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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Flow-mediated dilatation (FMD) and prevalence of cardiovascular risk factors: the value of FMD assessment in high risk patients is limited

Katarzyna Mizia-Stec[1], Joanna Wieczorek[1], Michał Orszulak[1], Magdalena Mizia[1], Klaudia Gieszczyk-Strózik[1], Agnieszka Sikora-Puz[2], Maciej Haberka[2], Bartosz Lasota[2], Artur Chmiel[2]

[1]1st Department of Cardiology, Medical University of Silesia, Katowice, Poland
[2]2nd Department of Cardiology, Medical University of Silesia, Katowice, Poland

Abstract

Background: Since flow-mediated dilatation (FMD) is influenced by different factors, its clinical usefulness and validation is widely discussed.

Aim: To assess the major factors that determine FMD values in a wide range of subjects with and without cardiovascular (CV) risk factors/diseases (CVRF/CVD).

Methods and results: 617 consecutive patients (mean age: 50.1 ± 14.9 years, males: 349/56.5%) hospitalised between 2005 and 2011 were enrolled into the study. Demographic data and CVRF/CVD with a significant impact on FMD values were analysed: hyperlipidaemia, active smoking, arterial hypertension, coronary artery disease, diabetes mellitus and heart valve disease. The population was divided depending on the number of coexisting CVRF/CVD (0-, 1-, 2-, 3-, 4-, 5-CVRF/CVD groups). The median FMD value in the entire group of patients was 10% (5–17). An analysis of the FMD percentage in particular groups showed significantly higher FMD values in patients without any CVRF/CVD (group 0), as well as in patients with one coexisting CVRF/CVD (group 1) compared to the other groups. The presence of two or more CVRF/CVD was not associated with a significantly higher FMD reduction. The analysis of patients with only one CVRF/CVD revealed the lowest FMD values in patients with coronary artery disease.

Conclusions: FMD is related to the number of traditional CVRF/CVDs; however, coronary artery disease has the most significant influence on FMD decrease among analysed factors. The value of FMD assessment in high risk patients is limited.

Key words: flow-mediated dilatation, brachial artery diameter, cardiovascular risk factors, cardiovascular diseases, endothelial dysfunction, clinical usefulness

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INTRODUCTION

Despite several decades of development and refinement, algorithms for the prediction of cardiovascular (CV) risk in humans that are based on 'traditional'or 'conventional' risk factors fail to predict a substantial proportion of CV events [1]. A noninvasive, cost-effective, reproducible screening method for CV events is still needed. Flow-mediated dilatation (FMD) as a marker of endothelial dysfunction has been found to be a simple, noninvasive method for identifying patients at risk of CV disease. For more than 20 years since the first study about FMD was published [2], many investigations concerning FMD have been performed and gradually FMD has become an important tool in cardiology. FMD reflects endothelial function. It is measured as the relative change of artery diameter due to reactive hyperemia following transient ischaemia.

This method is believed to be a simple predictor of CV events both in subjects already diagnosed with CV disease [3] and in asymptomatic individuals [4]. Many studies have been performed in order to explore the physiological basis, prognostic value and impact of interventions and risk factors/diseases on FMD. However, the relationship between FMD and overall CV risk is not yet well-assessed. In spite of

Address for correspondence:
Prof. Katarzyna Mizia-Stec, First Department of Cardiology, Medical University of Silesia, ul. Ziołowa 45/47, 40–635 Katowice, Poland, tel: +48 32 252 74 07, fax: +48 32 252 30 32, e-mail: kmizia@op.pl

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our eight-year experience in using this method both in research and clinical practice, we have some doubts regarding the interpretation of FMD in high risk patients.

Therefore, it seemed that further observation on the behaviour of FMD parameters may be important to develop a broader knowledge about its prognostic and diagnostic value. The aim of the study was to investigate the major factors that determine FMD in a wide range of subjects with and without CV risk factors/diseases (CVRF/CVD). We evaluated the association between FMD values and the number of major CVRF as well as demographic and anthropometric indices.

METHODS

Study group

In order to perform a retrospective analysis, 617 consecutive subjects (mean age: 50.1 ± 14.9 years, males: 349/56.5%) who had been hospitalised in the Department of Cardiology between 2005 and 2011 were enrolled into the study.

