ORIGINAL ARTICLE

Evaluation of Endothelial Dysfunction in Idiopathic Dilated Cardiomyopathy Patients

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Abstract

Background: Endothelial dysfunction has early been characterized in ischemic cardiomyopathy patients. The study was aimed to study evaluation of endothelial dysfunction in idiopathic cardiomyopathy patients (DCM).

Methods: Thirty newly diagnosed patients (age >18 years) of DCM were enrolled in the study from cardiology OPD, PGIMER, Chandigarh from January 2011 to June 2012. Age-and sex-matched 30 healthy controls were also enrolled. Idiopathic DCM was diagnosed by presence of left ventricular dilatation and systolic dysfunction (LVEF<40%) on echocardiography in the absence of coronary artery disease, hypertension or valvular disease. All patients underwent echocardiography and coronary arteriography. Flow mediated dilation (FMD) and carotid intima media thickness (IMT) were compared between patients and controls.

Results: There was no significant difference in mean IMT between patients (0.73±0.04 mm) and controls (0.747±0.03 mm) (P=0.18). There was significant difference in left IMT in NHYA class (P=0.010). There was significant difference in mean percentage of FMD (patients vs. controls; 4.37% vs. 8.35%; P=0.001) while baseline FMD was different (patients vs. controls; 3.6 mm±0.26 mm vs. 3.72±0.32 mm; P=0.13). There was no significant difference in percentage NMD (P=0.057) and mean NMD (P=0.26) between patients and controls. There was no correlation between FMD and IMT.

Conclusion: Endothelial dysfunction occurs in IDC patients. Also, there is a positive correlation with NHYA class; however, IMT is not affected in dilated cardiomyopathy.

Introduction

An insult to vascular endothelium is likely a preliminary event in most vascular diseases. Endothelial dysfunction has been found to be implicated in a number range of diseases from diabetes mellitus and essential hypertension, to vasospastic conditions such as systemic sclerosis and primary Reynaud's phenomenon.[1] Furthermore, it has been postulated that endothelial dysfunction is a precursor to atherosclerosis; indeed, it has been identified *in vivo* in healthy individuals exposed to various cardiovascular risk factors like cigarette smoking, obesity, increasing age etc. Cardiovascular disease (CVD) is currently a leading cause of morbidity and mortality in the Western world, a fact which has provided a drive for the development of methods, facilitating *in vivo* evaluation of endothelial function.[1]

Arterial physiology has recently been studied using a non-invasive ultrasound technique, brachial artery flow-mediated dilatation (FMD).[2] Nitric oxide released from arterial endothelial cells mediates the dilatation response with increased blood flow. Brachial FMD response is also found to be correlated with coronary endothelial function as tested by invasive methods.

Endothelial dysfunction results in the inability of a vessel to dilate in response to endothelium-derived relaxing factors after physiological stimuli, like increases in blood flow (an early characteristics of coronary atherosclerosis).[3] Major risk factors for atherosclerotic vascular disease (e.g., hypertension, diabetes, smoking, hypercholesterolemia and obesity) have been associated with endothelial cell dysfunction.[4-6] Carotid intima-media thickness (IMT) is considered as a marker of early atherosclerosis, it predicts future risk of cardiovascular disease, and it has been found to be high in individuals with coronary heart disease and myocardial infarction. Whether it is related to cardiomyopathy, this needs evaluation.[7]

Several studies have used the measurement of IMT at the common carotid artery, obtained by non-invasive high-resolution B-mode ultrasonography.[8] An increased IMT of the carotid artery wall is considered to be an early atherosclerosis index; evidences suggest an association between extra cranial carotid artery disease and incidence of coronary heart disease. As endothelial dysfunction and increased IMT are interrelated, indicative of different aspects of the atherosclerotic process, their early detection could have strong implications for cardiovascular prevention. Some studies have already related endothelial dysfunction and IMT in patients with atherosclerosis or coronary artery disease, but few data are available in cardiomyopathy patients. The purpose of present study was to study endothelial dysfunction in by FMD and assessment of correlation between endothelial dysfunction and carotid intima media thickness in idiopathic cardiomyopathy (DCM) patients.

