Carotid Intima –Media Thickness and Plaque as a Predictor for Ischemic Etiology in Patients with Severe Left Ventricular Systolic Dysfunction

Ahmed AhmedWafa Soliman[1], Mahmoud Muhammad Abdo Youssef[2], Ahmed Ibrahim Bedeir Abd Alnaby[3], Dina Ahmed Muhammad Abdelmoneim[4*]

Abstract

Background: Coronary artery disease (CAD) is the leading cause of death worldwide. Previously thought to affect primarily high-income countries, CAD now leads to more death and disability in low- and middle-income countries. **Aim of study:** This study was conducted to respectively evaluate the carotid intima –media thickness and plaque as a predictor for ischemic etiology in patients with severe left ventricular systolic dysfunction.**Methods:** This study was a descriptive comparative cross-sectional study conducted at Cardiology Department in Mansoura Specialized Medical Hospital. This study was conducted on patients with severe left ventricular systolic dysfunction with estimated EF ≤ 35% undergoing coronary angiography. **Results:** The mean RT IMT and LT IMT were associated with a highly statically significant increase in group (1) compared to group (2) (P<0.001). In addition, positive RT plaque and positive LT plaque were significantly increase in group (1) compared to group (2) (p<0.05). **Conclusion:** In the context of severe left ventricular systolic dysfunction the carotid intima –media thickness and plaque could be used as promising predictors for ischemic etiology.

KeyWords: Carotid Intima –Media Thickness; Plaque; Ischemic; Left Ventricular Systolic Dysfunction.

DOI Number: 10.14704/nq.2022.20.13.NQ88048 **NeuroQuantology 2022; 20(13): 358-364**

Correspondingauthor: Dina Ahmed Muhammad Abdelmoneim

Affiliations:
1. Professor of Cardiovascular Medicine, Faculty of Medicine; Mansoura University, Egypt.
2. Professor of Cardiovascular Medicine, Faculty of Medicine; Mansoura University, Egypt.
3. Lecturer of Cardiovascular Medicine, Faculty of Medicine; Mansoura University, Egypt.
4. MBBCH – MS Cardiovascular Medicine, Faculty of Medicine; Mansoura University, Egypt.

Relevant conflicts of interest/financial disclosures:
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Introduction

Coronary artery disease (CAD) is the leading cause of death worldwide. Previously thought to affect primarily high-income countries, CAD now leads to more death and disability in low- and middle-income countries (Murray CJ et al., 2012). Atherosclerosis is a systemic disease, and carotid and coronary arteries are the two most common sites of involvement of atherosclerosis (Robinson J et al., 2014).

Heart failure with reduced ejection fraction (HF-REF) and preserved ejection fraction each make up about half of the overall HF burden. The most common etiology of HF-REF in the developed world is ischemic heart disease, which is associated with more than 60% of diagnoses. Coronary artery disease (CAD) associated with left ventricular systolic dysfunction is a condition related to poor prognosis (Gheorghiade M et al., 2006).

Imaging of arteries to identify and quantify the presence of subclinical vascular disease has been suggested to further refine CAD risk assessment (Tierney ES et al., 2015). Whereas coronary angiography has stood the test of time to assess atherosclerotic burden in coronary arteries, the cost and skill needed to perform this test has left this test unaffordable and unreachable to many. Carotid intima-media thickness (CIMT) is a simple and inexpensive tool to assess the cumulative effect of atherosclerotic risk factors and has been proven to be an independent predictor of future cardiovascular risk in various studies (Touboul P et al., 2017).

The non¬invasive and reliable diagnostic tool for evaluating carotid artery atherosclerosis plaque or stenosis (CAS) is an ultra¬sound including measurement of intima-media thickness (IMT), which represents mainly medial layer hypertrophy (von Reutern GM et al., 2012). IMT is usually measured in the common carotid artery and the internal carotid artery (Touboul PJ et al., 2011). In recent years, automated and semi-automated measurements of IMT were developed (Molinari F et al., 2010).

