None of these studies included any assessment of physical function.

Cognitive function has been more extensively studied in patients with cardiovascular related disorders, including those undergoing cardiac surgery.[63-68] From a review of the literature it appears that even though there was a consensus statement published in 1995 on the assessment of neurobehavioral outcomes after cardiac surgery, there continues to be deviation from the recommended core neuropsychological battery in this consensus statement.[69] It has been demonstrated that patients who have cardiac disorders do demonstrate impaired neuropsychological function. For example, Zuccala et.al. and Riegel et.al. found that older patients with heart failure show cognitive impairments at an incidence of 26% and 28.6% respectively.[63,64] Zuccala et.al. determined that lower systolic blood pressure was selectively associated with cognitive impairment.[63,64] Other cardiac conditions that have been found to be related to impaired cognition would include patients with atherosclerosis of the common carotid artery, patients with arrythmias, particularly atrial fibrillation, and patients that undergo coronary artery bypass surgery.[65,67,70-72] Figure 6 is a summary of the studies reviewed in the cardiovascular literature that assess cognitive function and the variety of outcome measures utilized.

Investigators	Neuropsychologic Tests Used	Function Assessed
Riegel et. al.[64]	• Commands subset and Material subset of Boston Diagnostic Aphasia Examination[73] • Complex Ideational Material subset of Boston Diagnostic Aphasia Examination[73] • Mini-Mental State Examination (MMSE)[74] • Draw A Clock Test[73]	• Aural attention span, auditory comprehension, planning and execution and motor skills • Executive Brain Function • Orientation, attention, concentration, sequencing, visuospatial skills, verbal learning, immediate memory, oral reading and comprehension, verbal repetition • Attention and concentration, numerical sequencing, visual-spatial analysis and execution, abstract conceptualization and planning
Zuccala et.al.[63]	• Hodkinson Abbreviated Mental Test[75]	• Cognitive screen

Rao[62]	• Cambridge Cognitive Examination (CAMCOG)[76] • Behavioral Dyscontrol Scale (BDCS)[77] • Trail-Making Tests A and B[78] • Controlled Word Association Test[79]	• Abstract thinking, attention, calculation, memory, language, orientation, praxis, perception • Frontal lobe function • Frontal lobe function • Frontal lobe function
Breteler et. al.[60]	• Mini-Mental State Examination (MMSE)[74]	• Orientation, attention, concentration, sequencing, visuospatial skills, verbal learning, immediate memory, oral reading and comprehension, verbal repetition
van Exel et. al.[65]	• Mini-Mental State Examination (MMSE)[74]	• Orientation, attention, concentration, sequencing, visuospatial skills, verbal learning, immediate memory, oral reading and comprehension, verbal repetition

Auperin et. al.[61]	• Mini-Mental State Examination (MMSE)[74] • Trail-making B[78] Digit Symbol Substitution Test – Weschler Intelligence Scale – Revised[80] • Paced Auditory Serial Addition Test[81] • Benton Visual Retention Test[79] • Rey's Auditory Verbal Learning Test[82] • Word Fluency Test[79] • Raven Progressive Matrices[83]	• Orientation, attention, concentration, sequencing, visuospatial skills, verbal learning, immediate memory, oral reading and comprehension, verbal repetition • Frontal lobe function • Psychomotor performance • Auditory attention • Visuospatial perception • Verbal memory • Frontal lobe function • Logical intelligence and reasoning
Cerhan et. al[59]	• Delayed Word Recall Test84 • Digit Symbol subset of the Weschler Adult Intelligence Scale – Revised[80] • Controlled Oral Word Association Test[79]	• Verbal learning and recent memory • Psychomotor performance • Frontal lobe function

Mahanna et. al. 1996[67]	• Randt Memory Test (short story)[85] • Digit Symbol subset of the Weschler Adult Intelligence Scale – Revised[80] • Trail-making B[78] • Benton Revised Visual Retention Test[79]	• Short and long term memory • Psychomotor performance • Frontal lobe function • Visuospatial perception
Vingerhoets et. al.[71]	• Auditory Verbal Learning Test[86]	• Verbal memory performance
Stroobant et. al.[39]	• Rey Auditory Verbal Learning test[82] • Trail-making B[78] • Grooved Peg-Board Test[87] • Block Taps test • Line Bisection Test[88] • Controlled Oral Word Association Test[79] • Judgement of Line Orientation[79]	• Verbal Memory • Frontal lobe function • Complex motor coordination • Immediate memory and attention • Unilateral visual inattention • Frontal lobe function • Estimate angular relationships
BhaskerRao et. al.[89]	• Antisaccadic Eye Movement Test (ASEM)[90]	• Frontal lobe function

Pugsley et.al.[91]	• Letter Cancellation Test[27] • Trail Making Tests[78] • Computerized Symbol Digit Replacement Test[92] • Computerized Reaction Time task[91] • Purdue Pegboard Test[93] • Rey Auditory Verbal Learning test[82] • Computerized Nonverbal recognition Memory Tests[91] • Block Design subset of the Weschler Adult Intelligence Scale – Revised[94]	• Frontal lobe function • Attention • Reaction time • Motor skills • Verbal Memory • Memory • Psychomotor Performance
Taggart et. al.[95]	• Rey Auditory Verbal Learning test[82] • Digit Span subset of the Weschler Adult Intelligence Scale – Revised[80] • Trail Making Tests[78] • Nine Hole Peg-Board Test[87] • Bells Test[54] • Adult Memory Information Battery[94] • Short Orientation Memory Concentration Test[96]	• Verbal Memory • Psychomotor Performance • Frontal lobe function • Psychomotor speed • Visual search • Speed of information processing • General cognitive orientation

Figure 6: Summary of Neuropsychological Tests in Cardiovascular Disorders.

There has been some attention to subtle cognitive changes in patients undergoing carotid endarterectomy (CEA) with preoperative and postoperative assessments and follow-up.[58, 97-99] In these studies, a variety of neuropsychometric tests were used. The reasoning offered for preforming a neuropsychological assessment stemmed from the Statement of Consensus on Assessment of Neurobehavioral Outcomes after Cardiac Surgery, which advocated the assessment of central nervous system outcomes after cardiac surgery, specifically neurobehavioral outcomes.[69,99] The specific core neuropsychologic battery recommended in the Consensus Statement[69] includes the Rey verbal learning test, the Trail-making A test, Trail-making B test, and the Grooved pegboard test.[78,82,87]

Once again, in the studies investigating neurobehavioral outcomes after carotid endarterectomy, the wide variety of tests used are reflective of cognitive function in 3 main areas: fine motor control, executive function and verbal memory.[99] The chart below is a summary of the studies reviewed and neuropsychological tests used.[58,97-100] (Figure 7).

Investigators	Neuropsychologic Tests Used	Function Assessed
• Owens, Pressman, Edwards et.al.[97]	• Ravens standard progressive matrices[83] • Finger tapping[101] • Spatial orientation[102] • Arithmetic[103] • Vocabulary[104] • Short-term memory[94] • Short interval time perception[105]	• General intelligence • Motor performance • Comprehend visual space • Spatial/ verbal abilities • Verbal function • Short-term memory • General test of cerebral function
Cushman, Brinkman, Ganji	• Weschler Adult	• Intelligence

et.al.[98]	Intelligence Scale[80] • Russell's Revised Weschler Memory Scale[80] • Buschke's Selective Reminding Procedure[106] • Trail Making Test[78] • Digit Symbol Substitution Test[101] • Reitan Finger Tapping Test[101] • Reitan Sensory-Perceptual Examination[101]	• Complex Memory • Memory retention and retrieval • Visual conceptual and visuo-motor tracking • Spatial/ verbal abilities • Motor Performance • Sensory-perceptual processing
Heyer, Adams, Solomon et.al.[99]	• Halsted-Reitan Trails A & B[78] • Fine finger tapping[101] • Grooved pegboard test[87] • Buschke Selective Reminding test[106]	• Visual conceptual and visuo-motor tracking • Manual dexterity • Complex motor coordination • Verbal memory
Connolly, Winfree, Rampersad et.al.[58]	• Halsted-Reitan Trails A & B[78] • Controlled oral word association[79] • Rey complex finger test (copy portion)[82]	• Visual conceptual and visuo-motor tracking • Verbal fluency • Perceptual, visual/spatial organization
Fearn, Hutchinson, Riding et.al.[100]	• Cognitive Drug Research Ltd. (Reading, UK)[107] • Overall memory reaction time for word, picture and memory scanning, • Overall attention reaction time	• Memory • Attention

Figure 7: Summary of Neuropsychological Tests in Carotid Endarterectomy.

The possibility of impaired cognition appears to be significant as shown in a recent study by Connolly et.al. of 55 patients who underwent CEA. In this study, 20-25% of the patients were found to have subtle cognitive injuries postoperatively.[58]

In an additional review of related literature pertaining to patients at risk for stroke due to ruptured aneurysms resulting in the development of a subarachnoid hemorrhage, some other cognitive and physical assessment tools were used. Once again there is no suggested assessment tool for impaired cognition. The only outcome scale that consistently appeared in that literature was the Glasgow Outcome Scale.[108,109] This scale reflects recovery in general with no specific attention to cognitive or physical deficits. Others scales more specific to cognition that have been used for the ruptured aneurysm population of patients with subarachnoid hemorrhage include: the Weschler Intelligence Test[110] and Weschler Memory Scale,[94] short-term memory tests and sensori-motor coordination tests, digit span tests and recognition memory tests[111].[108,109,112] Once again, it is clear that there is no specifically identified and recommended mechanism for testing cognitive and physical function in patients with related neurological disorders.

2.4.1. Relationship of Cognitive Function and Instrumental Activities of Daily Living

Instrumental activities of daily living (IADL) include items that consider competence beyond the basic activities of daily living (grooming, toileting, feeding).[113] Examples of IADL's include light household tasks, shopping and money management, meal preparation, transportation, and responsibility for medications.[113] These activities render a person more functionally independent in their environment and social interactions beyond the limits of their home. Grigsby et.al. demonstrated a relationship between executive cognitive abilities and functional status through assessing ADL's and IADL's, and determined that executive function is an important determinant of functional status.[114] A similar finding was found by Pohjasvaara et. al. who tested 486 patients who were 3-4 months post ischemic stroke. The researchers found that a clinically significant decline in executive function was frequent in this group (40.6%), and that this significantly correlated ($p<.0001$) with a poorer performance in complex activities of daily living.[115] These researchers recommended that measures of executive functions including complex ADL's may be a more sensitive measure for early vascular impairment than an assessment of basic activities of daily living.[115] It has been shown in the literature that if a person is experiencing a disruption of cognition, then there is a related decline in IADL function.[116-118]

2.4.2. Assessment Tools for this Project

The assessment tools chosen for this project have been selected in order to focus on six cognitive domains and physical function, including instrumental activities of daily living. The cognitive tests chosen were the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and the Executive Interview (EXIT).[119-121] (Appendix A,B) The Physical Performance Test (PPT) was used as the physical function measure.[122] (Appendix C) The Instrumental Activities of Daily Living Scale (IADL) was used to assess complex activities of daily living.[113] (Appendix D)

2.4.2.1. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

The RBANS was developed to identify and characterize cognitive decline in the older adult, as well as serve as a neuropsychological screening battery for younger patients.[119] It tests 5 domains of cognitive function that include:

- Immediate (short-term) memory –list learning, story memory tests

- Delayed (long-term) memory – list recall, list recognition, story recall, figure recall tests
- Visuospatial/constructional function – figure copy, line orientation tests
- Language – picture naming and semantic fluency tests
- Attention - digit span and coding tests

The RBANS is a recently developed test battery that has been recognized as a clinically useful tool to rapidly screen neuropsychological status in the acute care setting for the purpose of medical and surgical decision making as opposed to using a lengthier test battery.[121] The length of the test is approximately 30 minutes.[119] At its creation, standard normal measurements were developed for each age group for each subtest of the RBANS.[121] Reliability was then calculated for each subtest in each age group and was reported to be greater than .8 for all age groups, with an overall total score reliability of .94.[121] The RBANS is also reported as a valid test in a mixed adult population with a variety of neuropsychologic and psychiatric problems.[121] Comparisons have been made to some select, well-established external measures such as the Weschler Memory Scale-Revised (WMS-R).[94] In this comparison, the RBANS total scale score was moderately correlated with the WMS-R verbal memory index at .7.[121] The test has been shown in the literature to have preliminary clinical validity in detecting and characterizing dementia.[119] It was also found to have sensitivity and specificity in people with dementia at 90%.[119] Many of the patients with symptomatic carotid artery disease complain of a loss of memory, forgetfulness, or trouble finding the right words during communications. Also, once asked, some patients that are asymptomatic or their family members recognize these types of difficulties in purported asymptomatic patients. The domains tested in the RBANS are functions similar to those reported by both patients and their families, thus this test was chosen for this project.

2.4.2.2. Executive Function

The sixth cognitive domain, executive cognitive function is assessed via the EXIT.[120] Executive cognitive function is the process of orchestrating relatively simple actions such as movements and ideas, into goal-directed behaviors. This function is associated with the frontal lobe; an area already identified at risk for decreased blood flow after carotid artery occlusion.[123] The EXIT is designed to be administered efficiently (10 minutes), conveniently (even at a patient's bedside) and by non-psychiatric personnel.[120] The internal consistency of the 25-item tool was found to be high (Cronbach's alpha = .87).[120] In the pilot validation study, it was shown to be a valid and reliable tool to assess executive impairment at the bedside, and discriminated between different functional levels of persons tested and severity of their dementia.[120] Additionally, the EXIT correlated strongly with the Mini-Mental State Examination (MMSE), however, was better able to discriminate between the functional levels of the patients studied.[120]

2.4.2.3. Assessment of Physical Performance

The Physical Performance Test can be either a 7-item or 9-item global measure of physical performance with items that reflect both basic activities of daily living (BADL) and instrumental activities of daily living (IADL).[122] The items include:

- Writing a sentence
- Simulated eating
- Donning and doffing a jacket
- Turning 360º while standing
- Lifting a book
- Picking up a penny from the floor
- Walking 50 feet

- Climbing one flight of stairs
- Climbing several flights of stairs (up to 4)

The measure was developed to assess the physical performance of older adults, however is useful in the population that is at risk for stroke due to carotid artery stenosis and occlusion, to determine if any of the possible physical and sensory symptoms are affecting their function. Recently, Brach et.al. used the 7-item PPT to identify deficits in a high-functioning sample of community-dwelling older women.[124] The tool was more useful in identifying deficits in physical function than the self-report comparison measure, the Functional Status Questionnaire.[124] The authors concluded that the performance-based measure (the PPT) could assist in early identification of minor problems in physical functioning, and allow for opportunity for early intervention for the patients.[124] The use of the PPT in this project is similar, to identify early the minor deficits in physical function that the patient may not otherwise report.

