The Journal of International Medical Sciences Academy
2018 ; (January – March); Vol 31; No. 1

ORIGINAL ARTICLE

Role of Carotid Doppler and Coronary CT Angiography as Predictors of Coronary Artery Disease in Patients of Acute Stroke

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Abstract

Introduction: Myocardial infarction is the most common cause of death & disability in stroke patients. However, the distressed state of patient as well as insufficient emphasis on comorbidity detection, leads to insufficient coronary artery disease (CAD) detection. Doppler evaluation of carotid vessels is utilized in these subjects as an indirect marker of CAD. In our study, we evaluate whether these patients would benefit by the addition of direct computed tomography of coronary arteries (CTCA).

Aims and Objectives: To evaluating the role of carotid Doppler andCTA in prediction of coronary artery disease (CAD) in patients with acute CVA and to find out correlation between Doppler and CT angiogram findings in the above set of patients.

Materials & Methods: Stroke patients, aged >35 years, were requested for consent to participate in the study. Exclusion criteria: 1) Deranged renal function tests (eGFR<30 ml/minute), 2) Subjects in whom bradycardia was unsafe and 3) Known history of contrast allergy, atopy or pregnancy. All data was de-identified and patient confidentiality was maintained. Baseline questionnaire to assess cardiac history was administered. Carotid vessels were evaluated by color Doppler. CTCA evaluation was done after achieving sufficient bradycardia (60-70 bpm) followed by intravenous injection of iodinated contrast to the patient. Coronary artery calcium score (Agatston's score) was calculated. Collected data was tabulated in Excel (Microsoft 2010).and analysed by Stata 14.0 (Stata Inc.). Statistical significance was set at 0.05. Correlation was calculated for the two main predictors. Correlation between two categorical variables was measured via Spearman's correlation coefficient (r).

Results: 68 subjects (M-54, 79%; Mean Age-64+/-14.2; F-14, 21%; Mean Age-66+/-14.4) were enrolled in the study. Preexisting cardiac risk factors were present in 71% (n=48) of the subjects, 28% (n=19) had multiple cardiac risk factors. Evaluation of carotid vessels showed carotid atherosclerosis in 78% (n=53) of subjects. Further CTCA evaluation demonstrated coronary atherosclerosis in 98% (n=67) of subjects. 20% (n=14) of patients with subclinical atherosclerosis would not have been detected on using carotid Doppler alone.

Conclusion: CTCA is more accurate than carotid Doppler for CAD prediction in acute stroke patients. Addition of a direct method of coronary evaluation would be a good management tool to stratify & prevent a cardiac event in near-future these subjects.

Introduction

According to World Health Organization (WHO), approximately 31% (17.2 million) of total deaths in 2015 were caused by cardiovascular diseases. 38% of these deaths were caused by cerebrovascular accidents, while 42% were due to myocardial infarction (MI) [1]. In stroke patients who survive the initial insult, myocardial infarction was the leading cause of mortality, causing approximately 20% of the deaths at 5 years [2]. This risk is higher in subcategory of patients who are considered "Young Stroke" patients (<50 years). Lifelong secondary prevention of MI is a plausible approach in these patients. Recurrence of neurovascular accidents (10% death at 5 year) is the second leading cause of death & disability after MI.

WHO also surmises that stroke is one of the leading causes of loss of disability adjusted life years (DALY's) due to

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Received: 01.02.19
Accepted: 15.03.19

the lengthy period of recovery and rehabilitation associated with it [3]. One of the ongoing care issues in these recovering patients is presence of coronary artery disease (CAD). It is of-ten missed in stroke patients due to their severely distressed state and may complicate rehabilitation. Consequently, occurrence of an acute cardiac event or even death might be the first sign of CAD in these patients [4,5].

In contrast to carotid vascular disease, where percentage of stenosis is an important marker of occurrence of cerebral ischemia; in coronary circulation, the nature, location and components of the plaque are additional predictors of an impending myocardial event [6,7]. Approximately, 68% of patients with acute MI may have a relatively mild (<50%) degree of coronary stenosis [6]. In fact, almost 76% of sudden cardiac deaths (SCDs) are caused by unstable minimally occluding plaques, and only 24% of SCDs may be attributed to severe stenosis [7].