According to Mannheim con¬sensus conference, measurement of IMT should be done on the far wall of the common carotid artery, with quality index greater than 0.5. IMT, plaque, and stenosis should be regarded as distinct phenotypes, with distinct bi¬ological aspects and determinants (Spence JD et al., 2004).

This study was conducted to respectively evaluate the carotid intima –media thickness and plaque as a predictor for ischemic etiology in patients with severe left ventricular systolic dysfunction.

Patients and Methods

This study was a descriptive comparative cross-sectional study conducted at Cardiology Department in Mansoura Specialized Medical Hospital. This study was conducted on patients with severe left ventricular systolic dysfunction with estimated EF ≤ 35% undergoing coronary angiography.

Sample size: Sample size was calculated using G Power program provided that: From a previous study (Ziembicka, et al; 2004), the carotid mean IMT in patients with ischemic coronary artery disease was 1.26 ± 0.27 mm, while its mean in patients with normal coronary arteries was 1.01 ± 0.19 mm.

Alpha error level is 5% & confidence interval is 95%. Beta error level is 10% & statistical power of the study is 90%

So, sample size was 48 at least. To compensate for non-responders and defaulters, we will increase sample size by 10%. So, sample size was 53.

Inclusion criteria: This study will include patients with severe left ventricul systolic dysfunction undergoing coronary angiography at Mansoura Specialized Medical Hospital.

Exclusion criteria: Patients not undergoing coronary angiography, Patients with valvular heart disease, Patients with hypertensive heart failure, patients with congenital heart disease, patients with pericardial diseases, patients with chronic renal failure, patients with liver cell failure, patients did not consent to the study.

Methods:

Patients were subjected to most of the following: Full history taking, full clinical examination: General examination, Local examination and investigations:12 lead electrocardiography, study of echocardiographic report, Carotid Doppler, revision of patients' laboratory data and assessment of angiographic outcome.

Ethical consideration: Study protocol was submitted for approval by Mansoura Medical Research Ethics Committee. Approval of the managers of the hospital in which the study was conducted. Informed written consent was obtained from each participant sharing in the study.

Statistical analysis:

Data were analyzed using the Statistical Package of Social Science (SPSS) program for Windows (Standard version 21). The normality of data was first tested with one-sample Kolmogorov-Smirnov test. Qualitative data were described using number and percent. Association between categorical variables was tested using Chi-square test while Monte carlo test was used when expected cell count less than 5. Continuous variables were presented as mean ± SD (standard deviation) for normally distributed data. The two groups were compared with independent t- test for normal data. The threshold of significance is fixed at 5% level (p-value). The results were considered significant when the probability of error is less than 5% ($p \leq 0.05$). The smaller the p-value obtained, the more significant are the results.

Results

There were no statistically significant differences among both groups regarding both age and sex (P>0.05).

Table (1): Demographic data among the studied groups

Demographic data	Group (1) (n=35)	Group (2) (n=35)	Test of significance	P value
Age (years)				
Mean ± SD	63.28±8.99	61.97±7.31	t=0.671	.505
Min-Max	45-78	45-75		
Gender				
Male	27 (77.1%)	21 (60.0%)	χ^2 =2.36	0.122
Female	8 (22.9%)	14 (40.0%)		

t: student t test, X^2 : Chi square test

There was a highly statically significant increase in chest pain in group (1) compared to group (2) with no significant differences among both groups regarding dyspnea and fatigue (P>0.05).

Table (2): Symptoms among the studied groups:

Symptoms	Group (1) (n=35)	Group (2) (n=35)	Test of significance	P value
Chest pain	33 (94.3%)	11 (31.4%)	χ^2 =29.61	≤0.001*
Dyspnea	23 (65.7%)	22 (62.9%)	χ^2 =0.062	0.803
Fatigue	26 (74.3%)	32 (91.4%)	χ^2 =3.62	0.057

*Significant p ≤0.05.

