Evaluation of Endothelial Dysfunction in Patients with Isolated Coronary Artery Ectasia by Ultrasonographic Brachial Artery Flow Mediated Dilation

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ABSTRACT

BACKGROUND

Evaluation of endothelial function in isolated coronary artery ectasia (ICAE) with flow-mediated dilation (FMD) is limited and use of flow mediated vasodilation as a surrogate marker for the extent of coronary atherosclerosis remains unknown. Thus, the following study was done to evaluate for endothelial dysfunction (ED) in subjects with ICAE by assessing the FMD in the brachial artery.

METHODS

This was an observational study, conducted at a referral hospital providing tertiary care in India between June 2017 and November 2018. Fifty patients with ICAE and fifty control patients with normal coronary arteries (NCA) on coronary angiogram, done by using a standard Seldinger technique via femoral route, were the subjects of the study. Brachial artery FMD was determined by using a high-resolution ultrasound system (Samsung RS80A) using a linear transducer of a frequency of 7.5 Mega Hertz.

RESULTS

The groups had same baseline characteristics in terms of age, sex etc. (all P values > 0.05). However, values of serum uric acid and low-density lipoproteins were statistically significantly higher in ICAE subjects (P < 0.0001). Whereas, dilatation of brachial artery in response to shear stress was significantly lower in patients with ICAE subjects than in patients with normal coronaries. (8.85 ± 0.49 vs. 12.83 ± 0.45, P < 0.0001). Marki's classification, type 1, type 2, type 3 and type 4 coronary artery ectasia (CAE) was present in 8 (16 %), 4 (8 %), 13 (26 %), and 25 (50 %), respectively.

CONCLUSIONS

Atherosclerosis may play a pivotal role in the genesis of ICAE. Hyperlipidaemia may have a specific role in the disease process. Further research is required to evaluate the exact molecular mechanisms involved in CAE.

KEYWORDS

Coronary Artery Disease, Ectasia, Endothelial Dysfunction, Hyperlipidaemia

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DOI: 10.18410/jebmh/2021/47

How to Cite This Article:
Imamuddin S, Arunavalli CV, Reddy PKM, et al. Evaluation of endothelial dysfunction in patients with isolated coronary artery ectasia by ultrasonographic brachial artery flow mediated dilation. J Evid Based Med Healthc 2021;8(05):246-250. DOI: 10.18410/jebmh/2021/47

Submission 12-10-2020,
Peer Review 20-10-2020,
Acceptance 12-12-2020,
Published 01-02-2021.

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BACKGROUND

Ectasia of the coronary vessels is a localised dilation of one or more of the epicardial coronary arteries, the size being more than 1.5 times that of the adjacent normal segment diameter.[1,2] Isolated coronary artery ectasia (ICAE) occurs without other significant cardiac disorders.[2,3] Prevalence of ICAE is approximately 0.12 – 1.3 % in diagnostic cardiac catheterisations,[4,5] with an incidence of 0.1 – 0.79 %.[6] 50 % of CAE cases are associated with atherosclerotic stenotic coronary artery disease. Congenital anomalies can cause coronary ectasia in 20 to 30 % cases.[7] Atherosclerosis is now considered as inflammatory disease of the vascular endothelium and is responsible for the disease spectrum of coronary artery disease. Processes such as atheroma formation, rupture of the plaque and vessel wall spasm.[5] Obstructive coronary heart disease is coexistent in more than 50 % of cases of ICAE.[4,8] As the two pathologies are seen together frequently, it is surmised that ICAE may also be a different manifestation of atherosclerosis which causes vessel wall remodelling.[9]

Endothelial dysfunction is an early feature of atherosclerosis, and probably occurs before there is evidence of plaque on ultrasonography or coronary angiogram.[10] Previous studies have shown ED in patients with ICAE.[5,11] Several techniques can be used to assess ED but flow-mediated dilation secondary to shear stress of the brachial artery is a non-invasive and well standardized method.[12] Impaired brachial FMD correlates significantly with invasive testing for coronary endothelial dysfunction, and with the magnitude of coronary atherosclerosis.[13] However, estimation of the ED in ICAE with FMD is limited. Thus, this research was conducted to evaluate for endothelial dysfunction in patients with isolated coronary ectasia by using FMD in the brachial artery.