The standard exclusion criteria for the FMD evaluation used in our lab were: acute coronary syndromes (in the preceding 3 months), a history of myocarditis and/or vasculitis, cardiomyopathy, left ventricular systolic dysfunction (ejection fraction < 40%), smoking cigarettes within 12 h before the examination, acute and chronic inflammatory diseases (in the preceding 3 months), spondyloarthritis, Tietz syndrome, gastrointestinal tract diseases, diseases of the aorta, hormone replacement therapy, arrhythmias that might disturb the evaluation of FMD (atrial fibrillation, increased number of ventricular extrasystolic beats, sinus tachycardia).

The study subjects were instructed to fast overnight, avoid exercise, caffeine and alcohol intake the day (minimally for 8 h) prior to the examination and not to take any medication that could potentially modify the measurement results, e.g. nitrates, calcium channel blockers, etc. Female subjects were not on hormone replacement therapy.

A thorough clinical examination of each subject was performed. Medical history (familial history, concomitant diseases, actual pharmacotherapy, alcohol and coffee intake, active tobacco smoking), physical examination (weight, height, body mass index [BMI], arterial blood pressure, heart rate), laboratory tests (cholesterol fractions were mainly analysed) and other accessory investigations (electrocardiography, transthoracic echocardiography, coronary angiography when necessary) were collected for all patients. The following coexisting CVRF/CVD of a potent impact on FMD values were analysed: hyperlipidaemia, active smoking, arterial hypertension, coronary artery disease (CAD), diabetes mellitus and heart valve disease.

Hyperlipidaemia was defined in accordance with the newest European Society of Cardiology (ESC) guidelines: European Guidelines on cardiovascular disease prevention in clinical practice (version 2012) [5] and European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) Guidelines for the management of dyslipidaemias (version 2011) [6].

Active smoking. Patients were still smoking.

Arterial hypertension was diagnosed previously or newly, based on the 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) [7].

Coronary artery disease. We included in the study patients with a history of acute coronary syndrome and/or confirmed by coronary angiography atherosclerosis of coronary vessels.

Diabetes mellitus. Patients with diabetes mellitus previously or newly diagnosed during hospitalisation were taken into consideration.

Heart valve disease. We defined valve disease as a haemodynamically significant heart valve insufficiency or stenosis.

The examined population was divided into the following groups depending on the number of coexisting CVRF/CVDs:
Group 0 — without any CVRF/CVD (77 patients =12.5%);
Group 1 — one CVRF/CVD (151 patients = 24.5%);
Group 2 — two CVRF/CVDs (172 patients = 27.9%);
Group 3 — three CVRF/CVDs (148 patients = 24%);
Group 4 — four CVRF/CVDs (60 patients = 9.7%);
Group 5 — five CVRF/CVDs (nine patients = 1.5%).

Informed consent was obtained from each patient. The study protocol was approved by the Bioethical Committee of the Medical University of Silesia and performed according to the ethical guidelines of the 1975 Declaration of Helsinki.

Flow-mediated dilatation — method of assessment

Continuous measurements of brachial artery velocity and diameter using duplex ultrasound were performed using a high frequency ultrasound machine (Toshiba Aplio Tochigi, Japan; VIVID 7 Dimension, GE Healthcare, USA) equipped with a high frequency vascular probe (7–10 MHz), internal electrocardiogram monitor and vascular software (for two-dimensional imaging, colour and spectral Doppler). ECG-gated, vessel end-diastole B-mode images were analysed. An experienced physician took all of the measurements in all subjects using the same investigation protocol and techniques in order to reduce inter- and intra-observer variability. The examinations of the brachial artery were conducted in the morning, in a quiet, darkened and temperature-controlled room after at least a 10-min rest. Measurements were obtained in a supine position. After the sphygmomanometer cuff was placed proximal to the visualised vessel, arterial baseline diameter 5–10 cm above antecubital fossa was assessed before cuff inflation. Brachial artery diameter (BAd) was defined as the average value of several measurements. Then, the cuff was inflated for 3 min to obtain vessel occlusion (200 mm Hg or 50 mm Hg above actual systolic blood pressure). The mean values of brachial artery velocity and diameter were obtained between –50 sec and –60 sec after cuff deflation. The proportional difference between the artery baseline and dilatation after