Figure (1) and **figure (3)** display risk factors among the studied groups. Smoking, HTN and Dyslipidemia demonstrated a highly statistically significant increase in group (1) compares to group (2) (P<0.001). In addition, DM was also significantly increase in group (1) compared to group (2) (P<0.05).

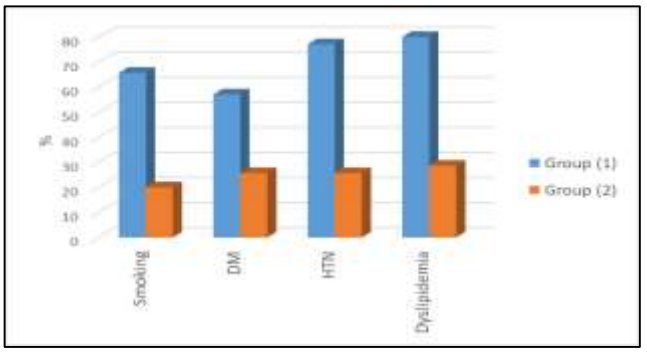

Figure (1): Risk factors among the studied groups

There was a highly statically significant increase in CABG among group (1) compared to group (2) (P<0.001).

Table (3): CABG among the studied groups

CABG	Group (1) (n=35)	Group (2) (n=35)	Test of significance	P value
CABG				
Positive	15 (42.9%)	0 (0.0%)	χ^2 =19.09	≤0.001*
Negative	20 (57.1%)	35 (100.0%)		

EF and RSWM among the studied groups in which there were no significant differences among both groups regarding both parameters (EF and RSWM) (P<0.05).

Table (4): EF and RSWM among the studied groups

Variables	Group (1) (n=35)	Group (2) (n=35)	Test of significance	P value
EF				
Mean ± SD	31.54±2.84	30.62±2.73	t=1.37	0.175
RSWM				
Anterior,lateral ,apical	(2.9%)	0 (0%)		
hypokinesia			MC	0.235
Gobal hypokinesia	32 (91.4%)	35 (100%)		
Anterior,lateral hypokinesia	2 (5.7%)	0 (0%)		

MC: monte carlo test

Figure (2) illustrate ECG among the studied groups. ECG abnormalities were significantly increased among group (1) compared to group (2) (P<0.001).

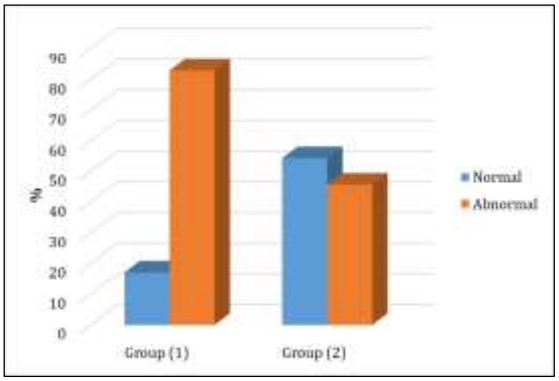

Figure (2): ECG among the studied groups

Figure (3) demonstrate angiographic results among the studied groups. No recorded obstruction in group 2 (100%), while only 17.1% of group (1) demonstrated non-obstructive manifestations. In addition, there was a highly statistically significant increase in obstructive vessels in group (1) compared to group (2). Regarding group (1), Single vessel obstruction, two vessel obstructions, three vessel obstructions were recorded in 31.4%, 20% and 31.4% respectively.

