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## **Endothelium-Dependent and -Independent Vasodilation in Young Males with Previous Myocardial Infarction**

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## Endothelium-Dependent and -Independent Vasodilation in Young Males with Previous Myocardial Infarction

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Flow-mediated vasodilation – a non-invasively measurable index of endothelial function – is a good predictor of cardiovascular risk. This study was undertaken to analyse the correlation between flow-mediated vasodilation and the severity of coronary artery disease in males less than 40 years of age and with myocardial infarction in their history. Coronary angiography demonstrated single-vessel disease in 16 patients (Group A) and multi-vessel disease in 12 (Group B). The control group comprised 14 healthy young males (Group C). Endothelium-dependent vasodilation produced by reactive hyperaemia, as well as nitroglycerine-induced, endothelium-independent vasodilation was appraised on the brachial artery, using a high-resolution duplex ultrasound device (ACUSON 128XP/10). Variations in vessel size recorded as prescribed by the protocol developed by Celermayer were expressed as percentage change compared to baseline.

Compared to controls, endothelium-dependent vasodilation was attenuated in patients with previous myocardial infarction ( $p < 0.01$ ). The same applies to multi-vessel disease, in comparison to single-vessel disease. There was no difference between controls and postinfarction patients as regards nitroglycerine-induced vasodilation.

Endothelium-dependent vasodilation is diminished in young males with previous myocardial infarction, and the magnitude of this reduction is related to the severity of coronary artery disease. *J Clin Basic Cardiol* 2003; 6: 73–6.

**Key words:** endothelium, prevention

The close relationship between the risk of cardiovascular (CV) disease and the vascular endothelium has been known since the beginning of the 1980s when endothelial structure and function were elucidated [1].

The principle function of the vascular endothelium is to maintain cardiovascular homeostasis. In addition to being an organ in the anatomical sense, the endothelium indeed has functions characteristic of an organ [2]. In particular, it forms a boundary between circulating blood and vascular smooth muscle in the tunica media (barrier function), triggers vascular reactions in response to external stimuli (eg, endothelial injury induces intimal hyperplasia or atherosclerosis – sensory function). It also produces hormones and hormone-like substances acting on the endothelium itself or on adjacent structures (autocrine or paracrine function).

Injury or activation of the endothelium modifies the regulatory functions of cells, and the resulting imbalance impairs endothelial function. According to current knowledge, the vascular endothelium is involved in all steps of the cascade of events culminating in the development of atherosclerosis (Figure 1).

Persistent risk factors and consequent oxidative stress alter the physiological processes of the endothelial system, degrading the balance between vasodilator and vasoconstrictive factors, and thereby damage the endothelium [3]. The ensuing endothelial injury is circumscribed initially; however, it becomes generalized if noxious factors persist. Endothelial dysfunction (ED) is associated with decreased production of nitric oxide (NO) and diminished activity of endothelium-dependent hyperpolarizing factor (EDHF), as well as with the elevation of the levels of angiotensin II, endothelin and other locally acting mediator substances. This disequilibrium leads to clinical consequences that include an increased propensity for thrombosis, inflammation, vasoconstriction, the development of vascular lesions, and the rupture of atherosclerotic plaques [4]. Non-invasive appraisal of endothelial function is feasible with the Celermayer protocol, which

involves measuring flow-mediated changes of the vascular lumen [5]. Under experimental conditions, the quantification of NO-production is the most useful method for the evaluation of endothelial function. In clinical practice, how-