Table 1. Clinical characteristics of the study group

	Mean	Standard deviation	Median	25–75 interquartile range
Body mass index [kg/m^2]	27.1	4.4	27.1	23.7–29.7
Cholesterol [mg/dL]	203	46	199	171–230
High density lipoprotein [mg/dL]	50	14	49	41–58
Low density lipoprotein [mg/dL]	125	39	124	97–149
Triglicerydes [mg/dL]	136	87	116	80–169
Age [years]	50.1	14.9	51.0	38–61
Flow-mediated dilatation [%]	11.7	7.8	10.3	5.4–16.7

Table 2. Values of flow-mediated dilatation depending on coexisting risk factor/diseases

	Risk factor						P
	Yes			No			
	N	Median	25–75Q	N	Median	25–75Q	
Diabetes type 2	80	7.9	4.6–12.4	538	11.1	5.5–17.4	0.002
Arterial hypertension	297	8.3	4.3–13.7	321	12.4	6.9–20.0	< 0.001
Valve heart disease	111	6.0	3.3–12.3	507	11.3	6.2–18.4	< 0.001
Coronary artery disease	230	7.0	3.7–11.2	388	12.8	7.0–19.9	< 0.001
Hyperlipidaemia	312	9.8	5.0–15.4	306	11.2	5.7–18.9	0.004
Active smoking	174	8.9	5.0–14.5	444	11.3	5.5–17.5	0.01

N — number of patients; 25–75Q — interquartile range

reactive hyperemia was calculated and defined as the FMD. Endogenous vasodilatory capability, independent of BAd, was defined as FMD × BAd index and calculated for all subjects.

Statistical methods

Continuous variables are reported as the mean with standard deviation or the median with the interquartile range (25–75Q) for non-normal distributions. Categorical variables are reported as absolute numbers and percentages. The Mann-Whitney test was used to compare two non-normally distributed variables, while the Student's t-test was used for the comparison of normally distributed continuous variables. Kruskal-Wallis tests were used to compare FMD values between groups. The ANCOVA test with Bonferroni correction was used to compare the FMD values between groups adjusted for age, gender, BMI and BAd. Stepwise multivariate analysis was performed with FMD and FMD × BAd index as the dependent variables. A p value of less than 0.05 was considered to indicate statistical significance. Statistical analysis was performed using Medcalc 10.0 for Windows software. All data was collected in a Microsoft Office Excel spreadsheet.

RESULTS

The mean age of the examined population (n = 617) was 50.1 ± 14.9 years, with a majority of males — males/females 349 (56.5%)/268 (43.5%). An analysis of clinical characteristics showed that hyperlipidaemia was the most widespread in the entire group — 50.5% (n = 312), while arterial hypertension was present in 48.1% (n = 297), CAD in 37.2% (n = 230), active smoking in 28.2% (n = 174), heart valve disease in 18% (n = 111), and diabetes mellitus type 2 in 12.9% (n = 80). The BMI and total cholesterol levels are presented in Table 1.

The median FMD value in the entire group was 10% (5–17). A comparison of FMD values between patients with and without any CVRF/CVD revealed significant differences (Table 2). Depending on the number of coexisting CVRF/CVDs, the highest FMD was observed in patients without any CVRF/CVDs, and the lowest was found in patients with five CVRF/CVDs (Table 3, Fig. 1). An analysis of the FMD percentage in particular groups showed significantly higher FMD values in patients without any CVRF/CVD (group 0), as well as in patients with one coexisting CVRF/CVD (group 1) compared to other groups. The presence of two and more CVRF/CVDs was not associated with a significantly greater reduction in the FMD percentage (Table 4).

The distribution of FMD × BAd index was comparable to the FMD values (Fig. 2). The median of FMD × BAd index, depending on number of coexisting CVRF/CVDs, was highest in patients without any CVRF/CVD, and lowest in patients who had two and more CVRF/CVDs (Table 3).

