Flow mediated dilatation and QT interval dispersion in patients with coronary artery disease with or without myocardial infarction

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Citation

I Simova, S Denchev, I Christov, M Matveev, S Dimitrov, L Vladimirova, S Kurtev. *Flow mediated dilatation and QT interval dispersion in patients with coronary artery disease with or without myocardial infarction*. The Internet Journal of Cardiology. 2007 Volume 5 Number 2.

Abstract

Objectives: To evaluate the changes in flow mediated dilatation (FMD) and QT interval dispersion (QTd) in stable coronary artery disease (CAD) patients with or without myocardial infarction (MI).
Results: 152 patients participated in the study - 64 patients with MI. MI patients showed a significantly lower FMD (3.58 ± 4.45 versus 5.16 ± 4.80, p = 0.040) and higher QTd (62 ± 36 versus 56 ± 32, p = 0.036 for QTd1; 19.45 ± 11 versus 16.25 ± 10, p = 0.021 for QTd2) compared to no-MI patients. There wasn't a significant difference in FMD and QTd according to coronary artery occlusion within MI patients. In the group of no-MI patients, those with coronary occlusion showed significantly lower FMD than patients without occlusion, whereas QTd values didn't differ significantly according to the occlusion status.
Conclusion: MI patients have significantly lower FMD and higher QTd compared to no-MI patients. Low FMD in no-MI patients may be an index of chronic coronary occlusion.

INTRODUCTION

Coronary artery disease (CAD) is the primary cause of morbidity and mortality in developed countries. Myocardial infarction (MI) represents one of the major cardiovascular adverse events associated with CAD and leads to substantial economical and social consequences.

Flow mediated endothelial dependent vasodilatation (FMD) of the brachial artery is an echographic method capable of detecting changes in the endothelial function. The method is first described and implemented in clinical practice by Celermajer et al ([1]). For over two decades the method has been used to evaluate the early atherosclerotic changes in patients with various risk factors for coronary atherosclerosis or with an already established CAD and has been shown to correlate with other well-established surrogates of coronary atherosclerosis as coronary flow reserve and intima-media thickness of the common carotid artery ([2]).

QT interval is the time for ventricular depolarization and repolarization. It provides a rough estimate of the duration of an average ventricular action potential. The dispersion of the QT interval (QTd) reflects the inhomogenities of electrical activity in the different segments of the left ventricle. An increase in its value is related to a greater risk of ventricular arrhythmias and sudden cardiac death and its measurement proves to have prognostic implication ([3]) although the results regarding the prognostic significance are quite conflicting ([4]).

FMD and QTd measurements are used as noninvasive tools for clinical assessment and risk stratification of patients. The extend to which their values differ in patients with an already experienced cardiovascular adverse event, such as MI, and which one is more sensitive to evaluate such patients, remains unknown.

The purpose of the present study is to evaluate how and to what extent the FMD and QTd differ in patients with previous MI as compared to patients with ischemic heart disease but without MI.

METHODS

STUDY GROUP

We studied 152 patients, admitted to the Clinic of Cardiology, University Hospital Alexandrovska between July 2006 and March 2007. All patients underwent coronary arteriography (CAG) as part of their diagnostic and therapeutic work-up

Patients were considered to have had previous MI if they had at least two out of three clinical signs (chest pain, ST segment elevation, positive markers of myocardial necrosis) during a documented hospitalization. The average time elapsed from an MI was 15.6 ± 6.7 months.

INCLUSION AND EXCLUSION CRITERIA

The study included patients regardless of their sex or age. Patients admitted in our clinic for elective CAG in order to evaluate and treat coronary artery disease were considered eligible.

The study excluded patients with acute coronary syndrome, patients with haemodinamically significant valvular disease as well as patients with previously performed coronary interventions or surgical revascularization.

ETHICS

All patients signed an informed consent for FMD measurement. The investigation protocol was approved by the local ethical committee.