Subjects and Methods

Thirty newly diagnosed patients (age >18 years) with idiopathic DCM were enrolled in the study from Department of cardiology, Post Graduate Institute

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Received: 23.12.2016; Accepted: 31.10.2017

of Medical Education and Research, Chandigarh from January 2011 to June 2012. Age-and sex-matched 30 healthy controls (family members of the patients) were also enrolled. The study was conducted following approval from Institutional Ethics Committee (IEC). All the subjects were included in the study after their consent.

Idiopathic DCM was diagnosed by presence of left ventricular dilatation and systolic dysfunction (LVEF<40%) on echocardiography in the absence of coronary artery disease, hypertension or valvular disease. Subjects with coronary artery disease, diabetes mellitus, cancer, hypercholesterolemia, concomitant infection, on sildenafil treatment, pregnancy, peripheral vascular disease, renal failure or autoimmune disease, rheumatic heart disease, hypertrophic cardiomyopathy, hypertensive heart disease, congenital heart disease, evidence of restrictive or constructive physiology, smoking, and alcohol intake >60 g/day were excluded from study. None of the subjects had family history of ischemic heart disease, history of smoking etc.

Echocardiography

Echocardiography was performed for all the subjects and ejection fraction was calculated using modified Simpsons method in apical 4 chamber view. Patients with ejection fraction less than 40% were enrolled in study. Normal value for EF was taken as 55-70%, end diastolic volume as 65-240 ml, end systolic volume as 16-143 ml.[9]

Coronary Arteriography

The patients enrolled for the study underwent coronary arteriography during the course of hospitalization. Selective coronary arteriography of left and right coronary arteries was performed and multiple cineangiographic views were selected to delineate coronary artery anatomy. Patients with normal coronaries were included in the study.

Brachial Artery Flow-Mediated Dilatation Measurement

FMD was measured for all the patients using a non-invasive method (ultrasound system), fitted with a high frequency vascular transducer operated at 10 MHz. All vasodilator drugs were withheld for at least 4 times their half-life period before the vascular studies. The measurement was conducted after overnight fasting with patients in supine position at a room temperature of 22 to 25ºC after resting for 30 minutes. Transducer was placed approximately 5 cm proximal to elbow joint at a fixed point for imaging brachial artery in the longitudinal plane. A segment with clear anterior and posterior intimal interfaces was selected for continuous 2-D gray scale imaging. Diameter measurement was selected from one intimal surface to the other, measured at end diastole taking beginning of R wave on ECG interface. Brachial artery flow was measured from the midpoint of the lumen using pulse Doppler. After taking baseline measurements, blood pressure cuff tied at forearm was inflated to about 50 mmHg above systolic blood pressure. After 5 minutes of cuff inflation, the cuff was deflated rapidly. For diameter measurements, readings were taken every 15 second from 15 to 120 seconds after cuff deflation and the greatest diameter was considered.

Nitroglycerin-mediated Dilation (NMD)

After a 10-minute rest, 25 mg GTN (glyceryl trinitrate) was given sublingually and, after waiting for 3 minutes to achieve plateau response to the drug, brachial artery images were recorded for 1 minute. Both FMD and GTN responses were expressed as percentage change, calculated as follows:

$$\frac{\text{Maximum brachial diameter - baseline brachial diameter} \times 100\%}{\text{Baseline brachial diameter}}$$

Statistical Analysis

The data were presented as mean ± SD or median as appropriate. Student t-test was used for normally distributed data. Pearson $\chi 2$ test or Fisher's exact test was used for analysis of categorical variables with two categories. A P value of <0.05 was considered to indicate statistical significance. Correlation was presented as coefficient. A P value of <0.05 was considered as statistical significance. All calculations were performed using SPSS version 15 (Statistical Packages for the Social Sciences, Chicago, IL).