METHODS

This is an observational study conducted at Osmania General Hospital, Hyderabad, India, between June 2017 and November 2018.

The study population selection was prospective. Coronary angiography was done for one hundred subjects, in our catheterization laboratory.

Patients presented with typical angina pain and either a normal ECG or nonspecific T wave changes at presentation. All of them had a negative troponin T test (unstable angina) and had a positive tread mill test (TMT). Out of the total, 50 patients had ICAE (study group) while 50 patients with normal coronary arteries on angiogram were the control group.

Inclusion Criteria

1. Study group: 50 patients with isolated coronary artery ectasia (ICAE) above 18 yrs. of age.
2. Control group: 50 patients with normal epicardial coronary arteries (NCA).

Exclusion Criteria

1. Current or previous non-ST elevation myocardial infarction.
2. Current or previous ST elevation myocardial infarction.
3. Coronary artery narrowing of more than 50 % in either the ectasia or non- ectasia arteries.
4. Systolic or diastolic heart failure.
5. Pericardial inflammation or infection.
6. Congenital diseases of the heart.
7. Valvular diseases of the heart.
8. Chronic bronchitis or emphysema.
9. Permanent pacemaker in situ.
10. Atrial arrhythmias.
11. Conduction disturbances.
12. Patients taking medication that can affect vessel wall function.
13. Peripheral arterial disturbances or diseases.
14. Alcoholism.
15. Renal, hepatic and / or thyroid disease.

Coronary Angiography (CAG)

CAG was done in Siemens Axiom Artis Cathlab, via rt or lt femoral arterial route, using a standard Seldinger technique. Two right sided angiographic views and two left sided views were taken for each coronary artery.

Definitions

ICAE was considered to be present when there was dilation of at least one epicardial coronary artery 1.5 times the adjacent normal vessel diameter and when there was less than 50 % stenosis in any of the coronary arteries. Normal coronary arteries were defined as when there was no stenosis on angiographic views.

Flow-Mediated Dilation

Brachial artery FMD was determined by using a Samsung RS80A HR ultrasound machine with a linear transducer of a frequency of 7.5 Mega Hertz. The testing was performed at a controlled room temperature of 25° C. All the patients were in fasting overnight for 10 to 12 hours before the imaging. The patients were resting for at least 10 minutes before the first imaging. A pneumatic cuff was tied around the forearm and inflated at more than 50 mm Hg for 5 minutes. The second imaging study was recorded 30 seconds after and 90 seconds after cuff deflation. The FMD was obtained through subtracting baseline brachial artery diameter from the brachial artery diameter at 90 seconds after hyperaemia. The FMD % was obtained by FMD divided by the baseline brachial artery diameter and multiplied by 100.

Statistical Analysis

Continuous variables were shown as mean ± standard deviation. Categorical variables were presented in the form of frequencies and percentages. Continuous variables comparison was compared by using the Student's t-test. A

P-value of < 0.05 was taken as significant. The software used was "Statistical Package for Social Sciences (SPSS) software (SPSS Inc.; 17.0 version, Chicago, Illinois, USA)".

RESULTS

Demographic and Clinical Characteristics

Among the 100 patients, 50 patients with ICAE had a mean age of 46.82 ± 4.27 and 50 patients with NCA had a mean age of 47.72 ± 3.81. The baseline characteristics were similar in both ICAE and NCA groups (all P > 0.05). The risk factor profiles and most of the biochemical profiles were similar in the two groups. In biochemical workup, serum levels of uric acid and low-density lipoprotein (LDL) cholesterol were higher in patients with ICAE (P < 0.0001). The baseline brachial artery lumen diameters were statistically similar between patients with ICAE and in patients with normal coronaries. (4.29 ± 0.21 vs. 4.26 ± 0.19, p = 0.20). But, the brachial artery FMD was statistically significantly lower in subjects with ICAE in comparison to those with NCA (8.85 ± 0.49 vs. 12.83 ± 0.45, P < 0.0001). Table 1 shows the baseline characteristics of both ICAE and NCA groups.