The PPT 9-item scale has been shown to demonstrate internal consistency (Cronbach's alpha=.87), and interrater reliability (r =.99).[122] The PPT has been found to demonstrate concurrent validity with other functional status assessments, namely the modified Rosow-Breslau,[125]and the Katz Activities of Daily Living[126] and the Spector scale[127] with a Pearson Correlation Coefficient of r=.50-.69.[128] In this study, the PPT was also found to demonstrate predictive validity for the outcomes of death and institutionalization in the elderly subjects tested. Reuben et.al. concluded that this tool, due to its assessment of actual performance, would be a useful tool in a research situation.[128] While the reliability and validity of this tool has not been tested in the population of patients with symptomatic or asymptomatic carotid artery disease, it appears to be a valuable test to use to reflect a patient's ability to complete important

ADL's. Also, the test takes approximately 10 minutes to administer, and uses very little equipment, thus it is a convenient and practical tool to use in this project.

2.4.2.4. Instrumental Activities of Daily Living

The Lawton assessment of instrumental activities of daily living was developed to assess everyday functional competence.[113] The tool consists of nine items that reflect more complex daily activities including: telephoning, shopping, food preparation, laundering, housekeeping, obtaining transportation, money management, use of medication, and handyman work. Persons self-report on the assessment if they are able to complete a task without help, with some help, or are completely unable to complete the task. The maximum score on the test is 27, which indicates complete independence with the tasks on the tool. The tool takes approximately 5-7 minutes to administer. At the time of the development of the tool, the Lawton IADL was found to be a valid measure, correlating moderately with similar scales.[113] It was also found to be a practical scale for use in a variety of elderly age groups.[113] In the initial publication of the tool, its reliability had not yet been extensively tested. However, the scale continues to be used frequently in the literature to reflect IADL function,[115,116,129,130] and has been recommended for the assessment of persons who have had a stroke as part of the Comprehensive Assessment Toolbox for Stroke.[131] Thus it is an appropriate measure for this project, which is focused on identifying a persons loss of function as a potential contribution to increase stroke prevention.

2.5. Summary:

Currently, there is no agreement in the literature regarding the management of patients with internal carotid artery stenosis and occlusion. There is more information regarding stroke risk and possible interventions to address prevention in cases of carotid stenosis and symptomatic carotid occlusion than in asymptomatic patients.[13] There also exists a better description of symptomatic patients from both a clinical perspective and a physiologic perspective. However, information regarding some cerebral functions and physical measures are missing from the clinical data currently being assessed and evaluated. There is no standardized protocol for the inclusion or evaluation of cognitive and physical functions. These clinical data may provide insight into the actual functional deficits of the patient, and the existence of symptoms that may be interpreted as warning signs of impaired cerebral function and possible stroke. Thus, the question remains as to the accurate clinical picture of the patient, both those with symptoms and those who are believed to be asymptomatic.

2.5.1. Specific Aim

The first specific aim of this research project is to determine if persons with asymptomatic carotid artery disease (high moderate stenosis through occlusion) demonstrate deficits in cognition and on physical performance measures.

The second specific aim is to determine if there is a correlation between the cognitive measures and the instrumental activities of daily living in persons with asymptomatic carotid artery disease.

III. Research Hypothesis:

Hypothesis 1:

Ho: Patients with asymptomatic carotid artery disease (moderate, severely stenotic or occluded) will demonstrate a deficit on the RBANS and EXIT measures of cognitive functioning and on the Physical Performance Test.

Hypothesis 2:

Ho: There will be a negative correlation between the persons with asymptomatic carotid artery diseases cognitive scores on the RBANS and EXIT and their scores on the Lawton Instrumental Activities of Daily Living Scale.

IV. Research Design and Methods

This was a prospective, observational, research study conducted at the Stroke Institute and Neurosurgery clinic at University of Pittsburgh Medical Center. Patients with a diagnosis of asymptomatic carotid artery stenosis of high moderate and severe degrees, and occlusion were included. Degree of stenosis and occlusion of the carotid artery was identified by the physician via angiography, CT, CTA, or MRI/MRA. All patients were 50 years of age or older. Patients were able to answer questions concerning memory and thinking skills, and participate in a physical assessment reflecting activities of daily living. Patient testing time took between 40 and 50 minutes.

Patients were identified by the neurologists of the University of Pittsburgh Stroke Institute and the neurosurgeon and nurse coordinator of the cerebrovascular center. The physician first consented the patient to participate in a research study, then the primary investigator spoke to the patient and explained the research study after the patient had consented. Data was typically collected at that time, unless it was inconvenient for the patient. Data collection required only one visit of the patient.

4.1. Inclusion/Exclusion Criteria for Patients.

The 39 patients included had a diagnosis of asymptomatic carotid artery stenosis of 50% or greater, through complete carotid artery occlusion and were placed in one of the following categories[28,49]:

- Unilateral moderate stenosis (50-69%)
- Unilateral severe stenosis (70-99%)
- Unilateral occlusion
- Bilateral moderate stenosis (50-69%)

- Bilateral severe stenosis (70-99%)
- Bilateral occlusion

Asymptomatic patients are by patient report, symptom free.

Patients were excluded from the study if they had experienced a previous stroke. They were also excluded if they were unable to understand the questions or to verbally respond in person. Persons with a preexisting dementia, as diagnosed by the physician, were excluded. Also, preexisting orthopedic conditions that could preclude the patient from completing the physical testing were excluded, such as being non-weight bearing or severe cardiopulmonary compromise.

4.2. Research Design:

4.2.1. Patients with Carotid Artery Disease:

Once a patient was identified as a candidate for the study and agreed to participate, he/she was approached by the primary investigator to give informed consent to participate. Once consented, each patient was tested one time on the cognitive and physical measures. These measures were: the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and the Executive Interview (EXIT), the Physical Performance Test (PPT), and the Instrumental Activities of Daily Living Scale (IADL). Prior to administration of the tests, the patient's demographic data (age, comorbidities, level of education), a list of medications, documentation of the absence of symptoms, documentation of the diagnostic tests used to make the diagnosis of stenosis and occlusion, which side or sides were involved, and if there is blood flow documentation from cerebral hemodynamic testing were obtained. Testing of the patient took place in the clinic, and took approximately 40-50 minutes, 30 minutes for the cognitive measures

(RBANS-25 minutes, EXIT-10 minutes), and 10-15 minutes for the Physical Performance Test and Lawton IADL score. The order of testing was randomly varied between patients, with the patient blindly selecting the 1st, 2nd 3rd, and 4th test via a drawing. There was a 2-3 minute rest between each test (RBANS, EXIT, PPT and IADL). No patient approached to participate in the study refused.

All testing was done by the primary investigator. The primary investigator had practiced each of the tests prior to the collection of the pilot data. The RBANS and EXIT were tested with a PhD Neuropsychologist through Western Psychiatric Hospital. The PPT was co-administered with a co-author (S.W.) who has tested a few hundred patients, and has published articles regarding the use of the test. The primary investigator has performed reliability testing on the PPT with S.W. with a strong correlation r = .92 .

4.3. Data Analysis:

The predicted sample size for this project was 26 patients in each group: unilateral high moderate stenosis (50-69%), unilateral severe stenosis (70-99%), unilateral occlusion, bilateral high moderate stenosis, bilateral severe stenosis and bilateral occlusion (156 patients total). In the case of bilateral disease, the patients were assigned to the group of the most involved artery. The sample size for patients was based on an alpha = .05 and power = 80% with a moderate effect size.

It was a challenge to identify the patients who were asymptomatic, as asymptomatic carotid artery disease is often an incidental finding to another problem for the patient. It was estimated that 6-8 patients in this category could be identified per month. It would take 1-2 years to identify and test the predicted number of subjects. Therefore, patients were identified and tested for 8 months after data collection began.

Descriptive data calculated for asymptomatic patients with carotid artery disease included a mean and standard deviation for each measure in each group. RBANS data for the asymptomatic patients were compared to the established norms for the tools used.[132] A one-sample t-test with one tail was used to compare the data to the assessment tools' established normal values, based on the patient's age. The rationale for use of a one-tail test was because it was not expected that patients would perform better than the established normal scores. A higher EXIT score would indicate greater executive dyscontrol. The mean score for each patient group (unilateral and bilateral high moderate, severe stenosis and occlusion) was used to characterize the group. This was compared to other similar populations that are described in the literature. The mean PPT score was compared to the perfect score (36), to identify decline in function. Additionally, a Pearson Correlation Coefficient was calculated comparing all the patients' cognitive scores (RBANS and EXIT) with the Lawton IADL scores.

The established standardized sample scores, by age group for each test in the RBANS was found in Appendix A of the Stimulus Booklet.[132] These values are standardized to a normal distribution, thus a mean score of 100 and a standard deviation of 15 was used in the statistical analysis.[121]

The EXIT is a 25-item test with a maximum possible score of 50. A higher score would indicate a greater amount of executive dyscontrol.[120] In the literature, there is a suggested cut-off score of

15/50 or greater for this test to denote a person as having executive dyscontrol.[120] There have been studies that have used the EXIT to investigate impaired executive function between institutionalized and non-institutionalized patients, between retirees that need different levels of care, and also between different types of dementias.[120,123,133] In two of these studies, there were samples of subjects who were living without assistance and non-institutionalized, for whom the EXIT score was expected to be relatively low, indicating that executive function was not impaired in those subjects.[120,123] In the pilot validation study, the average non-institutionalized subject age was 85.6 years, and the average EXIT score was 14.2/50.[120] In the later study that used the EXIT to assess executive dyscontrol and level of care, the average age of the community dwelling subjects was 74.6 years, and the average EXIT score was 9.4/50.[123] For this project, the expected average age of the patients was predicted to be less than those of the two studies discussed. It was expected that most of the patients would be between 50 – 70 years old. A score of 15/50 or greater, as has been suggested in the literature was used as the normal comparison by the primary investigator. This choice was based on the results of the previously described studies.

The Physical Performance Test is a test that was developed for elderly outpatients. The test was appropriate for this project due to the incorporation of activities of daily living which are an important physical measure, and the benefit of its being a direct observation test. While not all patients with carotid artery disease are elderly, the ages of the patients in the project were not anticipated to vary greatly from age 65. The average age in the study was 73 years old. The PPT was tested in 5 patient populations with ages greater than 65.[122] The score on the 9-item test ranges from 0-36, with 36 indicating the highest function. The mean score found in this study for the 9-item test was 27, with the 90th percentile score being 31 and the 75th percentile score being 29.[122] Sherman and Reuben used the 7-item PPT to assess the functional status of 363 community-dwelling elders and demonstrated that the test had no floor or ceiling effect.[134] The choice of the 7-item test eliminated the two activities that included stairs. In another validation study by Reuben et.al., the 7-item and 9-item PPT were evaluated in an elderly cohort. The 9-item average test score reported for 124 subjects with an average age of 79.8 years was 24.6, and this score was the same for the subjects of this group who were considered community dwelling.[128] Recently, in a study by Brach et. al. the 7-item PPT was used to assess a decline in function in community-dwelling older women (mean age = 74.3 years).[124] In this study, the researchers chose a perfect score of 28 (4 points in each category) as the expected score for normal performance. Any score below this indicated a deficit in physical performance of that particular task.[124] In contrast, unpublished data of 19 normal healthy subjects in the age range of 50-70 years (mean age 67.5) demonstrated a mean score on the 9-item PPT of 30/36.[135] This suggests that the concept of a perfect score 36 (4 points per task) might need to be reconsidered as a realistic expectation for the healthy normal population.

For this project, the 9-item test was selected, as negotiating stairs is an important part of function in some homes, and in the community. However, a 7-item score was also analyzed, to allow for individual item analysis. The PPT score was recorded from the 0-4 scale in the tool, and also time of completion for 7 of the 9 tasks was recorded. A score of 36 could be suggested as the "normal"comparison, considering the rationale offered by Brach et. al, that scores less than 4 on each item mean that the task requires more time to complete than the best performance, and this is an indicator of early physical decline.[124] Similarly, this project was designed to detect early decline, particularly in the persons with asymptomatic carotid artery disease.

V. Results

5.1. Demographic Data

Thirty-nine patients with asymptomatic carotid artery disease were tested. Table 1 includes the basic demographics regarding these patients. The sample was slightly dominant for males, with an average age of 73 years (48-87).

Table 1: Patient demographics by diagnostic group:

Diagnostic Group	Gender	Mean Age (yrs.) ± Standard Deviation	Age Range
Unilateral Stenosis Moderate n = 3, (7.7%)	2 male (67%) 1 female (33%)	78 ± 6.23	71-83
Unilateral Stenosis Severe n = 18, (46.2%)	11 male (61%) 7 female (39%)	75 ± 7.65	55-87
Unilateral Occlusion n = 3, (7.7%)	2 male (67%) 1 female (33%)	63 ± 15.5	48-79
Bilateral Stenosis Moderate n = 4, (10.3%)	3 male (75%) 1 female (25%)	76 ± 8.14	66-85
Bilateral Stenosis Severe n = 9, (23.1%)	5 male (56 %) 4 female (44%)	73 ± 5.48	64-79
Bilateral Occlusion n = 2, (5.1%)	1 male (50%) 1 female (50%)	63 ± 4.95	59-66
All Patients (n = 39)	23 male (59%) 16 female (41%)	73 ± 8.49	48-87 years

Most patients (70%) tested in this study were severely stenotic, with another 13 % being occluded, and the remaining 17% had moderate carotid artery stenosis.

Table 2 reflects which side was involved for the patients. Patients with bilateral involvement were grouped into the side of stenosis that the surgeon would be considering for surgery. For example, in a situation of mild or moderate stenosis on the left side, and severe stenosis on the right side, the patient was classified as having a right side that was involved. In situations when the level of stenosis was the same, or occlusion existed bilaterally, then the patient was classified with bilateral disease.

Table 2: Patient Demographics by involved side of stenosis:

Patient Group	Right side	Gender	Age (Mean)	Left side	Gender	Age (Mean)	Both sides	Gender	Age (Mean)
Unilateral Stenosis Moderate (n = 3)	2	1 male 1 female	82	1	1 male	84			
Unilateral Stenosis Severe (n = 18)	10	6 male 4 female	77 73	8					
Unilateral Occlusion (n = 3)	2	2 male	64	1	1 female	62			
Bilateral Stenosis Moderate (n = 4)				2	2 male	76	2	2 female	76
Bilateral Stenosis Severe (n = 9)				1	1 male	69	8	4 male 4 female	72 74
Bilateral Occlusion (n = 2)							2	1 male 1 female	63

In general for the 39 patients, there were 13 with right side involvement, 14 with left side involvement and 12 with bilateral involvement.