Results

The subjects' characteristics have been summarized in Table 1. 50% patients were in New York Heart Association (NHYA) class I followed by 46.6% patients in class II. There was no patient in NHYA class IV.

Carotid Intima Media Thickness (IMT)

Our study found that there was no significant difference (P=0.18) in mean IMT between the patients (0.73±0.04 mm) and the controls (0.747±0.03 mm) (Table 2). Amongst patients, mean IMT in right side was 0.74±0.04 mm (range 0.67-0.82 mm) and on left side was 0.72±0.04 mm (range 0.7-0.8 mm). Amongst controls, mean IMT in right side was 0.75±0.03 mm (range 0.7-0.8 mm) and on left side was 0.74±0.03 mm (range 0.7-0.8 mm). There was no sex-based significant difference between in mean IMT (0.72±0.032 vs. 0.70±0.171 female vs. male; P=0.551) in the DCM patients group. There was significant difference in left IMT in NHYA class (P=0.010).

Brachial Artery Flow Mediated Dilatation and Nitroglycerin-mediated Dilatation

There was significant difference in mean percentage of FMD (patients vs. controls; 4.37% vs. 8.35%; P=0.001) while baseline FMD was different (patients vs. controls; 3.6 mm±0.26 mm vs. 3.72±0.32 mm; P=0.13). There was no significant difference in percentage NMD (P=0.057) and mean NMD (P=0.26) between patients and controls (Table 3).

Relationship of FMD and IMT

There was negative correlation between baseline FMD and NYHA class with correlation coefficient of -0.259 (P=0.167) and no correlation FMD and IMT (P=0.185).

Discussion

This study was conducted to know about endothelial dysfunction in idiopathic DCM patients. The study showed that mean age was similar in both the groups. Patient group had 20 males (66.7%) and 10 (33.3%) females whereas control group had 16 (53.3%) males and 14 (46.7%) females.

Most of the patients were in NYHA class I (50%) and class II (46.7%) and only 1 (3.3%) was in class III and none in class IV. Our study found no significant difference in mean IMT between patients and controls. Badran et al have shown significantly increased carotid diameter and IMT were in ischemic cardiomyopathy in comparison to non ischemic DCM and control (P < 0.001).[10] Shah et al[9] measured common IMT and showed no difference in IMT between controls and patients with DCM, however, increased in IHD patients;

Table 1: Subjects' characteristics

	DCM (n=30)	Control (n=30)	P value
Mean age (± SD)	48.37±10.82	49.2±9.27	0.75
M:F	20:10	16:14	0.29
BMI (kg/m^2)	21.36±1.46	21.39±1.48	0.94
Mean PR (b/m)	74.3±3.98	75.2±4.3	0.4
Mean SBP (mmHg)	125.7±8.27	127.57±7.52	0.36
Mean DBP (mmHg)	75.83±4.19	76.13±3.71	0.77

Table 2: Carotid IMT in patients and controls

Category	Patients Mean ± SD (Range)	Controls Mean ± SD (Range)	P value
Right CIMT	0.74±0.04 (0.67-0.82)	0.75±0.03(0.7-0.8)	0.18
Left CIMT	0.72±0.04(0.7-0.8)	0.74±0.03(0.7-0.8)	0.04
Mean CIMT	0.73±0.04(0.68-0.83)	0.74±0.03(0.69-0.79)	0.08

