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## *Abstract*

Stroke is the second leading cause of death throughout the world, and the third leading cause of death in the United States, behind heart disease and cancer. The incidence of stroke has been gradually increasing with the aging population, and the outcome is often detrimental. It has been shown that the greatest impact on this disease comes from early prevention and intervention.

The purpose of this study was to establish an area in patients showing no symptoms with moderate carotid stenosis (50-79%) to help identify the individuals and risk factors that lead a patient to a higher risk for stroke. The severity of carotid artery stenosis and plaque composition determine the treatment options. The two imaging modalities utilized in assessing plaque intensity are the Ultrasound and Magnetic Resonance Angiogram (MRA). However, there remained an unknown correlation between components of plaque composition defined by ultrasound versus MRA. My objective was to find the correlation between the two components. With this objective, a hypothesis for the trial was formulated: Ultrasound is equally able to measure plaque volume and heterogeneity when compared with MRA. Twenty subjects who underwent a carotid artery ultrasound and were found to have moderate stenosis, were referred for carotid artery MRA. These imaging modalities assessed percent stenosis severity and plaque heterogeneity index. From the obtained data, the hypothesis was validated as there was no statistical significant difference between plaque volume and heterogeneity of the carotid plaque estimated by either Ultrasound or MRA.

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## Chapter I: Introduction and Literature Review

Stroke is the second leading cause of death throughout the world, and the third leading cause of death in the United States, behind heart disease and cancer. The incidence of stroke has been gradually increasing with the aging population [1], and the outcome is often detrimental. It has been shown that the greatest impact on this disease comes from early prevention and intervention; thus it is of the utmost importance to have a clear classification system for risk stratification, treatments and for the best diagnostic techniques. This paper will discuss: the main cause of stroke (CVA), risk stratification categories and criteria, the advantages to carotid endarterectomy (surgery) versus medical therapy, and the advantages and disadvantages seen between two major diagnostic techniques and their overall effect on morbidity and mortality.

Carotid artery atherosclerosis is a main cause of cerebrovascular disease, accounting for 7% presenting with initial stroke in one study [2] and 10% according to the National Institute of Neurological and Communicative Disorders and Stroke Data Bank [3]. Patients with carotid artery atherosclerosis are categorized within three categories of mild, moderate and severe stenosis. These categories are based on percent of artery stenosis. Several randomized, controlled trials including the North American Symptomatic Carotid Endarterectomy Trial (NASCET), European Carotid Surgery Trial (ECST), and the Veterans Affairs Cooperative Study Program, have reported relative and absolute risk reductions for those randomized to a carotid endarterectomy (CEA) [4,5,8] vs. those receiving medical therapy. After 2 years in NASCET, the combining risk of any stroke occurring on the same side of the body in CEA vs. medical therapy was 9 vs. 26% respectively. In those patients possessing the symptoms pertaining to moderate carotid stenosis (stenosis > 50-69%), the relative and absolute risk reductions for CEA, although not as good as those with severe, still had an overall statistical significance favoring surgery at 5 years [6].

For patients with no symptoms of carotid stenosis (mild), the benefit of CEA is less clear as seen in three large, randomized controlled trials, the Veterans Affairs Cooperative Study Group (VA trial), the Asymptomatic Carotid Atherosclerosis Study (ACAS), and the Asymptomatic Carotid Surgery Trial (ACST) [8-10]. An analysis of these trials found that in patients with no symptoms of carotid stenosis, there was a small absolute risk reduction of about 3% over three years for the outcome of any stroke in those with CEA; the relative number needed to treat to prevent one stroke at three years was approximately 33 [11]. If a subgroup of these patients, who are at an increased risk of stroke can be identified, then the benefits of CEA would be more clearly established. Various features of plaque morphology can be used to identify patients at risk such as: echogenicity, texture, plaque volume and progression of disease.

The morphology of such plaques can be studied through the usage of current imaging modalities. Two current imaging modalities, Ultrasound and Magnetic Resonance Angiogram (MRA), provide both advantages and disadvantages regarding their overall effect on morbidity and mortality. While ultrasound has proven useful in risk-classified patients according to plaque intensity, it has well-known limitations such as its subjectivity based on technician experience. In addition, the echogenicity (brightness) and texture of the plaque may be changed by instrument settings. Several studies associate echogenicity to histological components of carotid plaques [12,13] and have shown that heterogeneous, echolucent plaques were associated with

higher neurologic events due to their high lipid, more rupture-prone content [14-17]. In addition, echolucent plaques have been associated with an increased number of masses impeding blood flow after CEA [18-20].