Several important clinical risk factors are known to be associated with cardiovascular disease in stroke patients. While they are known to precipitate or cause cardiac disease, most of them are not accurate predictors of subclinical or preclinical coronary disease. The advantage of these risk factors remains in that they can be used as therapeutic targets [8].

Direct measurement of subclinical coronary atherosclerosis may augment the information provided by risk factor scoring [9]. Imaging evaluation of atherosclerosis is helpful in detection of diseases such as CAD, cerebral ischemia, peripheral claudication and as such, is better able to identify the individuals who would benefit from intensive interventions compared to those who might not [10].

Current evaluation protocols for a patient with an acute neurological event include carotid ultrasound / Doppler and neurovascular imaging with non-contrast and contrast-enhanced computed tomography (CT) scan. A cardiac echocardiogram (ECHO) may or may not be performed to investigate the source of an embolic focus. Also an ECHO is not optimal for assessment of coronary vessels. Carotid Doppler is used to identify operable carotid disease and as an indirect marker for identification of CAD. Evaluation of CAD is important in assessment of patients with CVA to prevent the next major mortality inducing event i.e. myocardial infarction (MI). There is a direct relationship of raised carotid intima-media thickness (cIMT) to adverse cardiac events. However, the use of carotid Doppler markers in practice has not been as successful since the prediction capability for cardiac disease especially in stable cardiac disease is not very accurate [10,11] and also because accurate cut-offs for raised cIMT have been difficult to arrive at. Additionally, cIMT standardization for age, gender and ethnicity are not available at present [12].

Early evaluation of the coronary arteries via Calcium scoring (CAC) & CTA may help manage and prevent a catastrophic cardiac event and/or excessive further hospitalization. CT coronary angiography (CTCA) is fast emerging as a reliable modality to assess the vasculature of the heart and to quantify coronary atherosclerosis. CTCA is able to detect and classify the degree of stenosis in the coronary arteries and characterise any coronary plaques with a high sensitivity, specificity, and negative predictive value. The value of CAC scoring vs carotid doppler based evaluation has been studied extensively in the prediction of the major adverse cardiac events (MACE) of myocardial infarction, CAD (>50% stenosis of major coronary arteries AND/OR three-vessel disease) and stroke or transient ischemic attack. CAC is known to much improve the reclassification, detection and prediction of coronary artery disease. So far, scant literature has reported on the comparative efficacy of CT criteria of coronary atherosclerosis and Doppler criteria of carotid atherosclerosis in predicting cardio-vascular disease risk.

cIMT and Carotid Plaque in CAD estimation

Atherosclerosis of carotid vessels can be easily estimated by measuring intima-media thickness (IMT) in the extracranial carotid arteries [13,14]. A cIMT<0.8 is considered normal in adults. Plaque location at bifurcation as well as ulceration and areas of hypoechogenicity suggest instability of plaque and as such an increased risk for CVA. Subclavian steal is suggested by a reversal of flow in vertebral artery on color Doppler [15]. Occlusive plaques may cause stenosis. All these factors constitute CAD risk.

Coronary Calcium scoring and CAD

Coronary calcium scoring has been shown to improve risk reclassification in all patients suspected of coronary atherosclerosis [16,17]. The CAC score substantially improves the accuracy of Framingham risk score in predicting the risk of MACE [18-20].

CTA evaluation of CAD [16-17, 21]

Coronary plaque characterization, detection of rupture prone soft plaques&degree of stenosis may be more reliably determined via CTA. CTA also helps monitorplaque in patients receiving preventive therapy.

With the above background, we planned a study in our institution with the following aims and objectives:

1. Evaluating the role of carotid Doppler and CTA in prediction of coronary artery disease (CAD) in patients with acute CVA.
2. Correlation between Doppler and CT angiogram findings in patients with acute CVA.

Materials and Methods

The study was conducted in the Department of Radiodiagnosis, Teerthanker Mahaveer Medical College & Research Centre, Moradabad, Uttar Pradesh, India with the following inclusion and exclusion criteria:

Inclusion criteria

Participants were selected from patients presenting with an acute CVA. All patients with stroke, aged >35 years, were requested for consent to participate in the study.