FLOW MEDIATED BRACHIAL ARTERY DILATATION

FMD was accomplished according to the Guidelines for ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery ($_5$). The investigator has had an experience of 100 supervised scans and measurements before claiming independency and then more than 100 scans per year to maintain competency. The inter- and intraobserver variability of the method was evaluated on a sample of 40 patients with a correlation coefficient $r > 0.92$, $p < 0.001$ ($_6$).

We performed the FMD measurements in the morning hours between 7 and 9 a.m. After 8 p.m. on the day before the patient refrained from eating, drinking alcoholic beverages or smoking. Long-acting nitrates were avoided for 24 hours. On the morning of the study the patient was asked not to consume anything but water, not to smoke, to postpone taking the prescribed medication till after the study and to refrain from vigorous physical activity.

After a fifteen-minutes-rest in a quiet and temperate room the investigation started with taking the blood pressure on the dominant arm. We placed the cuff of the sphygmomanometer on the forearm of the same arm, with the patient in a supine position and we obtained a longitudinal image of the brachial artery with optimal visualization of the intima using a linear array transducer 3 – 11 MHz and a Sonos 5500 echocardiograph. We performed a five-to-ten-seconds recording on video cassette recorder (VCR) of the baseline state of the brachial artery. The cuff was inflated to a pressure of 200mmHg or 50mmHg above the systolic arterial pressure of the respective patient, whichever is higher, and maintained so for 5 minutes. We executed a new recording on VCR during the last 30s of the ischemic phase (cuff inflated) and then 120s after cuff deflation. The whole image was ECG-gated.

MEASUREMENT

The analysis was made off-line. We considered two parameters: the baseline diameter of the brachial artery and the maximum post-ischemic stimulus diameter of the artery. All measurements were done in the end-diastole (the beginning of the R on ECG) from endothelial to endothelial surface along a line perpendicular to the artery's long axis. The FMD was measured in percentage terms and derived by the formula:

FMD (%) = [(post-ischemic diameter of the brachial artery – baseline diameter) / baseline diameter] x 100.

QT INTERVAL DISPERSION

QT interval was measured manually on a standard 12 lead surface ECG. QTd was calculated with two different methods: QTd1 – the difference between the maximal and minimal QT interval (QTd1 = QTmax – QT min) and QTd2 – the standard deviation between the QT intervals in all 12 leads using the formula

Figure 1

$$SD = \sqrt{\frac{\sum_{i=1}^{N} (Xi - \overline{X})^2}{N-1}}$$

where N = 12, Xi is the QT interval in a certain lead and X□ is the mean QT interval. Five experts (four cardiologists and one biomedical engineer) had participated previously in a project, creating a database of precise manual markings of Q onsets and T ends on 458 ECG recordings of the PTB Diagnostic Database ([7], [8]). Two of the experts, with reported mean and standard deviations of the Q onsets and T ends respectively 0.11 ± 3.23 ms and 0.75 ± 7.62 for the first, and 0.76 ± 2.45 ms and 2.45 ± 6.72 ms for the second, were involved in the current study and their mean value for each QT interval was further considered.

STATISTICS

We tested the distribution of data within groups using the Kolmogorov Smirnov test. The results for normally distributed scale data were expressed as mean ± standard deviation (SD), whereas non-normally distributed data were expressed as median and inter-quartile range (the difference between the first and the third quartile). We compared the results using an independent samples t test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. Categorical variables, presented in percentage terms, were compared with Chi square test. A two-tailed p value < 0.05 was considered significant. All tests were performed with SPSS 13 for Windows. Values were presented as mean ± SD unless stated otherwise.

RESULTS

The demographic characteristics and risk factor distribution of the patients are presented in table 1. The clinical characteristics with respect to CAD are presented in table 2.