An analysis of the FMD × BAd index in particular groups also showed significantly higher values in healthy patients

Table 3. Values of flow-mediated dilatation (FMD), brachial artery diameter (BAd) and flow-mediated dilatation index (FMD × BAd) depending on number of coexisting risk factors/diseases

No. of risk factors	N	Med FMD	25–75Q FMD	Med FMD × BAd	25–75Q FMD × BAd
0	77	20	13–23	60	47–70
1	151	14.1	8–21	53	32–70
2	172	8.4	4–14	34	19–60
3	148	7.7	3–12	30	18–49
4	60	7.5	3–12	30	11–51
5	9	6.1	3–8	32	10–34

Med — median; 25–75Q — interquartile range; 0 — group 0; 1 — group 1; 2 — group 2; 3 — group 3; 4 — group 4; 5 — group 5

Table 4. Mean difference between flow-mediated dilatation (FMD) depending on number of coexisting risk factors/diseases after adjusting for age, gender, brachial artery diameter (BAd) and body mass index (BMI)

Group	Mean difference FMD*	SE	P
0 vs. 1	2.2	0.89	NS
0 vs. 2	5.4	0.98	< 0.001
0 vs. 3	7.1	1.07	< 0.001
0 vs. 4	7.7	1.29	< 0.001
0 vs. 5	9.8	2.67	< 0.001
1 vs. 2	3.2	0.77	< 0.001
1 vs. 3	4.9	0.86	< 0.001
1 vs. 4	5.5	1.10	< 0.001
1 vs. 5	7.6	2.59	0.04
2 vs. 3	1.6	0.81	NS
2 vs. 4	2.3	1.04	NS
2 vs. 5	4.4	2.56	NS
3 vs. 4	0.6	1.05	NS
3 vs. 5	2.7	2.56	NS
4 vs. 5	2.1	2.63	NS

*After adjusting for age (p = 0.04), gender (p = 0.4), BMI (p = 0.02), BAd (p < 0.001); SE — standard error

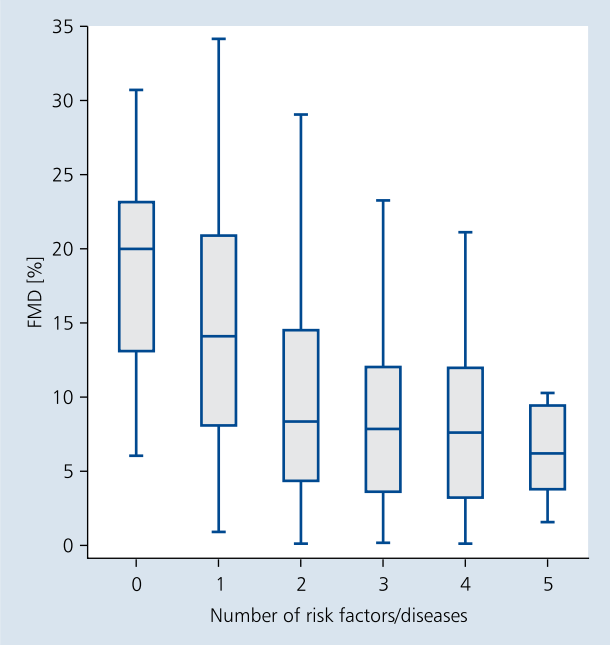

Figure 1. Illustration of flow mediated dilatation (FMD) depending on number of coexisting risk factors/diseases; 0 — group 0; 1 — group 1; 2 — group 2; 3 — group 3; 4 — group 4; 5 — group 5