Exclusion Criteria

1) eGFR <30 ml/minute

2) Subjects in whom optimal bradycardia was unsafe

3) History of contrast allergy, atopy or pregnancy

Baseline questionnaire was administered to the included patients to assess past medical history. Carotid vasculature was evaluated with Color Doppler and relevant data was collected. CTCA evaluation was done after achieving sufficient bradycardia (60-70 bpm) with metoprolol, followed by injection of 80 to 100 ml of iodinated contrast media to the patient with a pressure injector, at a rate of 5 to 5.5 ml/minute. Coronary artery calcium score (Agatston's score) was calculated. CT images of the coronary vasculature were archived in multiple planes and modes.

Statistical Analysis

Data was tabulated in Excel (Microsoft 2010). Statistical analysis was performed by Stata 14.0 (Stata Inc.). Demographic data was calculated and presented as mean and standard deviation for continuous and count (percentage) for categorical variables. Chi-square test was applied for comparing means of two categorical variables. Statistical significance was set at 0.05. Correlation was calculated for the two main predictors.Correlation between two categorical variables was measured via Spearman's correlation coefficient (r) and significance of correlation was set at p value of 0.05.

Observations and Results

Demography (Table 1)

Out of 68 enrolled patients, 79% (n=54) subjects were male. Preexisting cardiac risk factors were fairly common among the subjects, with 71% (n=53) reporting at least one risk factor and 28% (n=19) subjects having multiple risk factors. Overall 47% of patients (M-52%, F-29%) had diabetes mellitus. Preexisting hypertension was seen in 41% subjects (M-37%; F-57%). 22% of males were smokers. Approximately 24% of all patients had a first-degree relative with cardiac disease. Approximately 30% of our subjects did not give history of preexisting cardiac risk factors. Other major medical illnesses were seen in 39% (n=27) of the subjects (Table 2) emphasizing the distressed state of these subjects.

Many patients presented with multiple major complaints (n=36). Out of these, most common complaint was a combination of hemiparesis, gait disturbance and slurring of speech.

Carotid Vessel Disease (Table 4)

Fifty-three (78%) were found to have clinically significant carotid atherosclerosis on color Doppler. The mean cIMT thickness in these patients was 1.01 mm which was only slightly raised above the normal thickness of 0.8 mm. However, 72% of the patients with carotid atherosclerosis (cIMT>0.08) showed the presence of a plaque in one or more of the carotid vessels and only 6 patient (40%) without atherosclerosis showed the presence of a plaque in any of the vessels. Moreover, in patients with carotid atherosclerosis, the plaque length was almost 6 times and degree of stenosis almost 4 times of those without significant atherosclerosis.

Coronary Atherosclerosis & CAC Scoring (Table 5)

Amongst the 68 patients evaluated, 67 (98%) had a raised coronary artery calcium score for age & gender group, denoting coronary atherosclerosis. The mean CAC score was 927.6. However, angiographic findings of coronary stenosis / plaque were seen only amongst 43 (64%) of these 67 patients.

Correlation between Carotid Atherosclerosis & Coronary Atherosclerosis (Table 6)

Amongst the total 68 stroke patients, all those who had findings of carotid atherosclerosis on Doppler, were seen to have additional features of coronary atherosclerosis. However, in 14 of the 67 patients with coronary atherosclerosis on CAC scoring there was no evidence of carotid atherosclerosis on Doppler. The Pearson's correlation coefficient between the two findings was seen to be 0.23.

The mean cIMT was 0.6 in those without coronary atherosclerosis (Table 7), while in those with coronary

Table 1: Demographics of Study Population

	Male	Female	Total
Number	54(79%)	14 (21%)	**68**
Mean Age	64+/-14.4	66 +/-14.2	**65+/-14.3**
Known Hypertensives	20 (37%)	8 (57%)	**28 (41%)**
Family History of Cardiac disease	12 (22%)	4 (29%)	**16 (24%)**
Smokers	12 (22%)	0 (0%)	**12 (18%)**
Carotid Atherosclerosis (+/-) on Doppler	41 (76%)	12 (86%)	**53 (71%)**
Mean cIMT	0.917	0.971	**0.928**
Mean CAC score	941	879	**929**