Other data collected to further describe the patients was the number of comorbidities that each person had, and the types of medications that the patients were taking. Table 3 is a summary of the most common comorbidities that the patients displayed.

Table 3: Comorbidities in Patients with Asymptomatic Carotid Artery Disease:

Comorbidity	Number of Patients (% of the total 39)
Hypertension	15 (38.5%)
Diabetes Mellitus	13 (33.3%)
Coronary Artery Disease	12 (30.8%)
Cardiac Arrythmia	5 (12.8%)
Hypercholesteremia	14 (36%)
Other (various diseases not related to carotid artery disease)	49

Some examples of comorbidities in the other category would include glaucoma, non-disabling cancers (i.e. prostate cancer, breast cancer), arthritis, diverticulitis, and renal insufficiency. None of the comorbidities were present in a majority (over 50%) of the patients. Hypertension, diabetes, coronary artery disease and hypercholesteremia all were present in approximately one-third of the patients.

Table 4 is a summary of the medications that the patients were taking, divided into categories.[136]

Table 4: Medications in Patients with Asymptomatic Carotid Artery Disease.

Medication Classification	Medication	Number of Patients taking the medication
Anticoagulant	Plavix Coumadin	6 6 Total: 12
CNS Agent (Analgesic, Anticonvulsant, Antidepressive, Selective serotonin reuptake inhibitor, Sedative)	Aspirin Dilantin Effexor Celexa Zoloft Wellbutin Darvocet Celebrex Vioox	21 1 1 2 2 1 1 2 1 Total: 32

Antilipemics	Zocor Lipitor Lopid/Gemfibrozil Tricor	10 7 1 1 Total: 19
Antihypertensive	Lopressor Prinivil Diovan Atenol Corgard Hytrin Perindopril Zestril Cozaar Vasotec Diltiazem Capoten/Captopril	3 5 3 7 1 1 1 1 1 2 1 1 Total: 27
Antiplatelet	Aggrenox	2 Total: 2
Hormone and Synthetic Substrate	Flourinef Acetate Synthroid Metformin Glucosome Glucotrol Proscar Insulin Glyburide Glucovance Actos	1 5 4 1 1 1 3 2 1 1 Total: 21
Bronchodialator	Singular	1 Total: 1
Gastrointestinal Agent	Zantac Prilosac Ranitidine	2 3 1 Total: 6
ANS Agent	Detrol	2 Total: 2
Cardiovascular Agent (Calcium channel blocker, antiarrythmic, ACE inhibitor)	Norvasc Verapimil Accupril Lanoxin Digoxin Altace/ Ramipril	2 2 1 2 1 1 Total: 9

Antigout Agent	Allopurinol	1 Total: 1
Diuretic	Hydrochlorothyazide Lasix	3 3 Total: 6
Antiglaucoma	Isosorbide	1 Total: 1
Antivertigo Agent	Meclizine/Antivert	1 Total: 1
Anti-infective/Antiviral	Acyclovir	1 Total: 1

The medication categories most common in this patient group were the CNS agents (which included 5 different medications), the antihypertensives and the antilipemics. Fifty-four percent of the patients were taking aspirin, and 26% were taking the anitlipemic Zocor. They were the two most common medications. In this study, outcomes were analyzed from two perspectives, the severity of carotid artery disease, and also from the perspective of differences in outcomes based on laterality of disease.

5.2. Analysis by Severity of Carotid Disease

In order to determine differences in outcomes between the severity groups of the patients, an analysis of variance (ANOVA) was completed (Table 5).

Table 5: ANOVA for between group differences based on severity of carotid disease on the RBANS, EXIT, PPT and the Lawton IADL.

	Sum of Squares	df	Mean Square	F	Sig.
RBANS immediate memory					
Between Groups	701.520	2	350.760	.909	.41
Within Groups	13889.147	36	385.810		
Total	14590.667	38			
RBANS visualspatial/constructional					
Between Groups	722.601	2	361.301	1.556	.23
Within Groups	8358.322	36	232.176		
Total	9080.923	38			
RBANS language					
Between Groups	264.562	2	132.281	.684	.51
Within Groups	6960.874	36	193.358		
Total	7225.436	38			
RBANS attention					
Between Groups	811.112	2	405.556	1.441	.25
Within Groups	10130.324	36	281.398		
Total	10941.436	38			
RBANS delayed memory					
Between Groups	27.643	2	13.821	.045	.96
Within Groups	11155.947	36	309.887		
Total	11183.590	38			
RBANS total scale					
Between Groups	479.319	2	239.660	.832	.44
Within Groups	10373.655	36	288.157		
Total	10852.974	38			
EXIT Score					
Between Groups	82.886	2	41.443	1.569	.22
Within Groups	950.857	36	26.413		
Total	1033.744	38			
Physical Performance Test (nine-item total)					
Between Groups	96.812	2	48.406	2.884	.07
Within Groups	604.265	36	16.785		
Total	701.077	38			
Lawton IADL					
Between Groups	5.082	2	2.541	1.467	.24
Within Groups	62.353	36	1.732		
Total	67.436	38			

With the 39 patients, there was not a significance difference between the groups (unilateral or bilateral moderate, severe disease, or occlusion) on any of the outcome measures. The Physical Performance Test, however, was approaching significance ($p<.07$). In a Tukey post-hoc analysis of the 9-item PPT, the moderate stenotic and severe stenotic groups were significantly different at a $p<.10$ level. Because no significant differences between the groups were found at the $p<.05$ level, the asymptomatic patients with unilateral and bilateral moderate, unilateral and bilateral severe, or unilateral and bilateral occluded carotid artery disease will be considered together for the remainder of the data analysis.

5.2.1. Cognitive Test Results by Level of Severity

The results of the cognitive testing using the RBANS is reflected in Table 6.

Table 6: RBANS results for patients with moderate, severe carotid artery stenosis, or occlusion.

SEVERITY		Mean ± S.D.	Std. Error Mean
Occluded (n = 5)	RBANS immediate memory	97.6 ± 16	6.97567
	RBANS visualspatial/constructional	77.4 ± 11	4.79166
	RBANS language	94.2 ± 9	4.02989
	RBANS attention	87.2 ± 15	6.88767
	RBANS delayed memory	86 ± 11	4.84768
	RBANS total scale	85.6 ± 11	4.69681
Mod Stenosis (n = 7)	RBANS immediate memory	83.7 ± 19	7.05325
	RBANSvisualspatial/constructional	66.6 ± 9	3.51769
	RBANS language	90 ± 15	5.53345
	RBANS attention	78.9 ± 12	4.67734
	RBANS delayed memory	87.3 ± 19	7.07011
	RBANS total scale	75.6 ± 13	5.07025
Severe Stenosis (n = 27)	RBANS immediate memory	85.4 ± 20	3.92714
	RBANSvisualspatial/constructional	77.9 ± 17	3.24222
	RBANS language	96.8 ± 14	2.76065
	RBANS attention	90.9 ± 18	3.43077
	RBANS delayed memory	88.4 ± 18	3.49736
	RBANS total scale	84.4 ± 18	3.55116

A one-sample, one-tailed t-test was used to determine if these results were significantly different from the established normal score (100) on the test. A one-tailed test was used as we were particularly interested in looking for a cognitive decline in the patients. All 3 subgroups demonstrate a minimum of 3 cognitive areas of significant deficit as compared to the normal scores (Table 7).

Table 7: One-tailed t-test for cognitive function based on severity of disease.

Severity	RBANS DOMAIN	t –value	Significance (1-tailed, p<.05)
Occluded	Immediate Memory	-.344	.37
n = 5	Visuospatial/constructional	-4.717	.00*
	Language	-1.439	.11
	Attention	-1.858	.07
	Delayed memory	-2.888	.03*
	Total Scale	-3.066	.02*
Moderate Stenosis	Immediate Memory	-2.309	.03*
n = 7	Visuospatial/constructional	-9.503	.00*
	Language	-1.807	.06
	Attention	-4.520	.00*
	Delayed memory	-1.798	.06
	Total Scale	-4.818	.00*
Severe Stenosis	Immediate Memory	-3.716	.00*
n = 27	Visuospatial/constructional	-6.831	.00*
	Language	-1.154	.13
	Attention	-2.656	.01*
	Delayed memory	-3.315	.00*
	Total Scale	-4.370	.00*

*p<.05

In the occluded group, significant cognitive deficits were found in the visuospatial/ constructional (p<.00) and delayed memory domains (p<.03). In the moderately stenotic subgroup, there was significant cognitive decline in the immediate memory (p<.03), visuospatial/constructional (p<.00), and attention (p<.00) domains. In the severely stenotic subgroup, there was significant cognitive deficit in all domains; immediate memory, visuospatial/constructional, delayed memory and total scale score (p<.00) and attention (p<.01) except language. All subgroups showed a significant cognitive decline on the RBANS Total Scale score, $p<.02$ in the occluded group, and $p<.00$ for the moderate and severe stenosis groups.

Another area of cognition considered in this study was executive function. Table 8 shows the mean score on the EXIT for each of the subgroups.

Table 8: Executive dysfunction (EXIT) results in patients with moderate, severe carotid artery stenosis or occlusion.

	Number of patients	Mean score ± S.D.
Occluded	5	10 ± 5
Moderate Stenosis	7	12.9 ± 6
Severe Stenosis	27	9 ± 5
Total	39	9.8 ± 5

In considering a score of 15 or greater as indicating executive dysfunction, then the moderately stenotic subgroup is beginning to show a score closest to this. However, the scores are all below 15, and there is not a significant finding in these 39 patients.

5.2.2. Physical Performance Test Results by Level of Severity

In the area of physical performance, as tested via the PPT (9-item), it was found that no patient reached a perfect score of 36/36. For all 39 patients, scores ranged from 19/36 – 30/36 with a mean score of 27/36. Table 9 is a summary of the PPT scores for the three different subgroups.

Table 9: Physical Performance Test (9-item) in patients with carotid artery disease.

	Number of patients	Mean score ± S.D.
Occluded	5	26 ± 2
Moderate Stenosis	7	24 ± 2
Severe Stenosis	27	28 ± .8
Total	39	27 ± .7

The Physical Performance Test (7-item) was also analyzed. Although it was the goal of this project to include the ambulation on stairs categories on this test and report the 9-item scores, there were two patients who would not participate on the stairs for reasons not related to their cerebrovascular status. One patient had recently recovered from a sprained ankle and opted not to do the stair tests, and another refused to do the stairs due to undefined "leg problems". Table 10 is a summary of the 7-item PPT scores.

Table 10: Physical Performance Test (7-item) in patients with carotid artery disease.

	Number of patients	Mean score ± S.D.
Occluded	5	22 ± 2
Moderate Stenosis	7	19 ± 3
Severe Stenosis	27	22 ± 3
Total	39	21 ± 3

As with the 9-item PPT, no subject reached a perfect score on the 7-item PPT of 28/28. The range of scores for these patient groups was 19/28-22/28.

5.2.3. Instrumental Activities of Daily Living by Level of Severity

The final outcome measure, instrumental activities of daily living, was measured by the Lawton IADL scale. Most scores, at 26/27 or 27/27, were very close to the maximum score of 27/27 indicating independence in IADL's. Figure 8 is a histogram reflecting the distribution of the IADL scores.

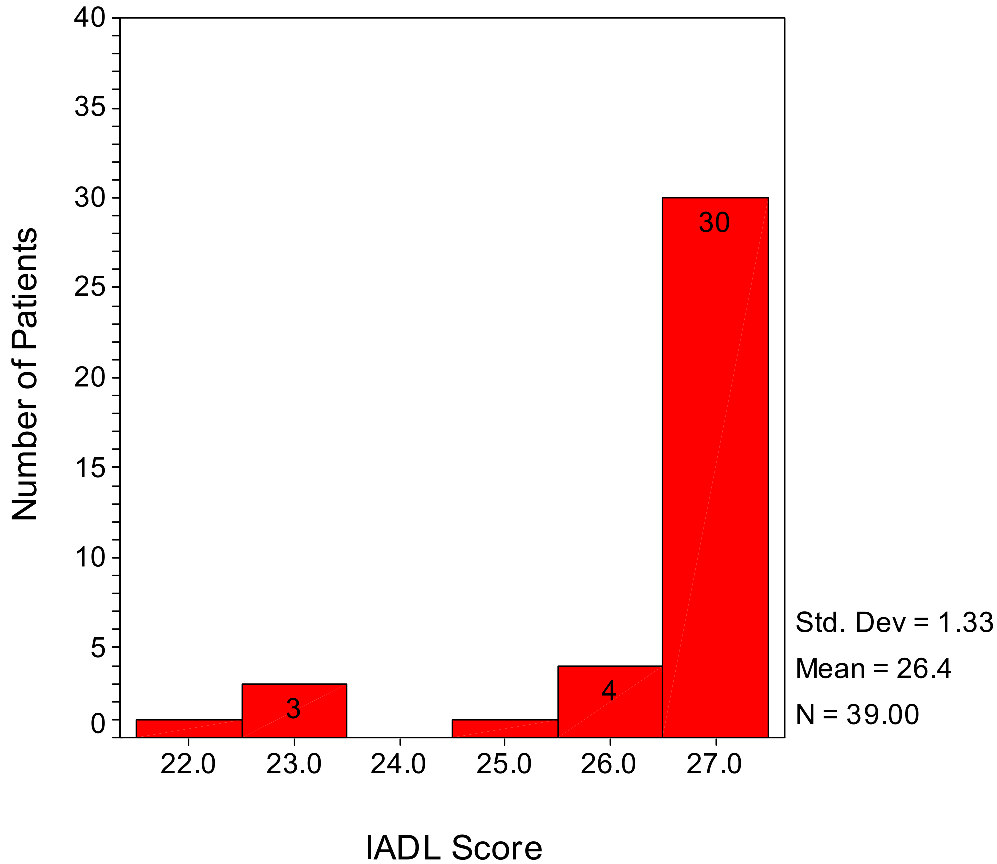

Figure 8: Histogram of Lawton IADL Scores for all Patients.

Table 11 is a summary of the IADL scores by severity of disease for these patients.

Table 11: Instrumental activities of daily living in patients with carotid artery disease.