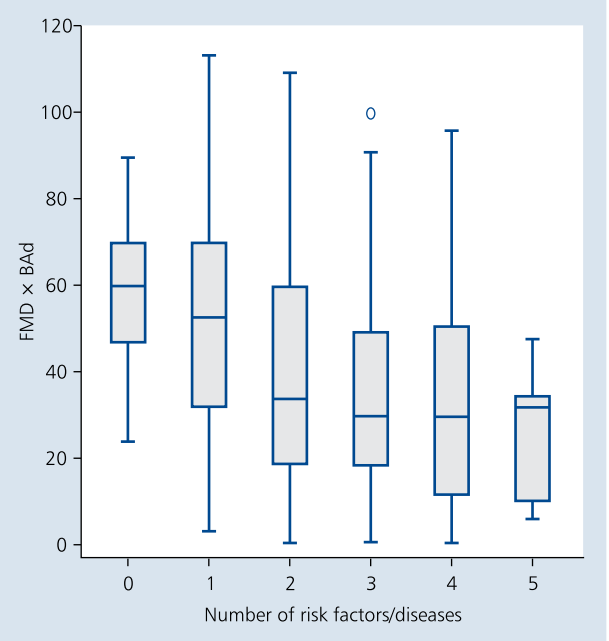

Figure 2. Illustration of flow-mediated dilatation (FMD) × brachial artery diameter (BAd) index depending on number of coexisting risk factors/diseases; 0 — group 0; 1 — group 1; 2 — group 2; 3 — group 3; 4 — group 4; 5 — group 5

without any CVRF/CVD (group 0), as well as in patients with one coexisting risk factor (group 1) compared to other groups. The presence of two or more CVRF/CVDs was not associated with a significantly higher reduction in endogenous vasodilatory capability.

Multiple regression analysis revealed that CAD, heart valve disease, BAd, hyperlipidaemia as well as age were independent factors that influenced FMD (Table 5). Multiple regression with FMD × BAd as a dependent variable showed the significant negative influence of CAD, heart valve disease

Table 5. Multiple regression. Dependent flow-mediated dilatation

Independent variables	Coefficient	SE	t	p
(Constant)	28.84			
Coronary artery disease	–6.44	0.77	–8.282	< 0.0001
Hyperlipidaemia	–1.90	0.53	–3.529	0.0005
Age	0.08	0.02	3.094	0.002
Valve heart disease	–5.18	1.02	–5.059	< 0.0001
Brachial artery diameter	–4.08	0.36	–11.159	< 0.0001

Multiple correlation coefficient 0.69; $p < 0.001$. Variables not included in the model: body mass index, arterial hypertension, active smoking, diabetes mellitus type 2, gender; SE — standard error

Table 6. Multiple regression. Dependent brachial artery diameter and flow-mediated dilatation index (FMD × BAd)

Independent variables	Coefficient	SE	t	p
(Constant)	47.83			
Coronary artery disease	–26.23	2.86	–9.156	< 0.0001
Hyperlipidaemia	–6.22	2.07	–3.001	0.002
Age	0.28	0.10	2.763	0.006
Valve heart disease	–28.42	3.41	–8.331	< 0.0001

Multiple correlation coefficient 0.48; $p < 0.001$. Variables not included in the model: body mass index, arterial hypertension, active smoking, diabetes mellitus type 2, gender; SE — standard error

and hyperlipidaemia, while age was a positive influence (Table 6).

A subgroup of patients with only one CVRF/CVD was analysed (n = 151). Results of post hoc test showed significantly lower median of FMD in patients with only CAD (median 6.7; 25–75Q 3.6–7.7), than in individuals who were active smokers (median 19.1; 25–75Q 13.9–25.8), with diabetes mellitus (median 18.0; 25–75Q 16.8–22.6), arterial hypertension (median 15.3; 25–75Q 8.5–25.0), valvular disease (median 12.0; 25–75Q 7.2–17.0) or hyperlipidaemia (median 14.1; 25–75Q 8.6–20.2); p = 0.003.

DISCUSSION

It is well established that FMD represents endothelial function indirectly [8, 9]. As the final status of endothelium depends on the impact of all pro- and antiatherogenic factors, it seems likely that FMD should be inversely related to the risk of CV.

The present study showed the relationship between FMD and accumulation of risk factors in a large cohort of patients for the first time.

Standard CVRF and concomitant diseases were evaluated and it was demonstrated that the degree of FMD impairment was dependent on the number of CVRF/CVDs. Significantly higher FMD values were observed in patients without any CVRF/CVD, as well as in patients with one coexisting CVRF/CVD, compared to other groups. The presence of two or more CVRF/CVDs was not associated with a further reduction in FMD. CAD had the most significant influence on FMD decrease among analysed CVRF/CVDs.

In the study, six conventional CVRF were taken into consideration: diabetes mellitus, hyperlipidaemia, active smoking, arterial hypertension, CAD and heart valve disease. In order to avoid the influence of standard demographic factors on FMD values, the results were adjusted for age, gender, BMI and BAd.