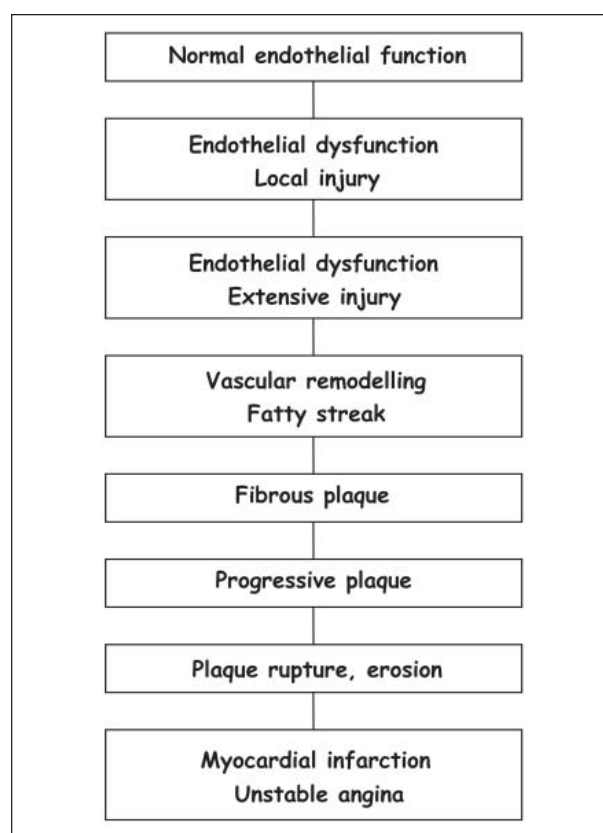


Figure 1. Atherosclerosis and endothelial dysfunction

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ever, indirect appraisal of vasodilation can be performed as a substitute [1].

Endothelium-dependent vasodilation is triggered by the activation of receptors (through the binding of acetylcholine, bradykinin, P-substance etc.) or distension of the vascular wall (ie, shear stress).

Non-invasive testing involves measuring the changes induced by acetylcholine administration – or the fluctuations of blood flow (ie, FMV) – in the diameter of vessels with duplex ultrasound [6]. The brachial or the femoral superficial artery is used instead of the coronaries, and vasodilation is induced by reactive hyperaemia.

FMV is a function of the NO-production of the endothelium – vasodilation is attenuated or absent if NO-production is reduced (eg, in atherosclerosis). In advanced coronary disease, paradox vasoconstriction can occur instead of vasodilation.

As demonstrated by Celermajer et al. [7], FMV is low before the age of 40. In males, ED appears at the end of the fourth – or, in females, the fifth – decade of life. The manifestations of ED are apparent in the whole population older than 65 years of age.

Although myocardial infarction is most prevalent among middle-aged males, it is not uncommon before 40 years of age and even without preceding angina.

## Objectives

This study was performed to answer the following questions:

1. Can ED be demonstrated in myocardial infarction occurring in the young?
2. Is the magnitude of ED related to the extent of coronary artery disease?

## Study Population

The study population comprised male patients aged 40 years or younger who had suffered myocardial infarction during the preceding 3 months. In view of their young age, coronary angiography was performed on all participants – irrespective of the verification of myocardial ischaemia. Diabetic patients were excluded in order to obtain homogeneous study groups.

Twenty-eight male patients with a mean age of  $35.3 \pm 3.7$  years were enrolled. Participants were stratified into one of two groups, according to the angiographically verified extent of coronary artery disease. The control group consisted of males less than 40 years of age, without apparent CV risk factors or any significant disease in their history:

Group A – single-vessel disease:  $n = 16$

Group B – multi-vessel disease:  $n = 12$

Group C – healthy controls:  $n = 14$

The demographic properties of the study population are summarized in Table 1. There were no significant differences between individual parameters of Groups A and B.

**Table 1.** The demographic properties of the study population

	A	B	C
N =	16	12	14
Age (mean)	34	37	30
Vessel disease	1	2–3	–
Hypertension	6	6	0
Cholesterol	6.0 mmol/l	6.4 mmol/l	4.6 mmol/l
HDL cholesterol	1.05 mmol/l	1.02 mmol/l	1.12 mmol/l
LDL cholesterol	3.2 mmol/l	3.56 mmol/l	2.8 mmol/l
Smoking	6	5	0

## Methods

Non-invasive, risk-free testing was done during the morning hours, in an air-conditioned office with constant ambient temperature (22 °C). Patients had rested in recumbent position for at least 10 minutes before the measurement. The consumption of alcoholic beverages, tea and coffee, as well as smoking was prohibited on the day of testing. At least 24 hours must have elapsed since the ingestion of the latest dose of calcium channel blockers,  $\beta$ -adrenergic receptor blockers, long-acting nitrates, or ACE inhibitors.