Angiographic Characteristics

Table 2 given below shows the CAG features of the study subjects. The rt coronary artery (RCA) showed ICAE most frequently, (51.6 %), followed by left anterior descending artery (LAD) (28.5 %), followed by left circumflex artery (LCX) (19.7 %). Majority of the population showed single vessel ectasia (58 %), followed by double vessel ectasia (22 %) and triple vessel ectasia (20 %), respectively. According to the Marki's classification of coronary ectasia, type 1, type 2, type 3 and type 4 CAE was present in 8 (16 %), 4 (8 %), 13 (26 %), and 25 (50 %), respectively.

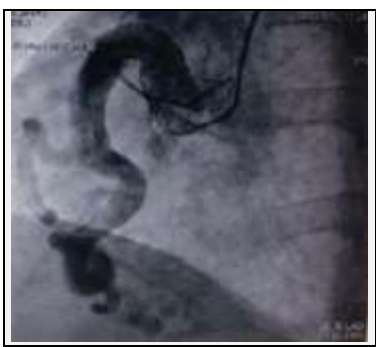

Figure 1. Diffuse Ectasia of RCA

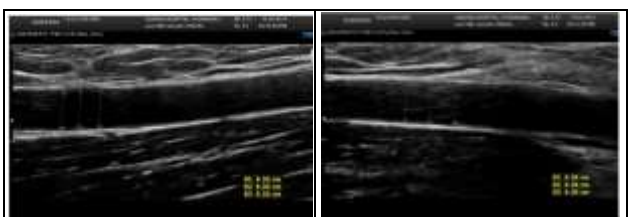

Figure 2. Ultrasonic Image of Rt. Brachial Artery at Baseline and One Minute after a Hyperaemic Stimulus

Characteristics	ICAE (N = 50)	NCA (N = 50)	P Value
Age, mean ± SD, in years	46.82 ± 4.27	47.72 ± 3.81	0.13
Male, n (%)	31 (62 %)	22 (44 %)	0.83
BMI (mean ± SD, kg / m2)	28.38 ± 2.45	29.08 ± 2.35	0.07
Heat rate (mean ± SD, per minute)	75.88 ± 6.02	74.86 ± 4.58	0.17
Clinical presentation			
Chronic stable angina, n (%)	38 (76 %)	42 (84 %)	0.31
Unstable angina, n (%)	12 (24 %)	8 (16 %)	
Risk factors			
Smoking, n (%)	15 (30 %)	10 (20 %)	0.24
Hypertension, n (%)	16 (32 %)	13 (26 %)	0.50
Diabetes mellitus, n (%)	5 (10 %)	4 (8 %)	0.72
Blood pressure (BP)			
Systolic BP (mean ± SD, mmHg)	118.54 ± 5.96	118.84 ± 6.83	0.40
Diastolic BP (mean ± SD, mmHg)	83.2 ± 6.23	82.98 ± 5.22	0.42
Fasting plasma glucose (mean ± SD, mg / dl)	97.1 ± 16.6	94.5 ± 16.61	0.18
Serum creatinine (mean ± SD, mg / dl)	0.95 ± 0.08	0.97 ± 0.07	0.15
Serum uric acid (mean ± SD, mg / dl)	6.66 ± 0.25	4.9 ± 0.13	< 0.0001*
Lipoproteins			
Total cholesterol (mean ± SD, mg / dl)	196.58 ± 15.76	192.3 ± 19.51	0.11
LDL cholesterol (mean ± SD, mg / dl)	119.9 ± 16.63	98.58 ± 17.09	< 0.0001*
HDL cholesterol (mean ± SD, mg / dl)	42.32 ± 4.93	42.08 ± 5.51	0.40
Serum triglycerides (mean ± SD, mg / dl)	176.36 ± 55.64	168.88 ± 47.74	0.23

Table 1. Baseline Demography and Clinical Characteristics of the Study Population

Data are shown as number (percentage) or mean ± SD.
Continuous variables are shown as mean value ± SD.
Categorical variables are presented as percentages.
Comparison of continuous variables was performed using Student's t-test.
If the P-value was less than 0.05 it was considered significant.