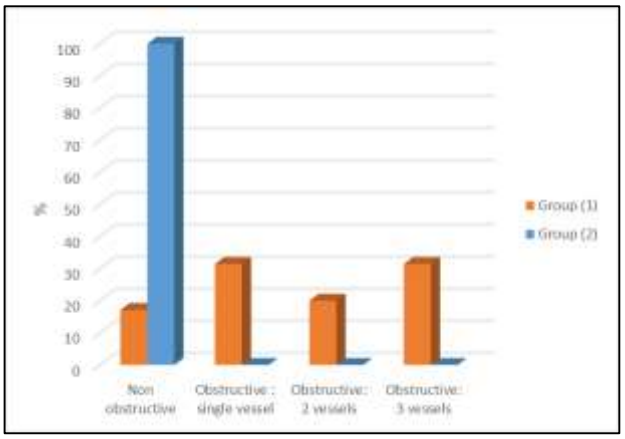

Figure (3): Angiographic results among the studied groups.

The mean RT IMT and LT IMT were associated with a highly statically significant increase in group (1) compared to group (2) (P<0.001). In addition, positive RT plaque and positive LT plaque were significantly increase in group (1) compared to group (2) (p<0.05).

Table (5): RT and LT IMT among the studied groups

	Group (1) (n=35)	Group (2) (n=35)	Test of significance	P value
RT IMT Mean ± SD	0.116±0.01	0.071±0.01	t=15.52	≤0.001*
RT plaque				
Positive	13 (37.1%)	5 (14.3%)	χ^2=4.78	0.027*
Negative	22 (62.9%)	30 (85.7%)		
LT IMT Mean ± SD	0.114±0.01	0.07±0.009	t=16.04	≤0.001*
LT plaque				
Positive	11 (31.4%)	4 (11.4%)	χ^2=4.16	0.041*
Negative	24 (68.6%)	31 (88.6%)		

Discussion

Coronary artery diseases (CAD) are the most common and hazardous cardiovascular disease. Its incidence and the resultant morbidity and mortality increase every year, especially in the elderly **(Rusnak et al., 2017).**

This was a prospective comparative study conducted at Cardiology Department in Mansoura Specialized Medical Hospital on patients with severe left ventricular systolic dysfunction with estimated EF ≤35% undergoing coronary angiography. Entire cases were further divided into two groups group A with IHD and group B without ischemic heart diseases.

Concerning demographic data, the current study demonstrates that there were no statistically significant differences among both groups regarding both age and sex.

Similarly, Suh and his colleagues have demonstrated There were no significant differences in age (68.3±13.7 years vs. 70.4±13.1 years), male sex (40.4% vs. 59.6%) between cases with CAD and cases without **(Suh et al., 2010).**

On the contrary, **Abd El-Aziz and his colleagues** have demonstrated that males were significantly associated with the development of ischemic changes compared to females **(AbdEl-Aziz et al., 2021).**

With regard risk factors, smoking, HTN and dyslipidemia demonstrated a highly statistically significant increase in group (1) compares to group (2) (P<0.001). In addition, DM was also significantly increase in group (1) compared to group (2) (P<0.05).

This came in the same line with Suh and his colleagues who have demonstrated that HTN was significantly increased among CAD cases compared to CAD free ones. However, they were in disagreement regarding DM and smoking as they reported no significant difference regarding DM (25% vs. 46.3%) and smoking (31% vs. 48.3%), **(Suh et al., 2010).**

In addition, Abd El-Aziz and his colleagues have demonstrated that smoking and hyperlipidemia were significantly increased among ischemic cases, while DM and HTN did not demonstrated any significant changes among ischemic and non-isomeric ones **(AbdEl-Aziz et al., 2021).**

Regarding hypertension, it has long been a major risk factor for heart disease through both oxidative and mechanical stress it places on the arterial wall

(Malakar et al., 2019).