Ultrasound scanning was performed on the right forearm, using an ACUSON 128XP/10 duplex scanner equipped with a 7.5-MHz linear transducer.

Changes in the diameter of the brachial artery (FMV) were measured approximately 4 centimetres above the cubital fossa. The mean of three readings was recorded.

Baseline values were recorded and then a 5-minute supra-systolic compression was applied with a sphygmomanometer cuff.

Three readings were taken during the 2-minute period following the deflation of the cuff. Endothelium-dependent changes in the diameter of the vessel caused by hyperaemia-related fluctuations in shear stress were recorded. The return of parameters to baseline values was verified by an additional series of measurements performed after 30 minutes of relaxation. Then, 3 readings were taken 90 seconds after the sublingual administration of 0.5 mg nitroglycerine to appraise endothelium-independent vasodilation.

## Statistical Analysis

Percentage changes compared to baseline were analysed by paired t-test.

## Results

1. No significant changes were detected between study groups as regards the diameter of the brachial artery or the velocity of blood flow at baseline.
2. Endothelium-dependent vasodilation:
  - a) FMV was significantly lower in postinfarction patients than in healthy controls ( $4.95 \pm 6.1\%$  vs.  $15.5 \pm 6.8\%$ ;  $p < 0.001$ ).
  - b) As shown by coronary angiography, FMV was significantly lower in multi-vessel, than in single-vessel disease ( $2.1 \pm 4.2\%$  vs.  $7.1 \pm 6.1\%$ ;  $p < 0.001$ ).
3. Endothelium-independent vasodilation:
  - a) The magnitude of nitroglycerine-induced vasodilation was similar in postinfarction patients and in controls; however,
  - b) it was (not significantly) lower in multi-vessel, than in single-vessel disease (Figure 2).
4. In four of the 28 postinfarction patients, hyperaemia induced vasoconstriction, instead of vasodilation. These patients had severe hypercholesterolaemia, and multi-vessel disease evidenced by coronary angiography.

## Discussion

Non-invasive measurement of FMV was first described by Celermajer et al. [7, 8], who demonstrated the attenuation of this phenomenon in (adult and paediatric cases of) familial hypercholesterolaemia, in adult smokers, and in patients with coronary artery disease (CAD). The brachial artery is suitable for the evaluation of endothelial dysfunction, as its status correlates closely with atherosclerotic changes that occur in the coronary and carotid arteries. The brachial artery is

a potential marker of early atherosclerosis both morphologically and functionally. In particular, several studies have shown a close correlation between acetylcholine-induced vasomotor response of coronaries and reactive hyperaemia-induced dilation of the brachial artery [9].

Neunteufl et al. [10] measured FMV in the brachial artery of 74 patients with angina pectoris and of 14 healthy controls, to ascertain potential relationships between the magnitude of endothelial damage and the severity of CAD. In patients with CAD, FMV was significantly attenuated compared to patients without CAD as well as to healthy controls (5.7 % vs. 12.6 % and 15.6 %, respectively). Despite the small size of the study population, subgroup analysis demonstrated a significant correlation between changes in FMV and the extent of CAD (1-, 2-, or 3-vessel disease). As evidenced by the results, the loss of the dilation of the brachial artery in response to changes in blood flow (distension of the vascular wall) is proportional to the severity of CAD (Figures 3 and 4). In this study, FMV-measurement was found to detect mild-to-moderate CAD with a diagnostic sensitivity of 89 %, and a specificity of 77 %.

In another study [11], 147 CAD patients were followed up for 7.7 years on average. Endothelial function was monitored by non-invasive methods. The primary end-point of the trial was the occurrence of CV-events. An association was found between attenuated endothelium-dependent vasodilation and a higher incidence of CV-events. FMV was reduced in all 16 patients who suffered any type of cardiovascular complication. The results of this study suggest that endothelial dysfunction is an independent predictor of the progression of atherosclerosis as well as of CV-event rate.

In their study conducted on 157 patients, Suwaidi et al. [12] found an increased incidence of CV-events in severe endothelial dysfunction – even in the absence of obstructive CAD. Six patients suffered a CV-event during the 28-month follow-up and all had severe endothelial dysfunction.

