Journal of Community Medicine, July-Dec, 2009, Vol, .5(2)

SHORT ARTICLE

STUDY OF ENDOTHELIAL DYSFUNCTION IN PATIENTS WITH ANGINAL CHEST PAIN AND NORMAL ANGIOGRAMS

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Introduction

Cardiovascular diseases have emerged as a major health burden worldwide. In India too, the reported prevalence of coronary heart disease (CHD) in adult surveys has risen 4-fold over the last 40 years (to a present level of around 10%), and even in rural areas the prevalence has doubled over the past 30 years (to a present level of around 4%). Cardiovascular disease is now the leading cause of death, accounting for 29% of all deaths in 2005, according to WHO. Coronary angiography is the invasive technique for imaging the coronary artery lumen and remains the most accurate for the diagnosis of clinically important obstructive coronary atherosclerosis. Many patients undergo coronary angiography each year for investigation of chest pain believed to be due to coronary artery disease. However, 10% to 30% of such patients are found to have normal coronary arteries on angiography [1]. Endothelial dysfunction is an early event in atherogenesis, preceding formation of plaques and hence is an early marker of atherosclerosis before angiographically demonstrable changes occur in the epicardial coronary arteries. Endothelial dysfunction is the earliest measurable functional abnormality of the vessel wall and is closely related to the risk factors of atherosclerosis[2].

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Endothelial dysfunction and hence the progression of atherosclerosis is reversible at this early stage by modification of risk factors by life style changes and pharmacotherapy. Hence, considerable interest has generated globally in the normal endothelial cell function and in its dysfunction. Because of the central role of the endothelium throughout the atherosclerotic disease process, a range of methods, both invasive and non-invasive have been developed to test different aspects of its function, which include measures of both endothelial injury and repair. Intracoronary studies using acetylcholine, an endothelium dependent vasodilator have served as the gold standard for endothelial function testing. The non-invasive methods to assess endothelial dysfunction include brachial artery flow mediated vasodilatation and measurement of brachial ankle pulse wave velocity (baPWV).

The present study aimed at studying endothelial cell dysfunction in patients with chest pain and normal angiograms using brachial ankle pulse wave velocity, a noninvasive surrogate index for clinical evaluation of endothelial dysfunction.

Methods

The patients presenting with anginal chest pain to the U. N. Mehta Institute of Cardiology and Research Center, Ahmedabad, a tertiary referral centre and University Hospital ,and having normal coronary angiograms were included in the study. Patients having peripheral arterial disease were excluded from the study. Brachial Ankle Pulse wave velocity was measured by the Vascular Profiler 1000 (VP-1000) waveform analysis and vascular evaluation system, an automated, non-invasive, screening device for early detection and quantification of atherosclerosis (Colin Corporation, Japan; marketed by Wipro GE Medical Systems Pvt Ltd).

Increased brachial ankle pulse wave velocity (baPWV), is associated with impaired endothelial function and is used as a noninvasive surrogate index for clinical evaluation of

endothelial dysfunction[3]. Brachial-ankle pulse wave velocity is a non-invasive and simple method of measuring arterial stiffness and an independent predictor of cardiovascular mortality in some lifestyle-related diseases. The validity and reproducibility of baPWV measurements are considerably high, and this method seems to be an acceptable marker reflecting vascular damages.

Jadhav and Kadam found statistically significant correlation between brachial ankle pulse wave velocity and flow mediated dilation in the brachial artery[4]. LIU Dong-hong et al found that brachial ankle pulse wave velocity is increased and flow mediated vasodilation is impaired in coronary artery disease patients, and that there is a close association between brachial ankle pulse wave velocity and flow mediated vasodilation ,suggesting that brachial ankle pulse wave velocity can be used clinically in noninvasive evaluation of endothelial function[3].Yamashina et al evaluated the applicability of baPWV for screening cardiovascular risk as well as for use as a marker of the severity of atherosclerotic vascular damage and screened 10,828 subjects. The Framingham risk score and Pocock's score were obtained. Multivariate analysis demonstrated that baPWV was associated with both scores independently from conventional atherosclerotic risk factors. Logistic regression analysis demonstrated that a baPWV>1400cm/s is an independent variable for the risk stratification by Framingham score and for the discrimination of patients with atherosclerotic cardiovascular disease[5].