Figure 2

Table 1: Demographic characteristics and risk factor distribution of the study population

Clinical variable	Distribution All cases – 152 (100%)
Female gender - n (%)	62 (40.8%)
Age (years)	59.5 (± 9.1)
Body mass index (BMI)	27.9 (± 4.3)
Arterial hypertension - n (%)	130 (85.5%)
Diabetes mellitus - n (%)	35 (23%)
Dyslipidemia* - n (%)	107 (89.2%)
Current smokers - n (%)	19 (12.5%)
Passed smokers - n (%)	90 (59.2%)

* missing values for 32 patients

Figure 3

Table 2: Clinical characteristics of the study population

Clinical variable	Distribution All cases – 152 (100%)
Angina Pectoris - n (%)	120 (78.9%)
History of myocardial infarction - n (%)	64 (42.1%)
Number of diseased vessels	1.2 (± 0.8)
Occlusion of coronary artery - n (%)	56 (36.8%)

Patients with a history of MI (n=64) were predominantly male and smokers, had greater average number of diseased vessels and occluded arteries, but had less often angina pectoris than patients with no history of MI (n=88) (table 3).

Figure 4

Table 3: Distribution of risk factors and clinical characteristics in patients with and without MI

Clinical variable	With MI	Without MI	Significance
Number	64 (42%)	88 (58%)	
Female gender - n (%)	14 (21.9%)	48 (54.5%)	< 0.001
Age - mean ± SD	58.9 (± 9.5)	60 (± 8.9)	0.454
BMI - mean ± SD	27.9 (± 4.6)	27.9 (± 4.1)	0.979
Arterial hypertension - n (%)	50 (78.1%)	80 (90.9%)	0.027
Diabetes mellitus - n (%)	13 (20.3%)	22 (25%)	0.498
Dyslipidemia* - n (%)	47 (83.9%)	60 (93.8%)	0.180
Current smokers - n (%)	10 (15.6%)	9 (10.2%)	0.320
Former smokers - n (%)	48 (75%)	42 (47.7%)	0.001
Angina Pectoris - n (%)	40 (62.5%)	80 (90.9%)	< 0.001
Coronary artery occlusion - n (%)	44 (68.8%)	12 (13.6%)	< 0.001
Number of diseased vessels	1.81 (± 0.8)	0.75 (± 0.6)	< 0.001

* missing values for 32 patients

Patients with coronary artery occlusion (n=56) were more frequently male (P<0.001), with a history of MI (p<0.001),

had greater number of diseased vessels (p<0.001) but less frequently angina (p=0.032) than patients without coronary artery occlusion (n=96).

FMD was significantly lower and QTD1 and QTD2 were significantly higher in patients with MI compared to patients without MI, which demonstrates that the former group had worse endothelial function and increased repolarization heterogeneity in the former group (table 4).

Figure 5

Table 4: FMD, QTd1 and QTd2 in patients with and without MI.

	With MI n = 64	Without MI n = 88	Significance
FMD (%)	3.58 (± 4.45)	5.16 (± 4.80)	0.040
QTd1 (ms)	62 (IQR - 36)	56 (IQR - 32)	0.036
QTd2 (ms)	19.45 (IQR - 11)	16.25 (IQR - 10)	0.021

IQR – interquartile range

Among patients without history of MI, those with coronary artery occlusion (n=12) had significantly decreased FMD compared to those without an occlusion (n=76) (figure 1) whereas QTd values showed no significant differences between these two subgroups (figure 2 and 3). However, in the group of patients with previous MI there were no significant differences in either FMD or QTd between those with (n=44) and those without (n=20) occluded arteries (table 5).

Figure 6

Figure 1: Mean FMD values in patients with and without MI, according to the presence or absence of coronary artery occlusion.