The results of the prospective study conducted by Gocke et al. [13] show that reduced FMV found in the brachial artery is an independent predictor of impending CV-events in patients undergoing vascular surgery. Non-invasive evaluation of endothelial function can thus provide prognostic information on the occurrence of CV-events.

Our results suggest that FMV is attenuated in male postinfarction patients under 40 years of age, and this finding evidenced endothelial damage. A relationship was found between the extent of CAD and the severity of endothelial dysfunction. In patients with single-vessel disease, the attenuation of FMV was more obvious than in controls, but less pronounced than in the group with multi-vessel disease.

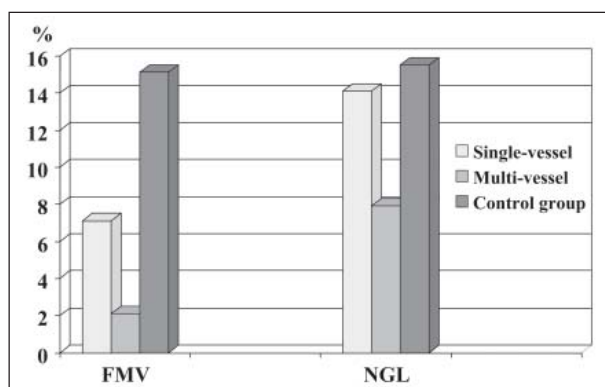


Figure 2. Endothelium-dependent and -independent vasodilation in single- and multi-vessel disease

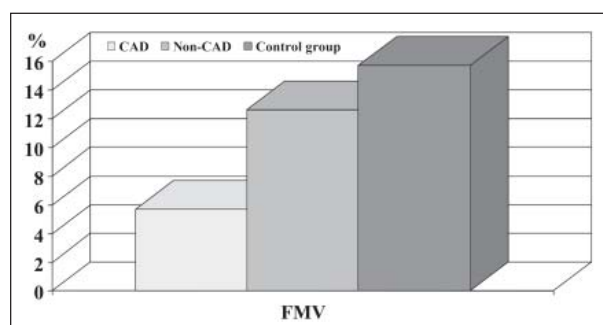


Figure 3. Flow-mediated vasodilation (FMV) in CAD and non-CAD patients

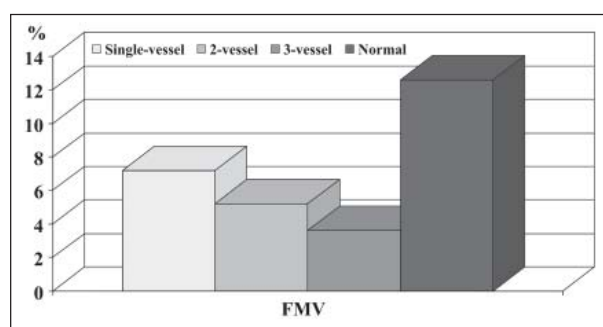


Figure 4. Flow-mediated vasodilation (FMV) in 1-, 2-, 3-vessel disease

It can be concluded in view of these observations that the appearance of endothelial dysfunction indicates a high risk of developing CAD, and severe endothelial damage is associated with an increased incidence of CV-events. Therefore, our results confirm that reduced endothelial function can predict the occurrence of cardiovascular complications.

The pathologic process of atherosclerosis is 'silent' and reversible until the onset of endothelial dysfunction. As evidenced by an abundance of clinical data, drug therapy (eg, with calcium channel blockers, ACE inhibitors, or statins) and non-pharmacological intervention (eg, diet, exercise) can mitigate endothelial damage [14].

The early recognition of endothelial dysfunction can assist the diagnosis of incipient – and therefore reversible – atherosclerosis.

Appraising endothelial function in due time might provide an opportunity for diagnosing CAD in its subclinical stage and thereby prevent cardiovascular complications. Non-invasive testing of endothelial function is straightforward for medical professionals and non-demanding on patients.

The early recognition of endothelial dysfunction can contribute to preventing the progression of atherosclerosis to an irreversible stage. Moreover, it might assist the primary prevention of life-threatening myocardial infarction by pharmacological and non-pharmacological interventions.

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