Elevated triglycerides have also been implicated in coronary artery disease; however, the relationship is more complicated as the association becomes attenuated when adjusted for other risk factors such as central adiposity, insulin resistance, and poor diet. Thus, it is challenging to determine an isolated effect of triglycerides on coronary artery disease **(Benjamin et al., 2019).**

The Center for Disease Control (CDC) reports that more than one out of every three adult patients in the United States have prediabetes, which puts one at risk of developing type 2 diabetes, heart disease, and stroke **(Brown et al., 2020).**

The heart disease rate is 2.5 times higher in men and 2.4 times higher in women in adult patients with diabetes compared to those without diabetes **(Mozaffarian et al., 2015).**

A 2017 meta-analysis indicated that patients with diabetes with an A1C > 7.0 had an 85% higher likelihood (hazard ratio 1.85, 95% CI 1.14-2.55) of cardiovascular mortality, compared to those with an A1C < 7.0%. It also revealed that non-diabetic patients with an A1C > 6.0% had a 50% higher likelihood (hazard ratio, 1.50, 95% CI 1.01-2.21) of cardiovascular mortality compared to those with an A1C of < 5.0%. Researchers also reported a significant study heterogeneity **(Cavero-Redondo et al., 2017).**

Cardiovascular disease is the leading cause of morbidity and mortality in patients with diabetes **(ADA, 2010).**

In addition, EF and RSWM demonstrated insignificant differences among both groups (P<0.05). With regard ECG, Group (1) was associated with a significant ECG abnormality compared to group (2).

Suh and his colleagues have found that there were no statistically significant differences among both groups regarding LVEDd (63.4±6.2 mm vs. 63.1±7.5 mm) and LVEF (22.6±4.6% vs. 24.0±4.7%). In addition, the prevalence of Q wave in V1-4 (6.3% vs. 14.3%, p<0.01) was significantly higher in the CAD group **(Suh et al., 2010).**

Concerning angiographic results among the studied groups, no recorded obstruction in group 2 (100%), while only 17.1% of group (1) demonstrated non-obstructive manifestations. In addition, there was a highly statistically significant increase in obstructive vessels in group (1) compared to group (2). Regarding group (1), Single vessel obstruction, two vessel obstructions, three vessel obstructions were recorded in 31.4%, 20% and 31.4% respectively.

In addition, the current study displayed that the mean RT IMT and LT IMT were associated with a highly statistically significant increase in group (1) compared to group (2) (P<0.001). In addition, positive RT plaque and positive LT plaque were significantly increase in group (1) compared to group (2) (p<0.05).

This came in the same line with Suh and his colleagues who conducted their study on a total of 73 patients hospitalized for heart failure with severe LVSD. The severity of CAD was analyzed by the Duke Jeopardy Score system, and carotid IMT and plaque were measured according to the Mannheim Carotid IMT Consensus. Significant CAD was found in 41 patients (56.1%, CAD group) on coronary angiography. Mean common carotid artery (CCA) IMT (0.74±0.05 mm vs. 1.04±0.04 mm, p<0.01) was significantly higher in the CAD group **(Suh et al., 2010).**

Plaque in CCA (6.25% vs. 19.5%, p<0.01) and plaque in bulb (25.0% vs. 60.9%, p<0.001) were significantly higher in the CAD group. Mean CCA IMT (odds ratio (OR) 2.61, 95% confidence interval (CI) 1.134-4.469, p<0.01) and plaque in bulb (OR 4.69, 95% CI 1.702-12.965, p<0.01) were significant predictors for the diagnosis of CAD according to multivariate logistic regression analysis. In patients with severe LVSD, mean CCA IMT and bulb plaque can be useful additional predictors for the diagnosis of CAD **(Suh et al., 2010).**

Another study conducted by Yoon and his colleagues demonstrated in their univariate analysis that, vascular events were significantly associated with age, gender, diabetes, renal function, lipid levels, left ventricular function, carotid plaque or IMT. In multivariate analysis, the presence of carotid plaque, diabetes, renal function and male gender were independent predictors of future vascular events in the patients with ischemic stroke, but carotid IMT was not a predictor of future vascular events. Event free survival was significantly lower in patients with carotid plaque than without carotid plaque on Kaplan-Meier analysis (log rank p < 0.001) **(Yoon et al., 2017).**