	Number of patients	Mean score ± S. D.
Occluded	5	26 ± 1
Moderate Stenosis	7	26 ± .6
Severe Stenosis	27	27 ± .2
Total	39	26 ± .2

5.3. Analysis by Side of Involvement in Carotid Artery Disease

Another way to consider the outcomes for these patients with carotid artery disease is to look for differences in function based on the sidedness of the brain involvement. Thus, data of the 39 patients was analyzed comparing the location of the lesion as being right, left or both sides involved. There were 14 patients with right side involvement, 13 patients with left side involvement, and 12 patients with bilateral disease. Table 12 is a summary of the descriptive data for the outcome measures based on side of involvement.

Table 12: Descriptive Data for RBANS, EXIT, PPT, IADL Measures Based on Location of Lesion.

	Outcome measure	Mean ± S.D.
Right Side (n = 14)	RBANS immediate memory	92 ± 20
	RBANS visuospatial/constructional	83 ± 19.2
	RBANS language	102 ± 16.2
	RBANS attention	96 ± 18.5
	RBANS delayed memory	94 ± 20
	RBANS total scale	92 ± 21
	EXIT Score	10 ± 5.9
	PPT	28 ± 5.3
	IADL	26 ± 1.5
Left Side (n = 13)	RBANS immediate memory	82 ± 16.7
	RBANS visuospatial/constructional	73 ± 13.8
	RBANS language	91 ± 11.8
	RBANS attention	85 ± 15
	RBANS delayed memory	85 ± 12
	RBANS total scale	79 ± 12.6
	EXIT Score	11 ± 5.7
	PPT	28 ± 2.8
	IADL	27 ± 1.1
Both Sides (n = 12)	RBANS immediate memory	86 ± 21.9
	RBANS visuospatial/constructional	71 ± 9.2
	RBANS language	92 ± 10
	RBANS attention	83 ± 15.3
	RBANS delayed memory	84 ± 17.7
	RBANS total scale	78 ± 12.1
	EXIT Score	9 ± 4
	PPT	26 ± 4.4
	IADL	26 ± 1.4

An ANOVA was performed to identify if these 3 groups were different on any of the outcome measures (Table 13).

Table 13: ANOVA table of between group differences for location of lesion in patients with carotid artery disease.

	Sum of Squares	df	Mean Square	F	Sig.
RBANS immediate memory					
Between Groups	774.566	2	387.283	1.009	.36
Within Groups	13816.101	36	383.781		
Total	14590.667	38			
RBANS visualspatial/constructional					
Between Groups	1068.119	2	534.060	2.399	.11
Within Groups	8012.804	36	222.578		
Total	9080.923	38			
RBANS language					
Between Groups	856.917	2	428.458	2.422	.10
Within Groups	6368.519	36	176.903		
Total	7225.436	38			
RBANS attention					
Between Groups	1216.382	2	608.191	2.251	.12
Within Groups	9725.054	36	270.140		
Total	10941.436	38			
RBANS delayed memory					
Between Groups	854.190	2	427.095	1.489	.24
Within Groups	10329.400	36	286.928		
Total	11183.590	38			
RBANS total scale					
Between Groups	1624.863	2	812.431	3.169	.05*
Within Groups	9228.112	36	256.336		
Total	10852.974	38			
EXIT Score					
Between Groups	16.843	2	8.422	.298	.74
Within Groups	1016.900	36	28.247		
Total	1033.744	38			
Physical Performance Test (9-item total)					
Between Groups	23.489	2	11.745	.642	.54
Within Groups	677.588	36	18.822		
Total	701.077	38			
Lawton IADL					
Between Groups	2.036	2	1.018	.560	.58
Within Groups	65.400	36	1.817		
Total	67.436	38			

* $p<.05$

In this analysis, for the specific cognitive domains, no difference was found between the groups with different sides of carotid artery disease, or both sides involved with carotid artery disease. However, the cognitive domains of visuospatial/constructional, and language were approaching significance with p values of p< .11, p< .10 and the RBANS total scale was significant p< .05 respectively. None of the other outcome measures were significantly different.

5.3.1. Cognitive Test Results by Side of Involvement

A one-sample t-test was conducted using right, left and both sides of involvement and was compared to cognition. Again, there were significant differences from the normal scores of cognitive function identified (Table 14).

Table 14: One-tailed t-test for cognitive function based on side of involvement.

	RBANS DOMAIN	t –value	Significance (1-tailed, p<.05)
Right Side n = 14	Immediate Memory	-1.457	.09
	Visuospatial/constructional	-3.381	.00*
	Language	.338	.37
	Attention	-.881	.20
	Delayed memory	-1.089	.15
	Total Scale	-1.492	.08
Left Side n = 13	Immediate Memory	-3.970	.00*
	Visuospatial/constructional	-7.029	.00*
	Language	-2.656	.01*
	Attention	-3.584	.00*
	Delayed memory	-4.617	.00*
	Total Scale	-6.138	.00*
Both Sides n = 12	Immediate Memory	-2.268	.02*
	Visuospatial/constructional	-11.071	.00*
	Language	-2.680	.01*
	Attention	-3.836	.00*
	Delayed memory	-3.119	.00*
	Total Scale	-6.340	.00*

* p<.05

From these data it was apparent that persons with either both carotid arteries affected, or the left side involved, cognitive function was impaired as compared to the normal scores in all cognitive domains measured with the RBANS ($p<.05$). Patients with right side involvement demonstrated significant impairment in visuospatial/constructional abilities ($p<.00$), and immediate memory and total scale domains were approaching significance ($p<.09$, $p<.08$ respectively). The side of involvement was not a significant factor in the other outcome measures of executive function, physical function on the PPT and the Lawton IADL scale.

5.4. Correlations between Outcome Variables

A Pearson's correlation coefficient was calculated to determine the relationships between cognitive function and IADL ability (Table 15).

Table 15: Relationship between cognitive function and IADL's.

		RBANS Total Scale	Lawton IADL	EXIT Score
RBANS Total	Pearson Correlation Scale	1	.023	-.57*
	Sig. (2-tailed)	.	.890	.000
	N	39	39	39
Lawton IADL	Pearson Correlation	.023	1	-.42*
	Sig. (2-tailed)	.890	.	.008
	N	39	39	39
EXIT Score	Pearson Correlation	-.57*	-.42*	1
	Sig. (2-tailed)	.000	.008	.
	N	39	39	39

There was not a significant correlation between the RBANS and the Lawton IADL scale. However, there was a moderately strong[137] negative correlation between the RBANS total scale and the EXIT measure of executive function ($r = -.57$). The EXIT also was moderately negatively correlated with the Lawton measure of IADL ($r=-.42$).

5.4.1. Correlations between Co-morbidities and Medications and Outcome Variables

Pearson correlation coefficients were also calculated to determine a relationship between the number of comorbidities of the patients and their performance on the RBANS total scale score, the EXIT, the PPT (9-item and 7-item), and the Lawton IADL scores. The same calculations were performed to determine a relationship between the effects of number of medications and performance. No significant correlations were found.

5.5. Detailed Analysis of Timed Items on the Physical Performance Test

The Physical Performance Test items were timed for performance. A detailed analysis of each of the items was also conducted. Table 16 is a summary of the items for all the patients tested.

Table 16: Physical Performance Timed Items for Patients with Asymptomatic Carotid Artery Disease.

(n = 39)	Mean seconds ± S.D.	Range	Normal PPT time (for score= 4)
Sentence writing	15.13 ± 6	8.7 – 35.9	≤10 sec
Eating (simulated)	13.87 ± 3	9.3 – 19.2	≤10 sec
Lifting a book	2.03 ± 1	.8 – 7.5	≤ 2 sec
Put on jacket	14.17 ± 4	7.7 – 26.3	≤10 sec
Pick up penny	4.05 ± 4	1.8 – 26.7	≤ 2 sec
50’ Walk	15.93 ± 4	0 – 25.5	≤15 sec
Climb one flight stairs	7.28 ± 3	0 – 20.6	≤ 5 sec

5.5.1. Analysis of the PPT Timed Items and the Level of Severity of Carotid Stenosis

Further analysis was done to see if there was a difference on any PPT item based on the severity of the carotid artery disease. Table 17 is the data for each timed item based on the severity groups.

Table 17: Physical Performance results on time items for patients with moderate, severe carotid artery stenosis or occlusion.

Item (Time for score = 4)	Group	Mean ±S.D.	Range
Sentence writing	unilateral stenosis mod (n=3)	18.9 ± 2	16.8 – 20.8
(</= 10 sec)	unilateral stenosis severe (n = 18)	14.0 ± 6	8.7 – 35.9
	unilateral occlusion (n = 3)	16.5 ± 9	11.2 – 26.7
	bilateral stenosis mod (n = 4)	14.5 ± 3	12.3 – 18.5
	bilateral stenosis severe (n = 9)	15.5 ± 5	9.2 – 24.5
	bilateral occlusion (n = 2)	16.8 ± 4	14.1 – 19.7
Eating (simulated)	unilateral stenosis mod	18.2 ± .8	17.7 – 19.1
(</= 10 sec)	unilateral stenosis severe	13.3 ± 3	9.5 – 18.6
	unilateral occlusion	13.4 ± .7	12.6 – 14
	bilateral stenosis mod	16.2 ± 3	13.2 – 19.1
	bilateral stenosis severe	13.5 ± 3	9.3 – 16.5
	bilateral occlusion	10.6 ± .8	10 – 11.1
Lifting a book	unilateral stenosis mod	1.6 ± .7	1.2 – 2.5
(</= 2 sec)	unilateral stenosis severe	2.0 ± .6	.1 – 3.5
	unilateral occlusion	2.5 ± 1	1.8 – 3.8
	bilateral stenosis mod	2 ± .6	1.5 – 2.8
	bilateral stenosis severe	2 ± 1	.76 – 5.5
	bilateral occlusion	4.1 ± 5	.79 – 7.4
Put on jacket	unilateral stenosis mod	20.8 ± 5	16.2 – 26.3
(</= 10 sec)	unilateral stenosis severe	14.5 ± 4	7.7 – 22.8
	unilateral occlusion	13.6 ± 3	10.9 – 16.2
	bilateral stenosis mod	13.1 ± 2	11.5 – 16.4
	bilateral stenosis severe	12.7 ± 3	8.0 – 16.9
	bilateral occlusion	10.7 ± 4	8.0 – 13.3
Pick up penny	unilateral stenosis mod	11.4 ±13	3.5 – 26.7
(</= 2 sec)	unilateral stenosis severe	3.5 ± 2	2.0 – 11.1
	unilateral occlusion	2.9 ± .5	2.5 – 3.5
	bilateral stenosis mod	3.7 ± 1	2.5 – 5.4
	bilateral stenosis severe	3.6 ± 2	2.2 – 8.0
	bilateral occlusion	2.1 ± .5	1.8 – 2.5
50’ Walk	unilateral stenosis mod	18.5 ± 6	14.8 – 25.5
(</= 15 sec)	unilateral stenosis severe	16.3 ± 3	12.4 – 24.5
	unilateral occlusion	16.6 ± .4	16.3 – 17.0
	bilateral stenosis mod	16.0 ± 3	12.7 – 19.5
	bilateral stenosis severe	13.1 ± 5	.00 - 18
	bilateral occlusion	19.8 ± 3	17.7 – 21.9

Climb one flight of stairs (</= 5 sec)	unilateral stenosis mod unilateral stenosis severe unilateral occlusion bilateral stenosis mod bilateral stenosis severe bilateral occlusion	5.1 ± 4 7.8 ± 2 6.4 ± .3 7.9 ± 2 6.4 ± 3 10.3 ± 15	.00 – 7.7 5.4 – 11.9 6.2 – 6.7 5.8 - 10 .00 – 9.5 .00

mod: moderate

An analysis of all 6 patient groups demonstrated a significant difference on 3 of the timed tasks. An ANOVA test demonstrated that there were significant differences between the groups on the three PPT timed items. (Table 18)

Table 18: ANOVA table for between group differences on the 7-item PPT.

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
Sentence writing	Between Groups	77.884	5	15.577	.471	.80
	Within Groups	1092.418	33	33.104		
	Total	1170.303	38			
Eating (simulated)	Between Groups	107.406	5	21.481	3.570	.01*
	Within Groups	198.542	33	6.016		
	Total	305.948	38			
Lift a book	Between Groups	9.915	5	1.983	1.320	.28
	Within Groups	49.560	33	1.502		
	Total	59.475	38			
Put on jacket	Between Groups	183.599	5	36.720	2.847	.03*
	Within Groups	425.632	33	12.898		
	Total	609.231	38			
Pick up penny	Between Groups	179.847	5	35.969	2.584	.04*
	Within Groups	459.287	33	13.918		
	Total	639.134	38			
50' Walk	Between Groups	123.199	5	24.640	1.677	.17
	Within Groups	484.990	33	14.697		
	Total	608.188	38			
Climb one flight stairs	Between Groups	48.868	5	9.774	.878	.51
	Within Groups	367.373	33	11.133		
	Total	416.240	38			

* $p < .05$

The three tasks of simulated eating, putting on a jacket and picking up a penny were all significantly different within the groups at the $p<.01$, $p< .03$ and $p< .04$ levels. A Tukey post hoc comparison was completed and revealed that the unilateral moderate stenosis group had a higher mean than the other groups for all 3 tasks, simulated eating, picking up a penny and putting on a jacket.

An analysis was also done combining the 6 patient groups by severity of disease into 3 groups, unilateral and bilateral moderate stenosis, unilateral and bilateral severe stenosis and unilateral and bilateral occlusion. (Table 19)

Table 19: ANOVA table for between group differences for the timed PPT items, based on severity of carotid disease.

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
Sentence writing	Between Groups	32.431	2	16.216	.513	.60
	Within Groups	1137.872	36	31.608		
	Total	1170.303	38			
Eating (simulated)	Between Groups	90.320	2	45.160	7.540	.00*
	Within Groups	215.628	36	5.990		
	Total	305.948	38			
Lifting a book	Between Groups	6.612	2	3.306	2.251	.12
	Within Groups	52.863	36	1.468		
	Total	59.475	38			
Put on jacket	Between Groups	52.083	2	26.042	1.683	.20
	Within Groups	557.148	36	15.476		
	Total	609.231	38			
Pick up penny	Between Groups	79.269	2	39.635	2.549	.09
	Within Groups	559.865	36	15.552		
	Total	639.134	38			
50' Walk	Between Groups	39.254	2	19.627	1.242	.30
	Within Groups	568.935	36	15.804		
	Total	608.188	38			
Climb one flight stairs	Between Groups	4.894	2	2.447	.214	.81
	Within Groups	411.347	36	11.426		
	Total	416.240	38			

* $p < .05$

Simulated eating was the only item that was significantly different ($p<.00$) between the levels of severity. Tukey post hoc comparisons revealed that the moderately stenotic group had a significantly higher mean than the severely stenotic and occluded groups. Thus, these subjects took significantly longer on the simulated eating task. This is a consistent finding with the previous analysis of the 6 groups.