CIMT: Carotid Intima-Media Thickness

Table 3: FMD and NMD in patients and controls

Category	Patients Mean ± SD (Range)	Controls Mean ± SD (Range)	P value
Baseline FMD	3.6±0.26 (3.19-4.12)	3.72±0.32 (3.22-4.45)	0.13
FMD 15s	3.66±0.25 (3.22-4.2)	3.75±0.33 (3.27-4.47)	0.25
FMD 30s	3.68±0.25 (3.27-4.26)	3.79±0.32 (3.31-4.5)	0.15
FMD 45s	3.72±0.25 (3.3-4.3)	3.85±0.32 (3.4-4.6)	0.081
FMD 60s	3.76±0.26 (3.3-4.3)	4.03±0.33 (3.5-4.8)	0.001
FMD 90s	3.75±0.26 (3.34-4.28)	3.97±0.33 (3.49-4.71)	0.006
FMD 120s	3.73±0.26 (3.3-4.3)	3.91±0.32 (3.4-4.6)	0.024
%age increase	4.37	8.35	0.001
NMD	4.15±0.3 (3.62-4.69)	4.24±0.33 (3.74-4.99)	0.26
%age increase	15.2	14.18	0.057

FMD: Flow-Mediated Dilation; NMD: Nitroglycerin-Mediated Dilation

because IMT is an early and sensitive marker of atherosclerosis, unlike coronary angiography, which could be unremarkable until a relatively advanced stage of atherosclerosis, these data indicated that our subjects with DCM had no significant excess underlying atherosclerosis. Tamura et al have that mean IMT was significantly higher in ischemic cardiomyopathy compared to DCM (P<0.001).[11]

Our study showed that FMD was impaired amongst DCM patients but NMD was similar in both the groups. Shah et al showed that FMD, but not NMD, was impaired in heart failure patients.[8]This suggested a specific impairment of endothelium-dependent vasodilatation in the brachial artery, without change in endothelium-independent vasodilatation. Importantly, the authors found that the impairment in FMD was seen specifically in patients with underlying ischemic heart disease (IHD), and not in patients with DCM, despite similar heart failure severity. This also suggests that impairment of endothelium-dependent vasodilatation is not a result of heart failure but is attributable to underlying atherosclerotic disease. Meyer et al[12] and Katz et al[13] have previously reported that patients with heart failure exhibit impaired FMD, independent of aetiology (IHD or DCM), and that FMD is an important determinant of outcome. It is possible that the DCM patients had unrecognized coincident atheromatous disease.

Nakamura et al suggested that patients with congestive heart failure nonischemic origin, exhibited a decrease in FMD and NMD of the brachial artery as compared with healthy controls.[14] However, coronary angiography has a restricted ability to detect non-occlusive atherosclerotic disease; and indeed, in this study, the patients exhibited higher IMT values than controls. On the other hand, findings by Shah et al., are consistent with those previously reported by Stolen et al.,[15] who found that patients with DCM had FMD responses similar to those of healthy control subjects, despite a decrease in myocardial perfusion reserve in the former group. In a study by Sigtes et al, FMD was significantly impaired in the DCM group as compared to the control group, while NTG- vasodilatation was not different in the 2 groups. There were no differences between the 2 groups in baseline brachial artery diameter or in reactive hyperemia.[16]

There was weak negative correlation between FMD and NYHA class in our study with correlation coefficient of -0.23 which implies that FMD decreases as NYHA class increases. However, Shah et al suggested that there was no relationship between FMD and NYHA functional class. This may be either no such relationship exists, or because our study was underpowered to detect the presence of such a relationship.[8] Our study did not found any correlation between FMD and IMT. On the other hand, Shah et al found a strong inverse relationship between FMD and common carotid IMT. Collectively, these data suggest that FMD is influenced much more importantly by atherosclerotic load than by heart failure.

Conclusion

Endothelial dysfunction occurs in DCM patients. Also there is a positive correlation with NHYA class; however, IMT is not affected in DCM. There is no correlation of IMT or FMD with NHYA class in our study. Our study has limitations including relatively unable to study any patients in NYHA Class IV which could have provided more information about vascular function in subjects with severe heart failure, unblind study, short follow-up period, and inclusion of only patients with DCM; the results therefore should not be extended to patients with other causes of impaired LVEF, such as hypertension or ischemic heart disease.

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