In utilizing the ultrasound diagnostic method, it is necessary to determine which form of ultrasound, 2D or 3D, offers the best assessment. Although 2D ultrasound is used widely to assess degree of stenosis, the ability to detect ulceration is poor with a sensitivity of 41% for plaques causing >50% carotid stenosis [23]. In addition, accurate assessment of plaque changes with 2D is complex because images are difficult to reproduce on serial exams. The atherosclerotic plaque often develops asymmetrically and therefore may not be representative of the entire plaque composition and morphology. Studies of 3D plaque volume measurement allow for the possibility of investigating volume changes that occur in multiple dimensions, such as plaque surface morphology, plaque geometry, and plaque distribution, with improved image quality. Although progress is still needed to develop this technique, several studies have demonstrated that plaque volume could be measured accurately and with low variability, making it a useful tool in clinical studies of progression and regression of carotid plaques [24-25]. It has therefore been hypothesized that the 3D ultrasound technique would improve the ability of identifying vulnerable plaques that are capable of causing cerebral ischemia (an inadequate bloody supply) [26].

Newer imaging models, such as high resolution MRA, can provide improved risk assessment of carotid plaques [21,22]; however, these models are not yet widely available, remain unproven and have limited possible data with clinical associations.

## Chapter II: Objectives and Hypothesis

The purpose of this study was to establish an area in patients showing no symptoms with moderate carotid stenosis (50-79%) to help identify the individuals and risk factors that lead a patient to a higher risk for stroke. The severity of carotid artery stenosis and plaque composition determine the treatment options. The two imaging modalities utilized in assessing plaque intensity are the Ultrasound and Magnetic Resonance Angiogram (MRA). However, there remained an unknown correlation between components of plaque composition defined by ultrasound versus MRA. My objective was to find the correlation between the two components. With this objective, a hypothesis was formulated for the trial: Ultrasound is equally able to measure plaque volume and heterogeneity when compared with MRA.

## Chapter III: Methods and Data Collection

This study was a prospective, blinded outcome study. Physicians evaluating ultrasound images were blinded to outcome and clinical information. To assess the trial's hypothesis, there was an enrollment of 30 subjects. Twenty subjects who underwent a carotid artery ultrasound and were found to have moderate stenosis, were referred for carotid artery MRA. The data was collected through patients' medical history (medications, height, weight, age, sex, physical exam, ethnicity, lab tests) and the assessment by both the ultrasound and MRA of percent stenosis severity and plaque heterogeneity index. Plaque heterogeneity index was displayed as 0 for "yes" and 1 for "no".

Each subject was followed for the duration of the trial to identify the start of stroke or other cerebrovascular symptoms. Any significant cardiovascular event or death was also documented, whether or not it was associated to carotid artery disease. Subjects could have decided to withdraw from participation in the study at their discretion or for any reason beyond their control. In this event, the discontinuation and the reason (if known) was noted on the case report form.

No compensation was provided to participating subjects. Subject participation did not lead to added costs to the insurance company or to him/herself. All efforts were made to keep subjects' personal information confidential. Only anonymous information was entered into the database. Outcomes were blinded to the physician evaluating the ultrasound images.

## Chapter IV: Data Analysis

Stenosis severity and plaque composition, as seen in ultrasound vs. MRA, were compared through statistical analysis. The t-test was used to assess whether the means of ultrasound and MRA variables were statistically different from each other. To test the significance, a risk level was chosen to be $p < .05$. Any values less than .05 were considered significant. From the assigned risk level, a Null Hypothesis was developed: There is no difference between Ultrasound variables and MRA variables.

**Chapter V: Results**

| Subject | Plaque Volume | | Heterogeneity | |
|---|---|---|---|---|
| | **Ultrasound** | **MRA** | **Ultrasound** | **MRA** |
| 1 | 6.2 | 6.1 | 0 | 0 |
| 2 | 5.9 | 6.3 | 0 | 0 |
| 3 | 6.3 | 5.8 | 0 | 1 |
| 4 | 6.1 | 6.0 | 1 | 1 |
| 5 | 4.5 | 4.2 | 1 | 1 |
| 6 | 5.9 | 6.1 | 0 | 1 |
| 7 | 6.0 | 5.8 | 0 | 0 |
| 8 | 8.2 | 7.9 | 1 | 1 |
| 9 | 8.4 | 7.9 | 1 | 1 |
| 10 | 3.9 | 4.1 | 0 | 0 |
| 11 | 6.0 | 6.2 | 1 | 0 |
| 12 | 6.9 | 5.7 | 1 | 0 |
| 13 | 4.5 | 4.3 | 1 | 1 |
| 14 | 8.2 | 7.8 | 0 | 1 |
| 15 | 4.8 | 4.5 | 1 | 0 |
| 16 | 6.5 | 6.2 | 0 | 1 |
| 17 | 6.1 | 6.0 | 0 | 0 |
| 18 | 5.5 | 5.8 | 1 | 0 |
| 19 | 6.3 | 6.1 | 1 | 1 |
| 20 | 5.3 | 5.6 | 0 | 1 |
| **Mean** | **6.025** | **5.920** | | |
| **t-test** | **0.7737** | | **0.7590** | |

## Chapter VI: Conclusion

From the obtained data, it was evident that the t-test values were greater than 0.05. Thus, the hypothesis was validated as there was no statistical, significant difference between plaque volume and heterogeneity of the carotid plaque estimated by either Ultrasound or MRA. The results of this study conclude that ultrasound and MRA are complementary modalities that should be utilized together in the attempt to develop an accurate assessment of plaque intensity.

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