Table 2: Prevalence of Cardiac & Other Risk Factors (Total n=68)

		Number	%
Diabetes Mellitus		32	47.06%
Known Hypertensive		28	41.18%
Family History Of Heart Disease		16	23.53%
Smokers		12	17.65%
Previous Cardiac Disease		15	22%
Other Major Medical Illness	**Total**	**27**	**39%**
	CKD	10	37.0%
	Recurrent CVA	9	33.3%
	Rheumatic Disease	4	14.8%
	Tuberculosis	3	11.1%
	Prior CABG	1	3.7%

Table 3: Clinical Presentation

	Number	%
Left Hemiparesis	20	**29%**
Right Hemiparesis	16	**24%**
Seizure	8	**12%**
Ataxia, Aphasia	6	**9%**
Altered Mental Status	4	**6%**
Progressive lower hemiparesis	4	**6%**
Recurrent right hemiparesis	4	**6%**
Severe Headache	3	**4%**
Vertebrobasilar Insufficiency	2	**3%**
Aphasia	1	**1%**
Grand Total	**68**	**100 %**

Table 4: Summary of carotid vessel disease

	No Carotid Atherosclerosis	Carotid Atherosclerosis	Grand Total
Number of subjects	15(22%)	53(78%)	**68**
Mean cIMT (in mm)	0.64	1.01	**0.928**
Carotid Plaque seen	6(40%)	38(72%)	**44**
Mean Length of plaque (in mm)	1.17	9.01	**7.3**
Percentage stenosis %	6	26	**21.6**

Table 5: Summary of coronary Atherosclerosis

	No Coronary Atherosclerosis	Coronary Atherosclerosis	Total
Number of patients	1(2%)	67(98%)	**68**
Mean Coronary Artery Calcium (CAC) score	97	927.6	**915.4**
Coronary stenosis (+/-)	0(0%)	43(64%)	**43**

Table 6: Correlation between coronary & carotid atherosclerosis

	Coronary Atherosclerosis (raised CAC)		
Carotid Atherosclerosis (cIMT>0.08 mm)	**Negative**	**Positive**	**Total**
Negative	1	14	**15**
Positive	0	53	**53**
Total	1	67	**68**

Pearson's correlation coefficient = 0.23 (p>0.05)

Table 7: Mean cIMT & CAC in patients with & without coronary atherosclerosis on CAC

	Coronary Atherosclerosis		
	Negative	**Positive**	**P value**
Mean cIMT	0.60	0.93	<0.05
Mean Coronary Artery Calcium (CAC) score	520	921.3	<0.05

atherosclerosis, it was 0.93. The mean CAC score followed a similar pattern. This difference in was seen to be significant, suggesting that cIMT increases with greater presence of coronary atherosclerosis.

Discussion

This study has shown that risk prediction for CAD in stroke patients is improved by the addition of a CAC score with or without CTA. Carotid Doppler underestimates the presence of CAD compared to direct CAC scoring of coronary vasculature.

Coronary imaging with CT (for CAC detection and scoring) and carotid ultrasound (for assessment of IMT and plaque presence) are increasingly utilized to identify subjects with atherosclerosis or those who are at a higher risk of CAD. These imaging techniques have been consistently shown to add value to the risk estimation by traditional risk factors and thus help in more efficient use of preventive resources [22, 23]. The Multiethnic Study of Atherosclerosis (MESA) has previously documented and analyzed the role of cIMT and carotid plaque versus evaluation of CAC in 6779 subjects with follow upat every two years to record the progression of atherosclerosis and document occurrence of MACE. Multiple studies using the MESA database have shown CAC to be better predictor of CAD compared to cIMT & carotid plaque [24].

The relationship between peripheral atherosclerosis and coronary atherosclerosis has also been previously investigated. However, peripheral atherosclerosis is at best an indirect marker of coronary disease and as our results, the concordance between the direct measurement of CAD and these methods is weak, At best they can be used as indirect indices of coronary disease [25].

cIMT is generally considered a better predictor of ischemic stroke, on account of the carotid vessels being directly responsible for the cerebral blood supply. Its role as a predictor of MI is limited by the fact that coronary disease does not necessarily correspond with carotid disease, CAD may precede or follow carotid disease, or may not have any association with it [25].