5.5.2. Analysis of the PPT Timed Items and the Side of Carotid Disease

In an analysis of the 7 timed items looking for differences based on location of the lesion, right ICA, left ICA or both sides, there were no significant differences found on any of the items at the $p<.05$ level.

VI. Conclusion:

This was a prospective observational study that was designed to address 2 specific aims: 1) to determine if patients with asymptomatic carotid artery disease of a moderate severity or greater demonstrate deficits in cognitive and physical function and 2) to determine if there was a correlation between the cognitive measures (RBANS and EXIT) and the patients' performance of instrumental activities of daily living.

It was found that patients with a moderate or severe degree of stenosis or an occluded carotid artery did have deficits in multiple cognitive domains, as assessed by the RBANS. There was not a significant difference if the disease was unilateral or bilateral, thus severity of disease was the category examined. However, there was a difference in cognitive function based on laterality of disease, and it appeared that patients with left sided and bilateral disease demonstrated deficits in more cognitive domains than the patients with right sided disease, who mainly demonstrated deficits in the visuospatial/constructional domain. The cognitive domain of executive function, as assessed via the EXIT was not found to be impaired in the study.

We also determined that physical performance as assessed via the PPT 9-item, 7-item tests and the 7 timed tasks were impaired, with all patient subgroups demonstrating sub-maximal scores on the tests. A sub-maximal score could be interpreted as an early indicator of preclinical disability and could suggest that the patient was not functioning optimally. In further analysis of the PPT results, the individual tasks of the test were timed, in order to determine if a certain task was difficult for persons with asymptomatic carotid artery disease. The task of simulated eating, a fine motor coordination task, was the task that was identified as taking the most time in the moderately stenotic subgroup of patients. The researchers suggest that this poorer performance on the PPT might be interpreted as a "symptom" in these reportedly asymptomatic patients.

With the Lawton Instrumental Activities of Daily Living assessment there was not a deficit in functional performance demonstrated in any of the patient subgroups. The researchers observed that for this population the assessment tool demonstrated a ceiling effect.

The second aim of the study was to correlate the patients' cognitive performance with performance of instrumental activities of daily living as assessed via the Lawton IADL scale. We did not find a relationship between cognitive function as assessed via the RBANS scale, however there was a moderately strong negative correlation between cognitive executive function as assessed via the EXIT and the Lawton IADL scale. The researchers concluded that the impairments noted in the detailed cognitive examination of the RBANS were not severe enough to have affected the more general activities assessed by the Lawton. Additionally, the Lawton was a self-report assessment tool, and these patients were not reporting any difficulties on clinical examination.

In conclusion, patients with asymptomatic carotid artery disease (moderately, severely stenotic or occluded) demonstrated deficits on the RBANS measure of cognitive function and on the Physical Performance Test. In addition, the EXIT assessment and IADL function were negatively correlated, whereas the RBANS and the Lawton IADL assessment were not correlated. Regarding the identified cognitive deficits, it cannot be unrecognized that these deficits in this patient sample may be related to other conditions that can impair cognition that have not been identified in this study. From this study, it is concluded that patients with carotid artery disease who are reportedly asymptomatic on clinical examination, when evaluated in greater detail might have symptoms that should be considered in the overall assessment and plan for intervention for the carotid artery disease and risk of stroke.

VII. Cognitive and Physical Performance in Patients with Asymptomatic Carotid Artery Stenosis and Occlusion

Abstract

Background and Purpose: The purpose of this study was to determine if patients with asymptomatic carotid artery stenosis and occlusion demonstrate deficits in cognitive and physical performance. The relationship between cognitive measures and performance of instrumental activities of daily living was examined.

Methods: Thirty-nine patients with asymptomatic carotid artery stenosis of moderate and severe degrees, or occlusion were tested. Cognition was assessed via the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and the Executive Interview (EXIT). Physical performance was assessed via the Physical Performance Test (PPT), and the Lawton Instrumental Activities of Daily Living.

Results: Deficits in cognitive function were found on the RBANS for all levels of stenosis and occluded subgroups in the domains of visuospatial/constructional and delayed memory, in the moderate stenosis subgroup in immediate memory, attention and visuospatial/constructional, and in the severe subgroup in all domains except language. There were no significant findings on the EXIT. Decreased performance on the PPT was identified in all 3 subgroups. The Lawton IADL did not identify any decrease in performance.

Conclusions: Deficits in cognitive and physical function were found in this observational study of patients with asymptomatic carotid artery stenosis and occlusion, indicating that asymptomatic patients may not be truly asymptomatic. This potential change in status needs to be considered as patients are being evaluated for interventions to manage their carotid artery disease.

Introduction

In asymptomatic patients with carotid artery stenosis and occlusion, stroke risk is not clear. Autret et.al. followed 242 asymptomatic patients for approximately 2.5 years and determined a .23% risk of stroke in patients with a low amount of stenosis, 2.48% risk in patients with moderate stenosis, and 1.71% risk in severe stenosis.[8] Other investigators have found similar low risk in these patients.[10] However, in the Asymptomatic Carotid Artery Study (ACAS), the researchers recommended that in asymptomatic carotid artery disease of 60% stenosis or greater, the procedure of a carotid endarterectomy in patients with good general health can help to reduce the risk of a stroke occurring on the ipsilateral side of the brain by 53% over 5 years.[19] Carotid endarterectomy is the intervention of choice in situations of high-grade (greater than 90%) asymptomatic carotid artery stenosis.[53] In asymptomatic patients with carotid artery occlusion, Hennerici et.al. determined a stroke risk of 16%, and a TIA incidence of 10% in 49 asymptomatic occluded patients over a 31.2 month period.[11] In contrast, studies by Power et al. al. and Bornstein and Norris found minimal risk of stroke (less than 3%) in asymptomatic patients with occlusion.[12,13]

The identification of asymptomatic patients is not as clear as symptomatic patients. There are no obvious clinical findings, and often the stenotic or occluded carotid artery is found as an incidental finding during a medical work-up. It is suspected that subtle physical, cognitive or emotional changes in function could occur due to disruption of the blood flow to the brain that is not recognized by the patient. It is the purpose of this research study to determine if patients with asymptomatic carotid artery stenosis and occlusion, demonstrate deficits in cognitive and physical performance measures. The study attempts to determine if there is a correlation between the cognitive functions and the patient's ability to complete instrumental activities of daily living (IADL's).

Methods:

Thirty-nine patients with asymptomatic carotid artery disease participated and were recruited from the Neurosurgery clinic at the University of Pittsburgh Medical Center. After the study was explained and consent was obtained, the patients were divided into six subgroups; unilateral and bilateral moderate stenosis (50-69%), unilateral and bilateral severe stenosis (70-99%) and unilateral and bilateral occlusion, based on the computed tomographic arteriography (CTA) scan, magnetic resonance imaging (MRI) study or carotid doppler study as read by the neurosurgeon. The patients were often referred to the neurosurgeon for evaluation of the status of the carotid artery pathology. Asymptomatic status was determined by patient report during the history and the clinical examination. Patients were excluded from the study if they had a history of stroke, dementia as determined by the physician, were unable to speak English and answer questions, were precluded from weight bearing due to an orthopedic condition, or had severe cardiopulmonary compromise.

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[119] and the EXIT[120] were used to measure cognition. The RBANS is a recently developed test battery that is recognized as a clinically useful tool to rapidly screen neuropsychological status in the acute care setting to help guide medical and surgical decision making regarding cognitive status.[121] It was developed to characterize cognitive decline in older adults, and serve as a screening battery for younger patients. The test assesses 5 domains of cognitive function including immediate memory, visuospatial/constructional, language, attention and delayed memory. Scoring on the test has been standardized in age groups with a mean score of 100 and standard deviation of 15 points as the standard score. The test has been shown to be reliable for all age groups with an overall total reliability score of .94[121] and has been found to be a valid test in a mixed adult population with a variety of neuropsychological problems.[121] The sensitivity and specificity of the test to the detection of dementia was found to be 90%..[119] The test was chosen for this study due to its ease of use and its ability to screen cognition within very definitive domains.

The EXIT test was used to assess the sixth cognitive domain of executive function. Executive function is the process of orchestrating relatively simple actions such as movements or ideas into goal-directed behaviors.[138] The 25-item tool has demonstrated high internal consistency (Cronbach's alpha = .87). It was shown in a pilot study to be valid and reliable to assess executive function and discriminate between different functional levels of persons tested and the severity level of their dementia.[120]

The Physical Performance Test (PPT) 9-item was used to assess physical function.[122] This test is a global measure of physical performance that assesses basic and complex activities of daily living (ADL's).[122] The test includes the items: writing a sentence, simulated eating, donning and doffing a jacket, 360 degree turn right and left, lifting a book to a shelf, picking up a penny from the floor, walking 50 feet, climbing one flight of stairs, climbing several flights of stairs (4 maximum). The PPT 9-item test has been shown to demonstrate internal consistency (Cronbach's alpha = .87) and interrater reliability (r = .99) in older adults.[122] In preparation for the study, the primary invesigator demonstrated strong interrater reliability (r=.92) with an experienced researcher who uses the PPT.

The Lawton Instrumental Activities of Daily Living Scale (IADL)[113] requires the patient to report if they are independent, need assistance, or are unable to complete the instrumental ADL skills. The Lawton IADL scale has been found to be valid and practical for use in a variety of elderly age groups.[113] Patients were tested once by a trained investigator.

Statistical Analysis

Descriptive data were collected on the demographic data of the patients, their medications, comorbidities and all the outcome tools (RBANS, EXIT, PPT, IADL). An analysis of variance (ANOVA) was used to determine if there were significant differences between the 6 patient groups based on severity of disease, unilateral vs. bilateral involvement, and also on laterality of the disease (left side vs. right side vs. both sides involved). A one-tailed t-test was used to determine if there was a difference in any of the RBANS cognitive measures from the established normal score. The use of a one-tail test was due to the expectation of a decline in function for the patient. The mean EXIT score for executive function was calculated for each group and compared to the recommended cut-off score of 15/50, with higher scores indicating greater executive dysfunction.[120,139] Similarily, the mean 9-item PPT score and the Lawton IADL score were calculated and compared to the maximum scores of 36/36 and 27/27 respectively. A lower score indicates that a person needs more time to complete a task on the PPT, or assistance with a task on the IADL, thus suggesting the beginning of a physical decline, and a possible status of preclinical disability.[124,140] Correlations were calculated between the cognitive scores (RBANS and EXIT scores) and the Lawton IADL scores via Pearson's Correlation coefficients.

Results:

Thirty-nine patients with asymptomatic carotid artery disease were tested (Table 20).

Table 20: Diagnostic groups by gender, age and side affected in patients with asymptomatic carotid artery disease.

Diagnostic Group	Gender	Mean Age (yrs.) ± Standard Deviation	Age Range	Side Involved (R=right L=left B=both)
Unilateral Stenosis Moderate n = 3, (7.7%)	2 male (67%) 1 female (33%)	78 ± 6.23	71-83	2 – R 1 – L
Unilateral Stenosis Severe n = 18, (46.2%)	11 male (61%) 7 female (39%)	75 ±7.65	55-87	6 – R 8 – L
Unilateral Occlusion n = 3, (7.7%)	2 male (67%) 1 female (33%)	63 ± 15.5	48-79	2 – R 1 – L
Bilateral Stenosis Moderate n = 4, (10.3%)	3 male (75%) 1 female (25%)	76 ± 8.14	66-85	2 – L 2 – B
Bilateral Stenosis Severe n = 9, (23.1%)	5 male (56%) 4 female (44%)	73 ± 5.48	64-79	1 – L 8 – B
Bilateral Occlusion n = 2, (5.1%)	1 male (50%) 1 female (50%)	63 ± 4.95	59-66	2 – B
All patients (n = 39)	23 male (59%) 16 female (41%)	73 ± 8.49	48-87 years	14 – R 13 – L 12 – B

The sample was slightly dominant for males, with a mean age of 73 years (48-87). Most patients (70%) tested in this study were severely stenotic, with another 13 % occluded, and the remaining 17% had moderate carotid artery stenosis. Patients with bilateral involvement were grouped into the side of stenosis that the surgeon would be considering for surgery. In situations when the level of stenosis was the same, or occlusion existed bilaterally, then the patient was classified with bilateral disease. For the 39 patients, there were 14 right side, 13 left side and 12 with bilateral involvement.

The most common comorbidities that the patients had were hypertension (38.5%), hypercholesteremia (36%) diabetes mellitus (33.3%) coronary artery disease (30.8%), and cardiac arrhythmia (12.8%). There were a wide variety of medications being taken. The most common categories of medications were the CNS agents which included 5 different medications, the antihypertensives and the antilipemics. The 2 most common medications were aspirin (54%), and the antilipemic Zocor (26%).

With the 39 patients, the ANOVA revealed no significance differences between the groups (unilateral or bilateral moderate, severe disease, or occlusion) on any of the outcome measures. Because no significant differences between the groups were found at the $p<.05$ level and due to the small sample size, the asymptomatic patients with unilateral and bilateral moderate, unilateral and bilateral severe, or unilateral and bilateral occluded carotid artery disease were considered together for the rest of the remaining data analysis.

On the RBANS cognitive test, a one-sample, one-tailed t-test was used to determine if these results were significantly different from the established normal score (100). A one-tailed test was used as the investigators were attempting to determine if the subjects had cognitive decline. All 3 subgroups demonstrated a minimum of 3 cognitive areas of significant deficit as compared to normal values. Individual domain scores ranged from 84-98 in the occluded group, 67-90 in the moderate stenosis group and 84-97 in the severe stenosis group. Table 21 is a summary of the RBANS mean scores and the t-test results.

Table 21: RBANS Scores, means, standard deviations, and t-test results based on level of stenosis.