In the same line, **Harada and Tabako** have

illustrated that; the mean values of Max-IMT and carotid PS were 2.41 ± 1.23 mm and 8.5 ± 6.3, respectively. The decreased mean E/A (0.94 ± 0.39) and mitral e′ (5.5 ± 1.9 cm/s) indicated LV diastolic dysfunction. A good correlation was observed between Max-IMT and PS (r = 0.83, p < 0.0001). **(Harada and Tabako, 2016).**

Bytyçi and his colleagues have searched all electronic databases until October 2020 for studies which reported relationship between carotid and coronary atherosclerosis. Eighty-nine papers with 22,683 patients comparing carotid and coronary atherosclerosis were included in the analysis. CIMT was increased linearly with severity of CAD irrespective of its significance (P<0.001), mono versus 2 vessel disease (P=0.003), and 2 versus multivessel disease (P<0.001) **(Bytyçi et al., 2021).**

Thus, they concluded that atherosclerosis affects both carotid and coronary systems, although not always in identical phenotypic manner. These findings highlight the beneficial examination of carotid arteries whenever CAD is suspected **(Bytyçi et al., 2021).**

Also, **Metwally and his colleagues** have demonstrated that in relation to wall motion score index (WMSI), there was significant elevation in CIMT (p=0.022) and carotid plaque (p=0.028) in the patients with positive stress study **(Metwally et al., 2020).**

It is efficient, relatively inexpensive and highly reproducible and does not expose patients to contrast dye or radiation. Previous studies demonstrated the relationship between carotid IMT and the extent and severity of coronary stenosis **(Lekakis et al., 2005).**

Therefore, it can be postulated that carotid IMT and plaque provide diagnostic clue for ischemic etiology in severe LVSD patients. Atherosclerosis is a systemic disease and, as such, increasing carotid IMT and plaque are correlated with CAD. However, this association remains debatable **(Suh et al., 2010).**

Hence the current study weighted on mean CCA IMT or the presence of plaque can be used as tools to support the presence of ischemic etiology in severe LVSD patients and normal CCA IMT in the absence of plaque support the non-ischemic etiology of severe LVSD patients. In practice, if severe LVSD patients have no history of ischemia with normal IMT and without plaque in bulb, we can initially classify them as non-ischemic LVSD. On the contrary, increased IMT with plaque in bulb in patients are indications to perform coronary angiography.

Conclusion

In the context of severe left ventricular systolic dysfunction, the carotid intima –media thickness and plaque could be used as promising predictors for ischemic etiology.

REFERENCES

A Kablak-Ziembicka, W Tracz, T Przewlocki, et al . (2004) , Association of increased carotid intima-media thickness with the extent of coronary artery disease , Heart , 90:1286–1290. doi: 10.1136/hrt.2003.025080

AbdEl-Aziz, H., Aziz, A., El-Magd, M. A., et al. (2021). CORRELATION BETWEEN MYOCARDIAL PERFUSION IMAGING AND CAROTID ULTRA-SONOGRAPHY IN PATIENTS WITH CHEST PAIN. Al-Azhar Medical Journal, 50(2), 1257-1270.

ADA. (2010). Standards of medical care in diabetes—2010. Diabetes care, 33(Supplement_1), S11-S61.

Benjamin, E. J., Muntner, P., Alonso, A., et al. (2019). Heart disease and stroke statistics—2019 update: a report from the American Heart Association. Circulation, 139(10), e56-e528.

Brown, J. C., Gerhardt, T. E., and Kwon, E. (2020). Risk factors for coronary artery disease. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554410/.

Bytyçi, I., Shenouda, R., Wester, P., et al. (2021). Carotid atherosclerosis in predicting coronary artery disease: a systematic review and meta-analysis. Arteriosclerosis, Thrombosis, and Vascular Biology, 41(4), e224-e237.