Naghavi et al proposed the SHAPE (Screening for Heart Attack Prevention and Education) guidelines where they proposed initially classifying cardiovascular risk based on CAC or values of cIMT. Their study suggested that both these markers add much value to risk prediction and stratification in the prevention of cardiac events, over and above that given by traditional risk assessment by the Framingham and other such risk scores [26, 27].

Few studies such as EDUCATE (Early Detection by Ultrasound of Carotid Artery IMT Evaluation) have suggested a robust association between MACE, CAD and carotid atherosclerosis. Other studies such as the MESA and ARIC have indicated that CAC scoring, either alone or in combination with other modalities, much improves the risk stratification specifically in low and intermediate risk groups [25].

In accordance with literature, our data shows that addition of cIMT and/or CAC scoring improves risk prediction over analysis of clinical risk factors alone. Among the two modalities, we found CAC scoring to be more strongly associated with CAD.

The majority of the studies showed improved detection of CAD by utilizing CAC score and/or CTA. However the reported improvement ranged from 1-4% in studies with enrollment of population based cohorts (Gepner et al) or other direct markers (Cho et al-Angiography of aorta), to 20-40% (Sillesen, Kim, Puchner) when the intermediate risk group was used [25, 28-31]. The latter group corresponded to our findings suggesting that cIMT was a weaker predictor than other CT-based predictors.

Wardlaw et al concluded in a meta-analysis of 41 studies (2541 patients) that amongst Doppler ultrasound, CTA and MRA, MRA was most accurate in detection of atherosclerosis specifically in higher degrees of stenosis (70-99%) and doppler ultrasound the least accurate [32]. Majority of reviewed studies consistently demonstrated the superiority of CTA over Doppler assessment. However, the major benefit of Doppler study was found in cost effectiveness analyses of resource and time constrained settings such as the NHS of UK [32].

In our subjects, CAC improved CAD detection over cIMT and/or carotid plaque detection in up to 20% stroke patients. Prior research attributes this to the fact that while calcium scoring directly evaluates coronary vessel disease, carotid evaluation is an indirect marker of presence of atherosclerosis in peripheral vessels. Thus, carotid evaluation may predict events within the cerebral vasculature (such as stroke/TIA) but its usefulness decreases for events related to the myocardium [25]. The primary conclusion of our study was that CAC / CTA

Table 8 : Percentage Improvement in diagnosis of CAD

	Indirect criterion	**Improvement in prediction of CAD by utilizing CAC/CTA**
Our Study	cIMT>0.8 mm	20%
Gepner et al (24)	Carotid plaque	4%
Tresoldi et al (25)	cIMT>1.0	20%
Cho et al (27)	Complicated Aortic Plaque	1%
Yoon et al (28)	Carotid Plaque	38%
Sillesen et al (29)	Carotid plaque burden	40%
Puchner et al (30)	High Risk Plaque	20%
	Any Plaque	11%
Kim et al (31)	Plaque	28%

evaluation improves prediction of coronary atherosclerosis over the traditional methods of clinical risk scoring and Doppler evaluation of peripheral vessels.

Limitations of the study

- Small sample volume
- Selective population - Our study was limited to stroke patients. Hence our subjects were selected for high CAD. In the general population where CAD is expected to have a more limited presence, results might not be generalizable.

Conclusion

Coronary artery calcium imaging (CAC) is much more accurate than carotid Doppler studies in the prediction and management of coronary vessel disease in stroke patients. Approximately 20% of all patients will benefit by addition of CAC / CTA to carotid evaluation and clinical risk scoring while evaluating cardiac risk. A majority of stroke patients are quite debilitated at the time of their hospitalization with other known comorbidities. This might be detrimental to additional evaluation. However, in light of the fact that an MI is the most common cause of death & disability in these patients, adding a direct coronary evaluation would be a good management tool to stratify & prevent a cardiac event.

Conflict of interest:	All authors declare no COI
Ethics:	There is no ethical violation as it is based on voluntary anonymous interviews
Funding:	No external funding
Guarantor:	Dr. Rajul Rastogi will act as guarantor of this article on behalf of all co-authors.

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