Severity	RBANS DOMAIN	Mean	t – value	Significance (1-tailed, *p<.05)
Occluded n = 5	Immediate Memory	98 ± 15.6	-.344	.37
	Visuospatial/constructional	77 ± 10.71	-4.717	.00*
	Language	94 ± 9.01	-1.439	.11
	Attention	87 ± 15.4	-1.858	.07
	Delayed memory	86 ± 10.84	-2.888	.03*
	Total Scale	86 ± 10.5	-3.066	.02*
Moderate Stenosis n = 7	Immediate Memory	84 ± 18.66	-2.309	.03*
	Visuospatial/constructional	67 ± 9.31	-9.503	.00*
	Language	90 ± 14.64	-1.807	.06
	Attention	79 ± 12.38	-4.520	.00*
	Delayed memory	87 ± 18.71	-1.798	.06
	Total Scale	76 ± 13.41	-4.818	.00*
Severe Stenosis n = 27	Immediate Memory	85 ± 20.41	-3.716	.00*
	Visuospatial/constructional	78 ± 16.85	-6.831	.00*
	Language	97 ± 14.34	-1.154	.13
	Attention	91 ± 17.83	-2.656	.01*
	Delayed memory	88 ± 18.17	-3.315	.00*
	Total Scale	84 ± 18.45	-4.370	.00*

In the occluded subgroup, significant cognitive deficits were found in the visuospatial/ constructional (mean score 77, p<.00) and delayed memory domains (mean score 86, p<.03). In the moderately stenotic subgroup, there was significant cognitive decline in the immediate memory (mean score 84, p<.03), visuospatial/constructional (mean score 67, p<.00), and attention (mean score 79, p<.00) domains. In the severely stenotic subgroup, there was significant cognitive deficit in all domains; immediate memory (mean score 85, p<.00), visuospatial/constructional (mean score 78, p<.00), attention (mean score 91, p<.01), delayed memory (mean score 88, p<.00) with the exception of language. All subgroups showed a significant cognitive decline on the RBANS total scale score, (p<.02 in the occluded subgroup), p<.00 for the moderate and severe stenosis subgroups).

For the cognitive domain of executive function, mean scores for each severity group were compared to the recommended cut-off score of 15/50..[120] All mean scores for the groups were below this level (occluded 10/50, moderate stenosis 13/50, and severe stenosis 9/50) indicating no executive dysfunction.

With the PPT, no patient reached a perfect score of 36/36. For all 39 patients, scores ranged from 19/36 – 30/36 with a mean score of 27/36. By severity group, the PPT mean scores were: occluded 26/36, moderate stenosis 24/36 and severe stenosis 28/36.

The final outcome measure, instrumental activities of daily living, was measured by the Lawton IADL scale. Eighty-seven percent of the scores, at 26/27 or 27/27, were very close to the maximum score of 27/27 indicating independence in IADL's. By severity group, the IADL mean scores for the occluded and moderate stenosis were 26/27, and severe stenosis 27/27.

An ANOVA was performed to identify if patients with right (n = 14), left (n = 13) and bilateral involvement (n=12) were different on any of the outcome measures. No difference was found between the groups with different sides of carotid artery disease, or both sides involved with carotid artery disease. However, the RBANS domains of visuospatial/constructional, and language were approaching significance with p values of $p< .11$, $p< .10$ and the RBANS total scale was significant $p< .05$ respectively. None of the other outcome measures (EXIT, PPT, Lawton IADL) were significantly different.

Laterality of brain involvement (right, left and both sides) was compared to the normal standardized cognitive score for the RBANS by a one-sample t-test. Significant differences from the normal standardized score (100) were found for most of the cognitive domains. (Table 22)

Table 22: RBANS scores by location of lesion group, and t-test results.

	RBANS DOMAIN	Mean	t – value	Significance (1-tailed, *p<.05)
Right Side n = 14	Immediate Memory	92 ± 20	-1.457	.09
	Visuospatial/constructional	83 ± 19.21	-3.381	.00*
	Language	102 ± 16.23	.338	.37
	Attention	96 ± 18.5	-.881	.20
	Delayed memory	94 ± 19.96	-1.089	.15
	Total Scale	92 ± 20.95	-1.492	.08
Left Side n = 13	Immediate Memory	82 ± 16.7	-3.970	.00*
	Visuospatial/constructional	73 ± 13.81	-7.029	.00*
	Language	91 ± 11.8	-2.656	.01*
	Attention	85 ± 15.01	-3.584	.00*
	Delayed memory	85 ± 11.95	-4.617	.00*
	Total Scale	79 ± 12.61	-6.138	.00*
Both Sides n = 12	Immediate Memory	86 ± 21.89	-2.268	.02*
	Visuospatial/constructional	71 ± 9.18	-11.071	.00*
	Language	92 ± 10.02	-2.680	.01*
	Attention	83 ± 15.27	-3.836	.00*

Persons with either both carotid arteries affected or the left side involved had impaired cognitive function as compared to the normal scores in all cognitive domains measured with the RBANS (p<.05). Patients with right side involvement demonstrated significant impairment in visuospatial/constructional abilities (mean score 83, p<.00). Also, immediate memory (mean score 92) and total scale (mean score 92) domains were approaching significance (p<.09, p<.08 respectively). The side of involvement was not a significant factor in the other outcome measures of executive function, physical function and IADL's.

A Pearson's correlation coefficient was calculated to determine the relationships between cognitive function and IADL ability. There was not a significant correlation between the RBANS and the Lawton IADL scale. However, there was a moderately strong negative correlation between the RBANS total scale and the EXIT measure of executive function ($r = -.57$). The EXIT was moderately negatively correlated with the Lawton measure of IADL ($r = -.42$).

Discussion:

Patients with asymptomatic carotid artery disease display deficits in cognition and physical function which might indicate that they are symptomatic. Analysis by severity of carotid disease revealed differences in the particular cognitive domains that were affected, however, 90 % of the patients were deficient in the visuospatial/constructional domain, and patients in the severe (70-99%) stenosis group were deficient in all of the cognitive domains assessed with the exception of language. Patients with occlusion showed deficits in delayed memory, and those with moderate stenosis demonstrated decline in immediate memory and attention. Poor cognitive functioning was previously identified in a community sample of males 59-71 years old with moderate carotid artery stenosis[61] consistent with our findings. Because these persons were community dwelling, it is assumed that they were asymptomatic. Cognition was evaluated by the Mini-Mental State Examination and seven additional neuropsychological tests that assessed attention, psychomotor rapidity, verbal abilities, memory and visuospatial perception.

The issue of cognitive impairment in patients with severe symptomatic and asymptomatic carotid artery stenosis has been explored in patients undergoing carotid endarterectomy.[99] An improvement on a neuropsychometric evaluation assessing higher cortical functions of fine motor control, executive function and verbal memory was demonstrated after endarterectomy and improvement continued through the 5 month follow-up.[99]

In our study, the cognitive scores of the RBANS were compared to age-matched standardized scores. Rao studied cognitive changes in symptomatic severe carotid artery stenosis and also identified an association between neuropsychological impairment and stenosis.[62] The study focused on frontal lobe function and results were compared to a control group. One of the limitations of this study is that there is not a control group. The choice of the RBANS allowed for comparisons with age-matched established normal scores. Recently, Johnston et.al. identified that cognitive impairment and decline are associated with patients that have left-sided severe asymptomatic carotid artery stenosis.[7] Our study analyzed cognitive function for left, right and both sides of involvement with moderate, severe and occluded levels of disease. Our results are similar for the left sided involvement, and all cognitive domains on the RBANS demonstrated scores below the normal standard score. Similarly, if a patient had bilateral involvement, then all cognitive domains were deficient. If a patient had right-side involvement, only the visuospatial/constructional domain was found to be deficient. This is reasonable, since visuospatial/constructional ability is primarily attributed to the right side of the brain.[27]

Heyer et.al.demonstrated an improvement in executive function via the Halstead Trails A and B tests in the follow-up assessments after endarterectomy.[99] Presently, there is no recognized gold standard for the evaluation of executive function.[138] The EXIT was chosen in this study due to its comprehensiveness and "clinical friendliness". It takes less than 15 minutes to administer and can be easily administered in the clinic. This study did not demonstrate that patients had executive dysfunction based on the EXIT. The lack of a significant finding in this area in this study may be due to the smaller sample size, or due to the EXIT being a more global measure of multiple executive function tasks as opposed to the Trails A and B, which are more specific to test the executive functions of visual conceptual and visuomotor tracking.

In other studies that assessed physical or motor performance in patients with carotid artery disease, none used a test that would evaluate physical function from the perspective of simple and complex daily activity completion.[98,99] The Physical Performance Test (9-item) identified slowed performance in all of the stenosis groups.[122] A score less than 36/36 indicates that a slower performance of a task and is possibly suggestive of an early indicator of disability.[124] None of the patients reached a score of 36/36. Mean scores for each stenosis subgroup demonstrated that the moderate stenosis subgroup revealed the largest deficit with a score of 24/36, the severe stenosis subgroup 28/36 and the occluded subgroup 26/36. These mean scores are far below the maximum desired score, suggesting that these patients are not asymptomatic.

Our IADL measure was chosen because it has been shown that a person experiencing a decline in cognition has a related decline in IADL function.[116-118] A decline in cognition has been specifically related to the domain of executive function.[114,115] Pohjasvaara et.al. have suggested that complex ADL's may be a more sensitive measure for early vascular impairment than basic ADL's.[115] Regardless of level of severity of stenosis or sidedness of involvement, all subjects scores ranged between 26 and 27 out of 27on the Lawton IADL scale. There was a ceiling effect for the Lawton in this study, since greater than 15 % of the subjects reached the maximum score on the measure.[141] There was a moderately strong negative correlation between the EXIT and the Lawton IADL (r = -.42). As the patient's score on the EXIT increased (indicating greater executive dysfunction), the IADL score decreased.

A main intention of this study was to assess a patient's clinical status in order to identify subtle indicators that patients may have previously experienced functional loss. Influencing factors that might have confounded this study were the presence of cardiovascular comorbidities such as congestive heart failures, hypotension, cardiac arrythmias and coronary artery bypass graft. These conditions have been shown to relate to impaired cognition.[63-65,67,70-72] In this study 31 % had coronary artery disease and 13% had cardiac arrhythmias. However, we feel that this is still not a full explanation for the incidence of cognitive decline demonstrated in our patients.

The amount of white matter changes that a patient may have displayed on computerized axial tomography (CT scan) or magnetic resonance imaging (MRI) was not assessed. There is a relationship between white matter changes and cognitive decline in healthy, community-dwelling older people (70 and greater).[142,143] The mean age of our patients was 73 years. Consequently, in future studies, the use of CT scanning or PET studies to assess the amount of white matter involvement may be useful.

Another issue in this study is the low number of patients (39) and the unevenness of patients in each stenotic subgroup. However, the authors felt that the results were impressive enough to substantiate the argument that asymptomatic patients are not functioning optimally. Substandard performance on the cognitive and physical tests may be considered a "symptom" for these patients, increasing their risk for stroke. Following these asymptomatic patients over time might help suggest whether any of the tools used can help to predict the incidence of stroke or TIA. Ferrucci et.al. studied patients 70 years old and older who were stroke free. They found that impaired cognition was significantly associated with an increase risk for stroke, especially if the cognitive decline extended over a 3-year period.[144]

In summary, deficits in cognitive and physical function were found in this descriptive study of patients with asymptomatic carotid artery disease. Deficits in IADL's were not pronounced in this group. We suggest that neuropsychological assessment of higher level cognitive skills and a performance based measure of physical abilities should be included in the clinical examination of asymptomatic carotid artery disease patients that present with carotid artery stenosis of a moderate or greater level of severity.

VIII. Use of the Physical Performance Test in Patients with Asymptomatic Carotid Artery Stenosis and Occlusion.

Abstract

Background and Purpose: The purpose of this study was to determine if patients with asymptomatic carotid artery stenosis and occlusion demonstrate deficits in physical performance. Subjects: Thirty-nine patients with asymptomatic carotid artery stenosis of moderate and severe degrees, or occlusion were tested. Methods: Physical performance was assessed via the 9-item and 7-item Physical Performance Test (PPT). Individual tasks were also timed. Results: Patients with asymptomatic carotid artery stenosis and occlusion demonstrated less than optimal performance on the PPT (9-item, 27/36; 7-item 21/28). Simulated eating was the slowest task to perform for the patients with moderate stenosis. Discussion and Conclusion: Patients with asymptomatic carotid artery stenosis and occlusion exhibit changes in function as indicated by their performance on the PPT. This may be indicative of preclinical disability, and a potential symptomatic status of the patient.

Introduction

The Physical Performance Test (PPT), developed by Reuben and Siu, was designed to be a direct observation method to assess multiple dimensions of physical function (basic and complex activities of daily living) of different levels of difficulty.[122] The principle target population for the PPT was the elderly, and the original study tested patients from 49-94 years old with an average age of 79.[122] The researchers advised that the PPT could be useful in the prediction of functional decline in patients.[122] Direct observational assessment of function verses patient self-report has suggested that direct observational assessment might provide more information regarding patient functional limitations than patients have reported.[124,145]

The PPT has been used for the purpose of both measuring functional improvement and predicting functional decline in recent research studies.[124,146] Brach et.al found that in community-dwelling older women (mean age 74.3 years) the PPT identified more physical limitations than self-report measures. The researchers suggested that in a "high-functioning" sample of older women who had minor problems with functional tasks, that the PPT was more effective in identifying functional problems than self reports.[124] The concept of preclinical disability has been offered to explain this situation.[140] In preclinical disability, there is a progressive decline in physical function that goes unrecognized, and often times is predictive of a subsequent clinically recognizable functional decline.[140] The change in function might include taking longer to complete a task, modifying a task in order to accomplish it, or not attempting a task as often.[140,145] Fried has continued to suggest that a progressive, unnoted functional decline might be the result of disease progression.[147]

Similarly, this concept of a decline in function prior to patient reported decline has been the concern of health care providers working with patients with asymptomatic carotid artery disease. For people with asymptomatic carotid artery disease, the stroke risk has been found to be less dramatic than for the symptomatic patients.[14,24,28,49,55] Thus, the medical management has been different, and patients are not as readily offered surgical intervention, such as a carotid endarterectomy, which has been shown to significantly reduce the risk of stroke in the symptomatic patients.[28,48,50,51] Asymptomatic patients with carotid artery stenosis and occlusion are typically identified during routine physical examinations, or during medical work-up for another medical problem. They are often referred to the neurologist or neurosurgeon to evaluate if further medical or surgical interventions are necessary. If no clinical symptoms are reported by the patient, such as weakness, paralysis, numbness or tingling affecting a side of the body, word finding or word slurring problems, they are treated as asymptomatic. However, if these types of things were occurring, they would impair physical performance. It has been found that changes in physical, cognitive and emotional function escape being communicated in the clinical history and examination of patients with asymptomatic carotid artery disease.[58] Therefore, the purpose of this study was to determine if patients with asymptomatic carotid artery stenosis and occlusion demonstrate deficits in physical performance. This study was part of a larger study that considered cognitive function and instrumental activities of daily living as additional indicators of impaired function in these asymptomatic patients with carotid artery disease.

Methods

Subjects

Thirty-nine consecutive patients with asymptomatic carotid artery disease participated and were recruited from the Neurosurgery clinic at the University of Pittsburgh Medical Center (UPMC).