Characteristics	ICAE	NCA	P-Value
Brachial artery lumen diameter at baseline (mean ± SD, mm)	4.29 ± 0.21	4.26 ± 0.19	0.20
Brachial artery FMD (mean ± SD, %)	8.85 ± 0.49	12.83 ± 0.45	< 0.0001*

Table 2. Brachial Artery Measurements at Baseline and on Flow Mediated Dilation

Characteristics	ICAE (N = 50)
Located coronary artery (N = 81 vessels)	
LAD, n (%)	23 (28.4 %)
LCX, n (%)	16 (19.8 %)
RCA, n (%)	42 (51.8 %)
No. of vessels involved	
Single vessel ectasia, n (%)	29 (58 %)
Double vessel ectasia, n (%)	11 (22 %)
Triple vessel ectasia, n (%)	10 (20 %)
Marki's classification of ectasia	
Type 1, n (%)	8 (16 %)
Type 2, n (%)	4 (8 %)
Type 3, n (%)	13 (26 %)
Type 4, n (%)	25 (50 %)

Table 3. Angiographic Characteristics of the Subjects

DISCUSSION

Endothelial dysfunction occurs early in atherosclerotic vascular disease and may actually facilitate the disease process.[14-16] Flow-mediated dilatation of the brachial artery is a safe, reproducible and non-invasive method of evaluation of endothelial function.

The main findings of this study showed that impairment of endothelial function is indicated by lower endothelium-dependent vasodilation in patients with ICAE compared to the patients with NCA. In biochemical workup, patients with ICAE have significantly higher serum uric acid and LDL cholesterol levels than the patients with normal coronaries.

The CAE may be a variant of CAD as it resembles atherosclerosis in many ways. Both disease processes have similar risk factor profile and similar histopathological features.[14,15] Besides, patients with CAE commonly have comorbid CAD.[16] All the pathogenesis of CAE is still unclear.[17]

"The demographic characteristics such as age, gender, clinical presentation, blood pressure, and lipoproteins were similar to a study conducted by Dursun et al."[4] Coronary atherosclerotic risk factors such as hyperlipidaemia have been shown to play an important role in ICAE. In this study, higher LDL cholesterol values and to a lower extent higher cholesterol values were present in patients with ICAE. Similarly, "a study conducted by Sudhir et al.[18] showed increased prevalence of CAE in patients with familial hypercholesterolemia." Moreover, it has been assumed that structural fragility of the connective tissue in the intimal layer of the arterial wall with ectasia may be as a result of an interaction of LDL with collagen and elastin present in the vessel wall, leading to increased endocytosis by macrophages and smooth muscle cells.[19] Thus, coronary ectasia may be vascular remodelling secondary to early atherosclerosis. Still, it is not clear why CAE develops only in some patients.[20]

Xanthine oxidase activity is an inflammatory response mediator and can cause cellular damage and its activation may activate matrix metalloproteinases-3 which in turn may increase proteolysis of extra cellular matrix and may thus contribute to vascular remodelling and CAE occurrence. Increased uric acid is a marker for this process.[21] Thus in the current study, serum uric acid levels were higher (statistically significant) in patients with ICAE when compared with subjects with normal coronary anatomy. A study by Nihat et al.[22] revealed similar findings.

The FMD evaluates the endothelial nitric oxide release in response to shear stress, causing vasodilation. It is a non-invasive, safe and reproducible test.[4,23] The brachial arterial endothelial function correlates highly with that of coronary vessels as well as with the of CAD severity on CAG.[24,25] In this particular study, patients with ICAE had lower values of FMD indicative of endothelial dysfunction, indicating a causal role of the atherosclerotic process in the formation of ICAE. "A study by Aksoy et al.[11] of patients with both CAE and CAD, revealed that FMD of patients with CAE and CAD was similar to FMD in the patients with CAD alone suggesting that the disease process in the intimal layer was similar". But they proposed that endothelial function was normal in ICAE and refuted the causal role of atherosclerosis in ectasia. Hence, studies that enable us to clarify this pathogenesis and explain the exact mechanisms that cause CAE are needed.

Study Limitations

The first limitation of this study was that only a small sample of patients was studied. Lack of identification of inflammatory markers was the second limitation. Only the intimal layer is evaluated by FMD but medial layer function contribution to impaired dilation cannot be assessed by this method.

CONCLUSIONS

Our findings suggest that ICAE may be caused by vascular inflammatory process and is associated with impaired endothelial function as shown by decreased FMD and may be due to atherosclerotic involvement. Hyperlipidaemia may have a specific role in the ICAE development process. Further research is needed to unveil the exact pathogenesis of ICAE. In addition, clinical investigations are required for understanding the pro- and anti-inflammatory mediators participating in ICAE.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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