Cavero-Redondo, I., Peleteiro, B., Álvarez-Bueno, C., et al. (2017). Glycated haemoglobin A1c as a risk factor of cardiovascular outcomes and all-cause mortality in diabetic and non-diabetic populations: a systematic review and meta-analysis. BMJ open, 7(7), e015949.

Gheorghiade M, Sopko G, De Luca L,et al.(2006). Navigating the crossroads of coronary artery disease and heart failure. Circulation , 114(11):1202-13.

Harada, M., and Tabako, S. (2016). Carotid atherosclerosis is associated with left ventricular diastolic function. Journal of echocardiography, 14(3), 120-129.

Lekakis, J. P., Papamichael, C., Papaioannou, T. G., et al. (2005). Intima–media thickness score from carotid and femoral arteries predicts the extent of coronary artery disease. The international journal of cardiovascular imaging, 21(5), 495-501.

Malakar, A. K., Choudhury, D., Halder, B., et al. (2019). A review on coronary artery disease, its risk factors, and therapeutics. Journal of Cellular Physiology, 234(10), 16812-16823.

Metwally, M., Abdelfattah, E., Mousa, M., et al. (2020). Increased carotid intima-media thickness as a predictor for abnormal myocardial perfusion by dobutamine stress echocardiography in patients with diabetes mellitus type 2. Fayoum University Medical Journal, 6(1), 1-17.

Molinari F, Zeng G, Suri JS, (2010). A state of the art review on intima-me¬dia thickness (IMT) measurement and wall segmentation techniques for carotid ultrasound. Comput Methods Programs Biomed , 100(3):201-21.

Mozaffarian, D., Benjamin, E. J., Go, A. S., et al. (2015). Heart disease and stroke statistics—2015 update: a report from the American Heart Association. Circulation, 131(4), e29-e322.

Murray CJ, Ezzati M, Flaxman AD, et al.(2012). GBD 2010: design, definitions, and metrics. Lancet , 380(9859):2063-6.

Robinson J, Gidding S ,(2014). Curing Atherosclerosis Should Be the Next Major Cardiovascular Prevention Goal. J Ame Coll Cardiol , 63(25):2779-85.

Rusnak, J., Fastner, C., Behnes, M., et al. (2017). Biomarkers in stable coronary artery disease. Current pharmaceutical biotechnology, 18(6), 456-471.

Spence JD,Hegele RA,(2004). Noninvasive phenotypes of atherosclerosis: similar windows but different views. Stroke 35(3):649-53.

Suh, S. Y., Han, S. W., Kim, S. H., et al. (2010). Carotid intima-media thickness and plaque as a predictor for ischemic etiology in patients with severe left ventricular systolic dysfunction. Korean circulation journal, 40(12), 665-670.

Tierney ES, Gauvreau K, Jaff MR, et al.(2015). Carotid artery intima-media thickness measurements in the youth: reproducibility and technical considerations. J AmeSociEchocardio , 28(3):309-16.

TouboulP,(2017). Intima-Media Thickness and Plaque Evaluation: Predictive Value of Cardiovascular Events and Contribution to Cardiovascular Risk Evaluation. Noninvasive Vascular Diagnosis ,171-5.

Touboul PJ, Hennerici MG, Meairs S, et al.(2011). Mannheim carotid intima-media thickness and plaque consensus. An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. Cerebrovasc Dis 2012; 34(4):290-6.

Von Reutern GM, Goertler MW, Bornstein NM, et al.(2012). Grading carotid stenosis using ultrasonic methods. Stroke ,43(3):916-21.

Yoon, H. J., Kim, K. H., Park, H., et al. (2017). Carotid plaque rather than intima-media thickness as a predictor of recurrent vascular events in patients with acute ischemic stroke. Cardiovascular Ultrasound, 15(1), 1-8