The study received Internal Review Board approval by UPMC. After the study was explained to the patient and consent was given, the patients were divided into three subgroups; unilateral and bilateral moderate stenosis (50-69%), unilateral and bilateral severe stenosis (70-99%) and unilateral and bilateral occlusion,[28,49] based on the computed tomographic arteriography (CTA) scan, magnetic resonance imaging (MRI) study or carotid doppler study as read by the neurosurgeon . Asymptomatic status was determined by patient report during the history and the clinical examination. Asymptomatic patients are often referred to the neurologist or neurosurgeon for an additional medical opinion due to the incidental finding of the carotid artery disease when worked-up for another medical issue or during routine physical examinations. Patients were excluded from the study if they had a history of stroke, dementia as determined by the physician, were unable to speak English and answer questions, or were precluded from weight bearing due to an orthopedic condition, or had severe cardiopulmonary compromise.

Measures

The Physical Performance Test (PPT) 9-item and 7-item, were used to assess physical function and the 7 timed tasks were also analyzed individually.[122] The PPT is a global measure of physical performance that assesses basic and complex activities of daily living (ADL's).[122] The 9-item test includes the items: writing a sentence, simulated eating, donning and doffing a jacket, 360 degree turn right and left, lifting a book to a shelf, picking up a penny from the floor, walking 50 feet, climbing one flight of stairs, climbing several flights of stairs (4 maximum). In the 7-item test, the tasks of climbing one flight of stairs and several flights of stairs were eliminated from the scoring. The test was administered and scored according to the protocol from its originators.[122] Test items were timed with a standard stop watch and rounded off to the nearest tenth of a second. The time of task completion was recorded. Also, time was also rounded to the nearest 0.5 second and was converted into the ordinal scale (0-4) as suggested in the original test.[122] On the PPT 9-item a score of 36/36 is the highest score possible, and would be considered normal function. On the 7-item test this score is 28/28. Scores below this would indicate less than optimal performance. The PPT was used in this study to determine if any unreported motor, sensory or cognitive problems were affecting the patient's physical function. The PPT 9-item test has been shown to demonstrate internal consistency (Cronbach's alpha = .87) and interrater reliability (r = .99).[122] It has also demonstrated concurrent validity with other functional performance measures such as the Katz ADL scale.[128]

Data Analysis

Descriptives were collected on the demographic data of the patients, their medications, comorbidities and the 9-item and 7-item PPT. Analysis of variance (ANOVA) was used to determine if there were significant differences between the 6 patient groups based on severity of disease and unilateral vs. bilateral involvement, and also on laterality of the disease, left side vs. right side vs. both sides involved.

The mean 9-item and 7-item PPT scores were calculated and compared to the maximum scores of 36/36 and 28/28 respectively. A lower score indicated that a person needs more time to complete a task on the PPT, thus suggesting the beginning of physical decline, and possibly preclinical disability.[124,140]

Pearson correlation coefficients were calculated between the PPT scores and the number of comorbidities that a patient had, and also with the number of medications that a patient was taking.

Results

Thirty-nine patients with asymptomatic carotid artery disease were tested. Table 23 includes the basic demographics regarding these patients.

Table 23: Diagnostic Groups by Gender, Age and Side Affected in Patients with Asymptomatic Carotid Artery Disease.

Diagnostic Group (n and % of total sample)	Gender (n and % of total sample)	Mean Age (yrs.) ± S.D.	Age Range (years)	Side Involved (R=right L=left B=both)
Unilateral Stenosis Moderate n = 3, (7.7%)	2 male (67%) 1 female (33%)	78 ± 6	71-83	2 – R 1 – L
Unilateral Stenosis Severe n = 18, (46.2%)	11 male (61%) 7 female (39%)	75 ± 8	55-87	6 – R 8 - L
Unilateral occlusion n = 3, (7.7%)	2 male (67%) 1 female (33%)	63 ± 16	48-79	2 – R 1 - L
Bilateral Stenosis Moderate n = 4, (10.3 %)	3 male (75%) 1 female (25%)	76 ± 8	66-85	2 – L 2 – B
Bilateral Stenosis Severe n = 9, (23.1%)	5 male (56 %) 4 female (44%)	73 ± 5	64-79	1 – L 8 - B
Bilateral Occlusion n = 2, (5.1%)	1 male (50%) 1 female (50%)	63 ± 5	59-66	2 - B
All Patients (n = 39)	23 male (59%) 16 female (41%)	73 ± 8	48-87 years	14 – R 13 – L 12 - B

The sample was slightly dominant for males, with an average age of 73 years (range 48-87). Most patients (70%) tested in this study were severely stenotic, with another 13 % being occluded, and the remaining 17% had moderate carotid artery stenosis.

Table 23 also reflects which side was involved for the patients. Patients with bilateral involvement were grouped into the side of stenosis that the surgeon would be considering for surgery. For example, in a situation of mild or moderate stenosis on the left side, and severe stenosis on the right side, the patient was classified as having a right side that was involved. In situations when the level of stenosis was the same, or occlusion existed bilaterally, then the patient was classified with bilateral disease. In general for the 39 patients, there were 14 with right side involvement, 13 with left side involvement and 12 with bilateral involvement.

The most common comorbidities that the patients had were hypertension (39%), hypercholesteremia (36%) diabetes mellitus (33%) coronary artery disease (31%), and cardiac arrhythmia (13%). Amongst the 39 patients, there were a wide variety of medications being taken. The most common categories of medications were the CNS agents which included 5 different medications, the antihypertensives and the antilipemics. The 2 most common medications were aspirin (54%), and the antilipemic Zocor (26%).

In this study, physical performance was analyzed from two perspectives, the severity of carotid artery disease, and also from the perspective of differences in performance based on laterality of disease. In order to determine differences between the severity groups of the patients, an analysis of variance (ANOVA) was completed. With the 39 patients, there was not a significance difference between the groups (unilateral or bilateral moderate, severe disease, or occlusion) on any of the physical performance measures at a $p<.05$ level of significance.

For the PPT (9-item), it was found that no patient reached a perfect score of 36/36. For all 39 patients, scores ranged from 19/36 – 30/36 with a mean score of 27/36 (Table 24).

Table 24: Physical Performance Test (9-item) in Patients with Carotid Artery Disease.

	Number of patients	Mean score ± S.D.	Range
Occluded	5	26 ± 2	21-30
Moderate Stenosis	7	24 ± 2	14-31
Severe Stenosis	27	28 ± 1	19-34
Total	39	27 ± 1	14-34

No subject reached a perfect score on the 7-item PPT of 28/28. The range of scores for these patient groups was 19/28-22/28 (Table 25).

Table 25: Physical Performance Test (7-item) in Patients with Carotid Artery Disease.

	Number of patients	Mean score ± S.D.	Range
Occluded	5	22 ± 2	19-24
Moderate Stenosis	7	19 ± 3	14-24
Severe Stenosis	27	22 ± 3	15-27
Total	39	21 ± 3	14-27

Another way to consider physical performance for these patients with carotid artery disease is to look for differences in function based on the side of brain involvement. Thus, data of the 39 patients was analyzed comparing the location of the lesion as being right, left or both sides involved. In an ANOVA to determine if there were differences on the 9-item PPT between these 3 groups, the finding was not significant. The mean score for the right and left side involved was the same (28/36), and in the patients with bilateral involvement the mean score was 26/36.

Pearson correlation coefficients were calculated to determine a relationship between the comorbidities and the medications of the patients and their performance on the the PPT (9-item and 7-item). No significant correlations were found.

The Physical Performance Test individual tasks were also timed and recorded. A detailed analysis of each of the timed items was conducted. Table 26 is a summary of the items for all the patients tested.

Table 26: Physical Performance Timed Items for Patients with Asymptomatic Carotid Artery Disease.

Descriptive Statistics

(n = 39)	Mean seconds ± S.D.	Range	Normal PPT time (for score= 4)
Sentence writing	15.13 ±6	8.7 – 35.9	≤10 sec
Eating (simulated)	13.87± 3	9.3 –19.2	≤10 sec
Lifting a book	2.03± 1	.8 -7.5	≤ 2 sec
Put on jacket	14.17± 4	7.7 – 26.3	≤10 sec
Pick up penny	4.05± 4	1.8 – 26.7	≤ 2 sec
50' Walk	15.93± 4	0 – 25.5	≤15 sec
Climb one flight stairs	7.28± 3	0 – 20.6	≤ 5 sec

Further analysis was conducted to see if there was a difference on any PPT item based on the severity of the carotid artery disease for the unilateral and bilateral moderate stenosis, unilateral and bilateral severe stenosis and unilateral and bilateral occlusion subgroups. Mean scores, standard deviations and ranges of the PPT timed items are reported in Table 27.

Table 27: Physical Performance Results on Timed Items for Patients with Moderate, Severe Carotid Artery Stenosis or Occlusion.

Item	Group	Mean ±S.D.	Range
Sentence writing	Occluded (n = 5)	16.5 ± 7	11.2 – 26.7
	Mod Stenosis (n = 7)	16.4 ± 3	12.3 – 20.8
	Severe Stenosis (n = 27)	14.5 ± 6	8.7 – 35.9
	Total (n = 39)	15.1 ± 6	8.7 – 35.9
Eating (simulated)	Occluded	12.3 ± 2	10.0 – 14.0
	Mod Stenosis	17.1 ± 3	13.2 – 19.1
	Severe Stenosis	13.4 ± 3	9.3 – 18.6
	Total	13.9 ± 3	9.3 – 19.2

Lifting a book	Occluded Mod Stenosis Severe Stenosis Total	3.2 ± 3 1.8 ± .6 2.0 ± .9 2.1 ± 1	.79 – 7.5 1.2 – 2.8 .76 – 5.5 .76 – 7.5
Putting on jacket	Occluded Mod Stenosis Severe Stenosis Total	12.5 ± 3 16.4 ± 5 13.9 ± 4 14.2 ± 4	8.1 – 16.2 11.5 – 26.3 7.7 – 22.8 7.7 – 26.3
Pick up penny	Occluded Mod Stenosis Severe Stenosis Total	2.6 ± .6 7.0 ± 9 3.6 ± 2 4.1 ± 4	1.8 – 3.5 2.5 – 26.7 2.0 – 11.1 1.8 – 26.7
50' Walk	Occluded Mod Stenosis Severe Stenosis Total	17.9 ± 2 17.1 ± 4 15.3 ± 4 15.9 ± 4	16.3 – 21.9 12.7 – 25.5 .00 – 24.5 .00 – 25.5
Climb one flight stairs	Occluded Mod Stenosis Severe Stenosis	8.0 ± 8 6.7 ± 3 7.3 ± 2	.00 – 20.6 .00 – 10.0 .00 – 11.9

mod: moderate

An ANOVA was done to determine if there were differences in time completion for the tasks between these 3 subgroups (Table 28).

Table 28: ANOVA Table for Between Group Differences for the Timed PPT Items, Based on Severity of Carotid Disease.

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
Sentence writing	Between Groups	32.431	2	16.216	.513	.60
	Within Groups	1137.872	36	31.608		
	Total	1170.303	38			
Eating (simulated)	Between Groups	90.320	2	45.160	7.540	.00*
	Within Groups	215.628	36	5.990		
	Total	305.948	38			
Lifting a book	Between Groups	6.612	2	3.306	2.251	.12
	Within Groups	52.863	36	1.468		
	Total	59.475	38			

Put on jacket	Between Groups Within Groups Total	52.083 557.148 609.231	2 36 38	26.042 15.476	1.683	.20
Pick up penny	Between Groups Within Groups Total	79.269 559.865 639.134	2 36 38	39.635 15.552	2.549	.09
50' Walk	Between Groups Within Groups Total	39.254 568.935 608.188	2 36 38	19.627 15.804	1.242	.30
Climb one flight stairs	Between Groups Within Groups Total	4.894 411.347 416.240	2 36 38	2.447 11.426	.214	.81

* p<.05

Simulated eating was the only item that was significantly different (p<.00) between the levels of severity. Tukey post hoc comparisons revealed that the moderately stenotic group had a significantly slower time recorded than the severely stenotic and occluded groups. There were no significant differences on timed item scores based on lesion location.

Discussion:

In persons with asymptomatic carotid artery stenosis and occlusion when clinically assessed by the PPT, patients perform below the optimal standard on the 9-item and 7-item tests. Additionally, those with moderate stenosis (50-69%) performed the worst, with an average 9-item PPT score of 24/36 and 7-item of 19/28. When comparing these scores to the percentile rankings established for community-dwelling older adults (65 years and older, this study's average age 73 years),[148] on the 9-item PPT, the average score for the moderate stenosis group placed them in approximately the 50th percentile of physical function, the severe stenosis group scored 28/36 placing them just below the 75th percentile of physical function, and the occluded group scored 26/36 placing them at approximately the 60th percentile of physical function.[122] On the 7-item test, the percentiles were approximately the same, with the exception of the occluded group increasing the percentile of function to 75th percentile on the 7-item PPT.[122] The 7-item

PPT has also been shown to be an independent predictor of death, with the lower scores indicating poor performance.[128] In this study, the results demonstrate that at all levels of carotid artery stenosis and occlusion tested, the patients demonstrated poor performance. Brach et. al, in a study evaluating physical decline in community-dwelling older women defined clinical decline as scoring below 4 (the highest score) on each PPT item.[124] Fried et.al. indicated that a score less than the maximal score would be significant for preclinical disability.[140] In this study, all asymptomatic patients with carotid artery stenosis and occlusion demonstrated scores at least 25% below optimal function. Thus, it is suggested that all patients tested demonstrated a functional decline that might be associated with a demonstration of early clinical symptoms of carotid artery disease.

However, it has also been suggested that the maximal score on the PPT may actually not be the standard for healthy normal subjects. In unpublished data of 19 healthy normal subjects with a mean age of 68 years, the mean 9 item PPT score was 30/36.[135] The researchers have suggested that the maximal score may be an unrealistic expectation for the normal population. The results of the asymptomatic patients with carotid artery disease remain below the 30/36 score as well.

The PPT scores when analyzed from the perspective of laterality of disease revealed the same finding of a potential status of preclinical disability, with the score of 28/36 (75th percentile) if either the right or the left side was the affected artery, and 26/36 (60th percentile) when both sides were involved. It was interesting to note that bilateral involvement led to a more impaired status. This is a reasonable finding since impaired blood flow to both sides of the brain should affect function more profoundly.

In its design, the PPT items were chosen to indicate a level of difficulty for the item, and also reflect different dimensions of function, specifically upper fine motor function, upper coarse motor function, balance, coordination, mobility and endurance.[122] In order to analyze the physical function of the patients in this study in more detail, an analysis of time to perform each task was done to determine if any task was significantly more difficult for any one group of patients. More difficult in this case would imply taking a longer time to complete.