The VP-1000 Vascular Profiler recorded electrocardiogram (ECG), phonocardiogram (PCG) and pulse volume recording (PVR) simultaneously and calculated time delay of the pulse to obtain pulse-wave transmit time (PTT). Distance of each segment was automatically calculated based on the patient's height by the Vascular Profiler and was derived from statistical studies. . The subject was examined in the supine position, with electrocardiogram electrodes

placed on both wrists, a microphone for detecting heart sounds placed on the left edge of the sternum, and cuffs wrapped on both the brachia and ankles. The cuffs were connected to a plethymographic sensor that determines volume pulse form and an oscillometric pressure sensor that measures blood pressure. The pulse volume waveforms were recorded using a semiconductor pressure sensor (the sample acquisition frequency for PWV was set at 1,200 Hz). Volume waveforms for the brachium and ankle were stored, and the sampling time was 10 s with automatic gain analysis and quality adjustment.

Observation

A total of 100 patients with chest pain and having normal coronary angiograms were examined. The baseline characteristics are shown in Table **I.**.

Table I. Baseline characteristics

Age (mean) (years)	50.66 ± 9.3
Gender	
Male	58
Female	42
Hypertension	30 (30)
Diabetes	17 (17)

*Values in parenthesis are percentages

In these patients the brachial ankle pulse wave velocity (baPWV) was studied and the distribution of patients according to their baPWV is shown in Table . **II**

Table II. Distribution of baPWV

Total No. of patients	baPWV<1400 cm/s	Percentage (%)	baPWV>1400 cm/s	Percentage (%)
100	24	24	76	76

baPWV was elevated(>1400 cm/s) in 76 of the 100 patients. Table 2 shows that abnormal baPWV predominated over normal baPWV in the ratio of 76:24 i.e. about 3.2 times. This shows that there is a high prevalence of endothelial dysfunction in patients with anginal chest pain having normal coronary angiograms.

Hypertension was present in 26 of the 76 (34 %) patients having an elevated brachial ankle pulse wave velocity while it was present in only 4 of the 24 (16.6 %) patients having brachial ankle pulse wave velocity less than 1400 cm/s. 14 of the 76 (18.4 %) patients with elevated brachial ankle pulse wave velocity had diabetes mellitus while only 3 of the 24 (12.5 %) patients with brachial ankle pulse wave velocity less than 1400m/s were diabetic. This is in correlation with the causative role of hypertension and diabetes mellitus in endothelial dysfunction.

Discussion

Normal endothelial function plays a central role in vascular homeostasis, including inhibition of thrombus formation, inhibition of leukocyte adhesion, oxidative modification of LDL, and regulation of vascular smooth muscle proliferation. An impaired ability of the endothelium to release vasoactive substances may facilitate inflammation, platelet aggregation, and coronary vasoconstriction. Recent observations indicate that endothelial dysfunction may be able to predict future cardiovascular events even in patients with mild CAD. Interestingly, endothelial dysfunction may also predict cardiovascular events in patients with angiographically normal coronary arteries. All of these studies clearly suggest that endothelial vasodilator dysfunction implicates proatherosclerotic and prothrombotic effects that may provide a link between dysfunction itself or the degree of dysfunction and adverse cardiovascular outcome.

The vast majority of patients with anginal chest pain and normal coronary angiograms had endothelial dysfunction. Endothelial dysfunction in a setting of normal coronary arteries is a sign of future development of atherosclerosis. Another area of great interest is the potential use of endothelial function to stratify risk in individual subjects. Traditional and newly recognized risk factors account for only a portion of estimated risk for cardiovascular events such as myocardial infarction or coronary heart disease death. It is likely that genetic factors and other unrecognized environmental factors also play a role. Because the traditional and unknown risk factors target and damage the vascular endothelium, it has been proposed as a potential barometer of atherosclerosis risk, and as such, studying endothelial function may guide risk assessment and therapy for individuals.

Conclusions

Increased brachial ankle pulse wave velocity, is a well established marker of endothelial dysfunction and can be measured non-invasively. In this study it was found that the majority of patients with anginal chest pain had endothelial dysfunction. Such patients are at an increased risk for adverse outcomes in future even though their coronary arteries are normal at present and so should be subjected to regular follow up. Since endothelial dysfunction is an early event in atherogenesis, early identification of patients with endothelial dysfunction can retard the progression of atherosclerosis, by life style changes and modification of risk factors. This method to measure brachial ankle pulse wave velocity does not require any specialized technique, and the examiner has only to wrap cuffs on the brachium and ankle. After these simple preparations, brachial ankle pulse wave velocity is automatically measured. The simplicity of this method makes it suitable for screening large populations.

References

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