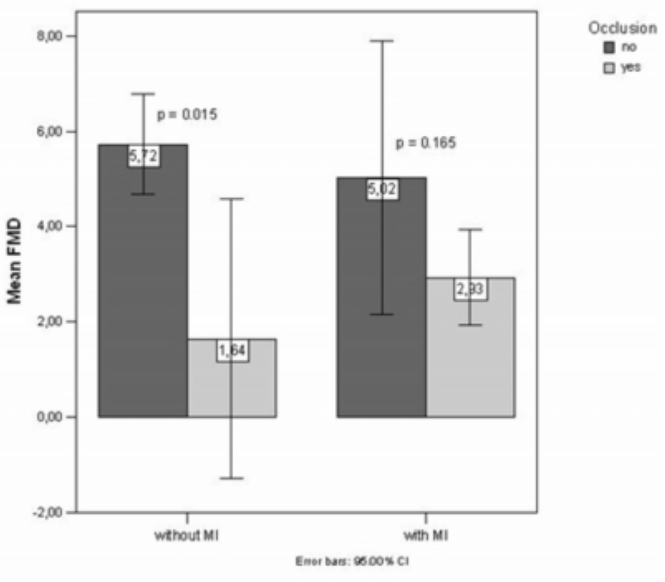

Figure 7

Figure 2: Median QTd1 values in patients with and without MI, according to the presence or absence of coronary artery occlusion.

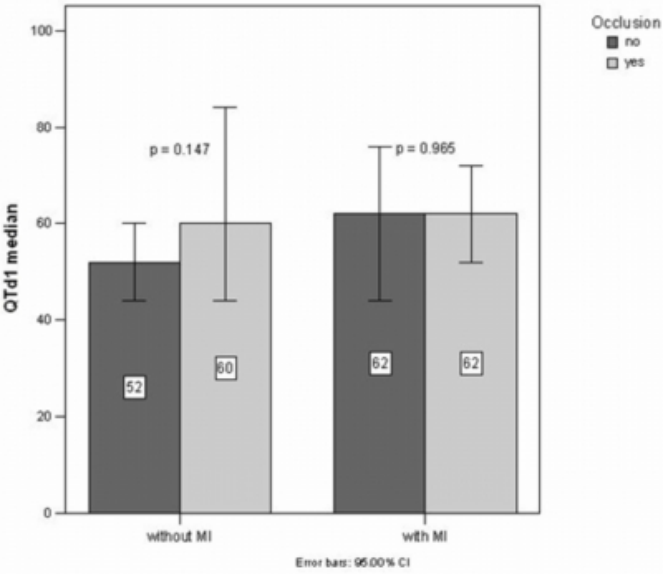

Figure 8

Figure 3: Median QTd2 values in patients with and without MI, according to the presence or absence of coronary artery occlusion.

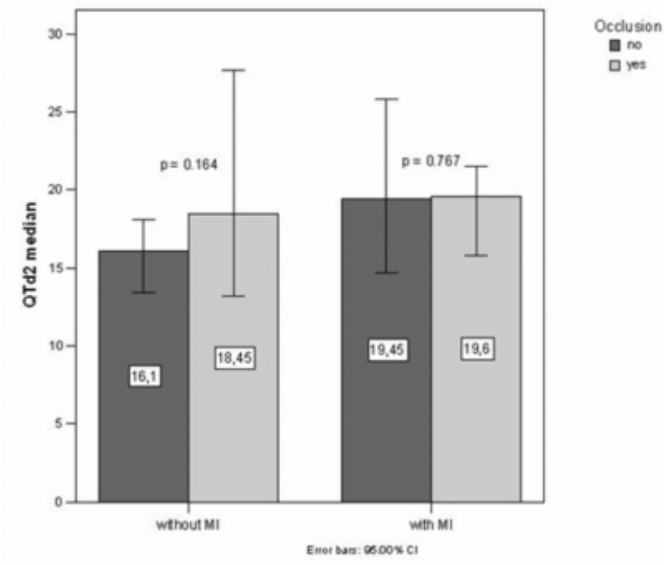

Figure 9

Table 5: FMD, QTd1 and QTd2 in patients with and without MI according to the presence or absence of an occluded artery.