When comparing the 3 subgroups of patients, the patients with moderate stenosis demonstrated a significant difference in time to complete the task simulated eating. This item has been identified as demonstrating a perceived minimal level of difficulty.[122] The timed items also reflect a different functional dimension that the test was developed to assess, simulated eating tested upper fine motor function.[149] An explanation for the deficit on this task might possibly be related to the patterns of blood flow and loss of blood flow to the brain as internal carotid artery stenosis might compromise the flow of blood to the areas of the brain responsible for the function of simulated eating. The physiology of blood flow to the brain and compromise thereof remains an area of continued study.[3,5,22] In cases of carotid artery occlusion, there is an increase in collateral blood supply from the opposite side of the brain that compensates for the lack of flow to the side of the brain fed by the occluded carotid artery.[13] Additionally, Derdeyn et.al. found that asymptomatic patients with carotid artery occlusion were at a much lower risk of demonstrating an impaired hemodynamic state than patients with symptoms.[4] However, this has only been researched in situations of carotid artery occlusion. The data from this study demonstrated a functional decline in all asymptomatic patients, and a significant difference for a particular task in the moderately stenotic patients. No studies have been found that address the hemodynamic status of stenotic patients. The detection of impaired functional performance might make us consider that these patients "are" symptomatic, with a status of preclinical disability.[140] Further research is needed to assess the physiologic status of the blood flow in patients with carotid artery disease and the functional status, to determine if we might be "missing something" in our clinical assessment of these patients.

Conclusion:

The use of the PPT in patients with asymptomatic carotid artery stenosis and occlusion demonstrated less than optimal performance in all patient subgroups for both the 7-item and the 9-item tests. The time taken to perform the tasks on the tool was longer than the expected norm for the tool, which is an indication of preclinical disability. Pre-clinical disability has been explained as a functional status that is a precursor to clinical functional impairment. Therefore, in patients with asymptomatic carotid artery stenosis and occlusion, we conclude that they might not be asymptomatic, but are exhibiting changes in functional status that have not been routinely clinically identified or comprehended and communicated by the patient. The authors suggest that a more detailed clinical assessment of the reportedly asymptomatic patients incorporating a functional measure might be useful in determining those patients who might be "symptomatic" and thus at an increased risk for stroke. Ultimately, this could contribute to increasing stroke prevention by improving the identification of potentially symptomatic patients that have been currently unrecognized, resulting in more appropriate medical management for these patients.

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Appendix A

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

Appendix B

The Executive Interview (EXIT)

NUMBER-LETTER TASK

1. **"I'd like you to say some numbers and letters for me like this. 1-A, 2-B, 3-what would come next?"________**

   "Now you try it starting with the number 1. Keep going until I say 'stop'."

1	2	3	4	5	
A	B	C	D	E	"STOP" ________

   Score: 0 = No errors
   1 = Complete task with prompting (or repeat instructions)
   2 = Doesn't complete task.

WORD FLUENCY

2. **"I am going to give you a letter. You will have one minute to name as many words as you can think of which begin with that letter. For example, with the letter 'P' you could say 'people, pot, plant. . .' and so on. Give rule about proper nouns and using same word with a different ending. For example, big, bigger, biggest. Are you ready? Do you have any questions? The letter is A---GO!"** * mark off 15" increments*

   Score: 0 = 10 or more words
   1 = 5 – 9 words
   2 = Less than 5 words

DESIGN FLUENCY

3. **"Look at these pictures. Each is made with only four lines. I am going to give you one minute to draw as many DIFFERENT designs as you can. The only rules are that they must each be different and be drawn with four lines. Now go."** (Correct figures can contain curves.)

   Score: 0 = 10 more unique drawings, no copies of examples
   1 = 5 – 9 unique drawings
   2 = Less than 5 unique drawings

ANOMALOUS SENTENCE REPETITION

4. "Listen carefully and repeat these sentences exactly." (Read sentences in a neutral tone.)

1. I pledge allegiance to those flags.
2. Mary fed a little lamb.
3. A stitch in time saves lives.
4. Tinkle, tinkle little star.
5. A B C D U F G

Score: 0 = No errors
1 = Fails to make one or more changes
2 = Continues with one or more expressions (e.g. Mary had a little lamb whose fleece was white as snow.)

THEMATIC PERCEPTION

5. Patient shown picture by examiner. **"Tell me what is happening in this picture."**

Score: 0 = Tells spontaneous story (story=setting, 3 characters, action)
1 = Tells story with prompting x1 (anything else?)
2 = Fails to tell story despite prompt
*score 2 if not a clear story

MEMORY/DISTRACTION TASK

6. "Remember these three words – BOOK, TREE, HOUSE." (Patient repeats till all three words registered. (# trails = ________)
"Remember them—I'll ask you to repeat them for me later."
"Now—spell CAT for me . . ." ________
"Good. Now spell it backwards." ________
"OK. Tell me those three words we learned." ________

Score: 0 = Patient names some or all of the three words correctly without naming 'cat' (examiner may prompt "anything else?")
1 = Other response ________________________________
2 = Patient names 'cat' as one of the three words (perseveration)

INTERFERENCE TASK

7. "What color are these letters?" (SWEEP hand back and forth over letters)

Score: 0 = black
1 = brown (repeat question x1) then black
2 = brown (prompt) brown (intrusion)

AUTOMATIC BEHAVIOR I

8. "Please hold your hands forward, palms down. Relax while I check your reflexes." (Rotate arms one at a time at the elbow as if to check for cogwheeling. Gauge patient's active participation/anticipation of rotation.)

Score: 0 = Patient remains passive.
1 = Equivocal re: passive vs. active
2 = patient actively copies the circular motion (Mihelten) or resists (Gegenhalten)

AUTOMATIC BEHAVIOR II

9. "Please hold your hands out palms UP. Just relax." (Examiner pushes down on patient's hands-gently at first, becoming more forceful. Gauge patient's active participation in response.)

Score: 0 = Patient offers no resistance (remains passive)
1 = Equivocal re: passive vs. active
2 = Actively resists or complies with examiner

GRASP REFLEX

10. "Please hold your hands out with open palms down. Just relax." (Both palms are lightly stroked simultaneously by the examiner, who looks for grasping/gripping actions in the fingers.)

Score: 0 = Absent.
1 = Equivocal
2 = Present

Patient grasps firmly enough to be drawn up and out of chair by examiner.

SOCIAL HABIT I

11. Fix subject's eyes. Silently count to three while maintaining subject's gaze, then say **"Thank you."**

Score: 0 = Replies with a question (e.g. Thank you for what?) or says nothing.
1 = Other response
2 = "You're welcome"

MOTOR IMPERSISTENCE

12. "Stick out your tongue and say 'aah' until I say stop . . . GO!" (Count to three silently.) (Subject must sustain a constant tone, not "ah . . ah . . ah")

Score: 0 = Completes task spontaneously.
1 = Completes task with examiner modeling task for patient.
2 = Fails task despite modeling by examiner.

SNOUT REFLEX

13. "Just relax." (Examiner slowly brings index finger toward patient's lips, pausing momentarily 2" away. Finger is then placed vertically across lips and then is lightly tapped with the other hand. Observe lips for puckering.)

Score: 0 = Not present
1 = Equivocal
2 = Present

FINGER-NOSE-FINGER TASK

14. (Hold up index finger.) **"Touch my finger."** (Leave finger in place.) **"Now touch your nose."**

Score: 0 = Complies, using same hand.
1 = Other response
2 = Complies, using other hand while continuing to touch examiner's finger.

GO/NO-GO TASK

15. "Now . . . When I touch my nose, you raise your finger like this." (Raise index finger.) **"When I raise my finger, you touch your nose like this."** (Touch nose with index finger.) Have patient repeat instructions if possible. Examiner begins task. Leave finger in place while awaiting patient's response. Give directions up to three times. Repeat directions when error occurs.

Examiner	Patient
F	N F
N	F N
F	N F
F	N F
N	F N

Score: 0 = Performs sequence correctly.
1 = Correct, requires prompting/repeating instructions.
2 = Fails sequence despite prompting.repeat instructions.

ECHOPRAXIA I

16. "Now listen carefully. I want you to do exactly what I say. Ready? Touch your ear." (Examiner touches nose and keeps finger there.)

Score: 0 = Touches ear.
1 = Other response __________________________ (Look for mid-position stance.)
2 = Touches nose.

LURIA HAND SEQUENCE I

17. "Can you do this?" (Invite patient to watch while alternating palm/fist with either hand. Once patient begins, ask to **"Keep going"** while examiner stops. Count # of successive palm/fist cycles.)

Score: 0 = 4 cycles without errors after examiner stops.
1 = 4 cycles with additional verbal prompt ("keep going") or modeling.
2 = Unsuccessful despite prompting/modeling (watch for mid-position stances.)

LURIA HAND SEQUENCE II

18. "Can you do this?" (Examiner models SLAP, FIST, CUT – while patient imitates each step). **"Now follow me."** (Examiner begins to repeat sequence.) **"Keep doing this until I say stop."** (Examiner stops.)

Score: 0 = 3 cycles without error after examiner stops.
1 = 3 cycles with additional verbal prompt ("keep going") or modeling.
2 = Unsuccessful.

GRIP TASK

19. "Squeeze my fingers." (With both hands, form a pistol.)

Score: 0 = Patient grips fingers.
1 = Other response __________________________
2 = Pulls examiner's hands together.

ECHOPRAXIA II

20. (Suddenly and without warning, the examiner slaps his hands together while facing the patient.)

Score: 0 = Does not imitate examiner.
1 = Hesitates, uncertain.
2 = Imitates slap.

COMPLEX COMMAND TASK

21. "Put your left hand on top of you head and close your eyes. That was good." (Examiner remains aloof, begins next task.)

Score: 0 = Stops when next task began.
1 = Equivocal = holds posture during part of next task.
2 = Maintains posture through completion of next task—has to be told to cease.

(Quickly go on to next task.)

SERIAL ORDER REVERSAL TASK

22. (Have patient recite the months of the year.) **"Now start with January and say them all backwards . . ."**

Score: 0 = No errors, at least past September.
1 = Get past September but requires repeat instructions ("Just start with January and say them all backwards.")
2 = Can't succeed despite prompting.

COUNTING TASK

23. (Examiner taps each picture around the figure in a clockwise direction.) **"Please count the fish in this picture out loud."**

Score: 0 = 4
1 = Less than 4.
2 = More than 4.

* Perseveration means 2 or more full circuits.

UTILIZATION BEHAVIOR

24. (Examiner holds pen near point and dramatically "presents" it to patient asking:) **"What is this called?"**

Score: 0 = "pen"
1 = Reaches, hesitates.
2 = Takes pen from examiner (utilization behavior).

IMITATION BEHAVIOR

25. (Examiner flexes wrist up and down and points to it asking:) **"What is this called?"**

Score:
0 = "wrist"
1 = Other response ___________________________
2 = Flexes wrist up and down (echopraxia).

Appendix C

Physical Performance Test

	Physical Performance Test Time	Scoring	Score
1. Write a sentence (Whales live in the blue ocean)	______sec*	≤ 10 sec = 4 10.5 - 15 sec = 3 15.5 - 20 sec = 2 >20 sec = 1 unable = 0	
2. Simulated eating	______sec*	≤ 10 sec = 4 10.5 - 15 sec = 3 15.5 - 20 sec = 2 >20 sec = 1 unable = 0	
3. Lift a book and put it on a shelf	_____sec*	≤ 2 sec = 4 2.5 - 4 sec = 3 4.5 - 6 sec = 2 >6 sec = 1 unable = 0	
4. Put on and remove a jacket	______sec*	≤ 10 sec = 4 10.5 - 15 sec = 3 15.5 - 20 sec = 2 >20 sec = 1 unable = 0	
5. Pick up penny from floor	______sec*	≤ 2 sec = 4 2.5 - 4 sec = 3 4.5 - 6 sec = 2 >6 sec = 1 unable = 0	
6. Turn 360 degrees	discontinuous steps 0 continuous steps 2 unsteady (grabs, staggers) 0 steady 2		
7. 50-foot walk test	______sec*	≤ 10 sec = 4 10.5 - 15 sec = 3 15.5 - 20 sec = 2 >20 sec = 1 unable = 0	
8. Climb one flight of stairs **	______sec*	≤ 5 sec = 4 5.5 - 10 sec = 3 10.5 - 15 sec = 2 >15 sec = 1 unable = 0	

9. Climb stairs **	Number of flights of stairs up _____ and down (maximum 4).

TOTAL SCORE (maximum 36 for nine-item, 28 for seven-item)	______ nine-item ______ seven-item

* For timed measurements, round to nearest 0.5 seconds. ** Omit for seven-item scoring.

Appendix D

Instrumental Activities of Daily Living (Lawton IADL)*

INSTRUCTIONS: Use the prompt cards when asking the patient these questions.

1. Can you use the phone:
   - 01 completely unable to use the phone
   - 02 with some help
   - 03 without help

2. Can you get to places out of walking distance:
   - 01 completely unable to travel unless special arrangements are made
   - 02 with some help
   - 03 without help

3. Can you go shopping for groceries:
   - 01 Completely unable to do any shopping
   - 02 With some help
   - 03 Without help

4. Can you prepare your own meals:
   - 01 Completely unable to prepare meals
   - 02 With some help
   - 03 Without help

5. Can you do your own housework:
   - 01 completely unable to do any housework
   - 02 with some help
   - 03 without help

6. Can you do your own handyman work?
   - 01 Completely unable to do any handyman work
   - 02 With some help
   - 03 Without help

7. Can you do your own laundry:
   - 01 completely unable to do any laundry at all
   - 02 with some help
   - 03 without help

8. A. Do you take medicines or use any medications?
   - 01 Yes (Go to question 8B.)
   - 02 No (Go to question 8C.)

   B. Do you take your own medicine:
   - 01 completely unable to take own medicine
   - 02 with some help (if someone prepares it or reminds you)

03 without help (in the right doses at the right time)

C. If you had to take medicine, could you do it:
   - 01 completely unable to take own medicine
   - 02 with some help (if someone prepares it or reminds you)
   - 03 without help (in the right doses at the right time)

9. Can you manage your own money:
   - 01 completely unable to manage own money
   - 02 with some help
   - 03 without help

TOTAL IADL: ____________

From Lawton MP: Assessing the competence of older people. In Kent D, Kastenbaum R, Sherwood S (eds): Research Planning and Action for the Elderly. New York, Behavioral Publications, 1972.