The traditional CVRF are largely associated with the presence of endothelial dysfunction, which is the driving force of the atherosclerotic process [10]. The relationship between traditional risk factors and an impairment of FMD was found in our study. Most previous studies have shown the negative effect of a single risk factor: smoking [11], hypercholesterolaemia [12], hyperglycaemia [13] or arterial hypertension [14] on FMD. There has been only limited data on the combined impact of different risk factors [2, 15]. This is of special value since endothelial dysfunction seems to be a final common target for all of the known and unknown risk factors [16]. It is defined by some authors as a "barometer" of health. On the other hand, it should be noted that our findings indirectly confirm the hypothesis that overall CV risk is determined first of all by traditional/conventional risk factors. This is in accordance with the epidemiological studies that have also established the role of standard risk factors in the development of CVDs [17].

According to the literature data, FMD is universally recognised as a risk factor of vascular complications, not as a quantifier of risk in patients with recognised CVD. Nevertheless, FMD and its vascular predictive value remain an effectual risk estimator in asymptomatic, low-risk subjects. Recently, the occurrence of CV events in healthy, young people has

been widely discussed. Raiko et al. [18] found significant correlations between CV disease risk scores and markers of subclinical atherosclerosis, e.g. FMD. Those results confirmed the research performed by Witte et al. [19], who described a negative correlation between FMD and CVRF assessed as the Framingham risk score. The correlation was clearest in populations with a low baseline CV risk, whereas in medium- and high-risk populations, FMD was not related to risk. This is in agreement with our study, as we found that overt atherosclerosis — CAD had the most significant influence on FMD decrease. Moreover, we observed that in patients with two or more CVRF/CVDs, FMD assessment does not allow any further stratification of CV risk.

As was presented in our results, not only the quality of risk factors/diseases, i.e. CAD play an important role in lowering FMD, but also their quantity. Multivariate analysis showed that CAD, heart valve disease, BAd, hyperlipidaemia as well as age were independent factors that influenced FMD.

A number of studies have assessed whether a change in FMD provides any important prognostic information in humans [20]. One meta-analysis suggested a 13% decrease in the future risk of CV events for every 1% increase in FMD [21]. Endothelial dysfunction has also been shown to be a reversible disorder following interventions such as cholesterol lowering, antihypertensive therapy, exercise training and weight loss [22–24].

Our study was designed to examine FMD in a large cohort of consecutive patients. This fact resulted in a non-heterogeneous group of patients with different underlying diseases. However, all of the factors that were evaluated disturb the correct wall function, which finally leads to endothelial dysfunction. Therefore, we can assume that ultimately FMD reflects the influence of all harmful factors independent of their origin.

Data concerning the effect of BAd on ultimate FMD have been widely presented in the literature [25]. Most of the studies support our finding that there is a negative relationship between BAd and FMD. However, most papers do not refer to vessel size differences when interpreting investigation results. FMD × BAd index was introduced in our previous study [26]. This represents vasodilatory capability and allows endothelial function to be compared independently of BAd. In the study, the FMD × BAd values showed a similar relationship to CV risk as the FMD values. Thus, the relationship between endothelial dysfunction and the number of risk factors remains independent of baseline BAd.

Limitations of the study

There are some limitations of our study. One of the limitations of the FMD method is the influence of factors which may alter FMD results: the measurement itself, gender, age [27], BAd and others. In our study, two demographic factors (age, gender) and BMI were taken into consideration. After adjustment for the aforementioned factors, the relationship remained statistically significant.

The final limitation is the moderate reproducibility of FMD. FMD results are very susceptible to external factors such as: the use of tobacco a few hours before the examination, dietary intake, time of the examination [28], mental stress, medication use [29] and others. This makes it impossible to evaluate the influence of all of the common factors on the final measurement result of FMD. Even attempts to render the same environmental conditions may fail, thus leading to faulty results. In addition, the measurement method itself is affected by many factors. Differences in cuff positioning, artery occlusion time, measurement duration following cuff deflation and other methodological approaches can result in inconsistent values. We were aware of all of these factors, therefore in our lab all measurements were taken by an experienced physician using the same investigation protocol and techniques on all subjects. We believe that this way allowed us to avoid most of the disturbing factors.