	Pts with MI		Pts without MI	
	With occlusion	No occlusion	With occlusion	No occlusion
FMD (%)	2.93 (± 3.3)	5.02 (± 6.15)	1.64 (± 4.61)	5.72 (± 4.62)*
QTd1 (ms)	62 (IQR – 38)	62 (IQR – 35)	60 (IQR – 38)	52 (IQR – 35)
QTd2 (ms)	19.6 (IQR – 10)	19.45 (IQR – 14)	18.45 (IQR – 13)	16.1 (IQR – 10)

* p<0.05 for comparison between pts with and without coronary artery occlusion in the group without MI

IQR – interquartile range

DISCUSSION

We examined 152 patients with angina pectoris or already established CAD and found a significant difference in both the FMD and QTd values between those with and those without a history of MI. It must be stated however that the two groups differ significantly in the distribution of risk factors (male gender, hypertension and smoking), the presence of angina pectoris and the number of diseased vessels. There was not a significant difference in the FMD and QTd values in the group of patients with MI according to the presence or absence of coronary artery occlusion. Patients without MI showed a lower FMD value when they had an occluded coronary artery, but the QTd values did not differ significantly according to the occlusion status.

We assume that the process of atherosclerosis in patients with MI is more advanced and the methods used are incapable to detect further subtle changes due to the presence or absence of coronary artery occlusion.

On the other hand an occlusion of a coronary artery without the occurrence of a MI is a gradual process. It reflects an advanced atherosclerosis and is associated with endothelial dysfunction, hence with decreased FMD. It does not however lead to myocardial scaring and to profound inhomogenities in ventricular repolarization which can explain the absence of significant QTd changes.

FMD has been studied in the setting of MI by other researchers as well. Vertes et al ([9]) compared the endothelial function of young men with a history of MI with healthy controls and demonstrated a significant reduction for FMD values in MI patients. On the other hand the reactivity of the brachial artery has been shown to be an independent predictor of adverse cardiovascular events in survivors of acute coronary syndrome without ST segment elevation ([10]).

A meta-analysis, including 18 studies with 2525 post-MI patients, showed that the QTd was significantly higher in acute MI, as well as in the chronic phase of MI although with a trend towards lower values compared with the acute phase of MI ([11]). The changes in QT interval dispersion have also been correlated with the patency of the infarct-related coronary artery in a study including 244 patients with acute MI treated with fibrinolytics, where a significantly higher QTd was found in patients with an occluded culprit vessel ([12]).

Our findings are in accord with the results of other previously cited studies. An exception is the study by Moreno et al ([12]) which demonstrated a significant increase in QTd in the presence of an occluded infarct-related artery, whereas our results did not show a significant difference in the QTd values between the patients with and without coronary artery occlusion.

Both methods we use, FMD and QTd measurement, are noninvasive, relatively easy to perform and cost-effective. Still some studies have questioned their reproducibility and reliability ([11], [13]). Because of this we have tested the inter- and intraobserver variability for both methods performed in our laboratory and have demonstrated a good reproducibility of the results ([6], [7]).

Our study group of 152 patients was relatively small so the results from the comparison of FMD and QTd between the subgroups could be influenced by some incidental findings. Another possible limitation is that our study was

retrospective and therefore there is a risk of selection bias due to the available research data. The two groups of patients, with and without MI, differ significantly in terms of risk factors distribution, presence of angina pectoris and number of diseased vessels. But this is the real world distribution of consecutive patients admitted in our clinic for a limited time frame.

A further limitation in our study is the fact that only 13.6% of the patients without MI had an occluded coronary artery compared to 68.8% in the MI group. Therefore we cannot exclude the possibility that the difference in FMD values in the group of patients without MI based on the presence or absence of an occluded coronary artery could be incidental.

It was not in the scope of our study to monitor these patients for cardiovascular adverse events. In future studies we would like to investigate the FMD and QTd values in the acute phase of MI and to record the changes in these parameters in one and the same patient.

CONCLUSION

The results of the present study can be summarized as follows: 1. Patients with MI demonstrate a significantly lower FMD and higher QTd values compared to patients with CAD without a history of MI; 2. On the basis of FMD and QTd measurements an occluded coronary artery cannot be distinguished within the patients with MI and 3. Low FMD in patients with CAD without MI may be an index of chronic coronary occlusion.

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