Valvular heart disease constitutes a potent factor influencing left ventricular ejection fraction (LVEF) value. Especially in patients with valve insufficiency, LVEF does not directly reflect left ventricular systolic function. This is why valve heart disease was defined as a haemodynamically significant valve insufficiency or stenosis, although left ventricular systolic dysfunction (LVEF < 40%) was an exclusion criterion.

CONCLUSIONS

1. FMD representing endothelial function is related to the number of traditional CVRF/CVDs independent of age, gender, BAd or BMI. Patients with two CVRF/CVDs are characterised by a significantly lower FMD; however, any further increase in the number of CVRF/CVDs does not lead to any further/proportional decrease in FMD. The value of FMD assessment in high risk patients is limited.
2. Coronary artery disease has the most significant influence on FMD decrease among analysed CVRF/CVDs.

Conflict of interest: *none declared*

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Dylatacja naczyń wywołana przepływem i współwystępowanie czynników ryzyka sercowo-naczyniowego

Katarzyna Mizia-Stec[1], Joanna Wieczorek[1], Michał Orszulak[1], Magdalena Mizia[1], Klaudia Gieszczyk-Strózik[1], Agnieszka Sikora-Puz[2], Maciej Haberka[2], Bartosz Lasota[2], Artur Chmiel[2]

[1] I Klinika Kardiologii, Śląski Uniwersytet Medyczny, Katowice

[2] II Klinika Kardiologii, Śląski Uniwersytet Medyczny, Katowice

Streszczenie

Wstęp: Wiele czynników wpływa na dylatację naczyń wywołaną przepływem (FMD), a ich kliniczna przydatność jest wciąż powszechnie dyskutowana.

Cel: Celem pracy było ustalenie wpływu współwystępowania istotnych czynników ryzyka/chorób sercowo-naczyniowych (CVRF/CVD) na wartości FMD.

Metody i wyniki: Do badania włączono 617 chorych (śr. wiek 50,1 ± 14,9 roku, płeć męska: 349/56.5%), hospitalizowanych w Klinice Kardiologii w latach 2005–2011. Analizie poddano współistniejące CVRF/CVD o potencjalnym wpływie na FMD: hipelipidemię, aktywne palenie tytoniu, nadciśnienie tętnicze, chorobę wieńcową, cukrzycę typu 2 i wady zastawkowe serca. Populację badaną podzielono ze względu na liczbę współistniejących CVRF/CVD (grupy 0-, 1-, 2-, 3-, 4-, 5-CVRF/CVD). Mediana procentowej zmiany wartości FMD w całej grupie badanej wynosiła 10% (5–17). Analiza w poszczególnych grupach wykazała natomiast znacząco wyższe wartości FMD wśród chorych bez CVRF/CVD (grupa 0), a także z jednym współistniejącym CVRF/CVD (grupa 1), w porównaniu z pozostałymi grupami. Współwystępowanie dwóch i więcej CVRF/CVD nie wiązało się z większą redukcją FMD. Wyniki uzyskano niezależnie od wieku, płci, wskaźnika masy ciała i wyjściowej średnicy tętnicy ramiennej.

Wnioski: Wartość FMD jest związana z liczbą powszechnie uznanych CVRF/CVD. Chorzy z dwoma CVRF/CVD charakteryzują się znacząco niższym FMD; jednak dalszy wzrost liczby współistniejących CVRF/CVD nie wiąże się z proporcjonalnym spadkiem FMD. Znaczenie FMD w przypadku chorych obarczonych dużym ryzykiem sercowo-naczyniowym wydaje się ograniczone.

Słowa kluczowe: dylatacja wywołana przepływem, dysfunkcja śródbłonka, czynniki ryzyka sercowo-naczyniowego

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Adres do korespondencji:
prof. dr hab. n. med. Katarzyna Mizia-Stec, I Klinika Kardiologii, Śląski Uniwersytet Medyczny, ul. Ziołowa 45/47, 40–635 Katowice, tel: +48 32 252 74 07, faks: +48 32 252 30 32, e-mail: kmizia@op.pl

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