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ORIGINAL ARTICLE

Cardiology Journal
2018, Vol. 25, No. 1, 120–127
DOI: 10.5603/CJ.a2017.0096
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ISSN 1897–5593

A pilot study with flow mediated skin fluorescence: A novel device to assess microvascular endothelial function in coronary artery disease

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Abstract

Background: *Endothelial dysfunction is one of the earliest vascular manifestations in the pathogenesis of cardiovascular disease. Noninvasive, simple, and inexpensive methods of endothelial function assessment are therefore needed.*

Methods: *Microvascular endothelial function was assessed in coronary artery disease (CAD) patients by flow mediated skin fluorescence (FMSF), based on measurements of reduced form of nicotinamide adenine dinucleotide (NADH) fluorescence intensity during brachial artery occlusion (ischemic response [IR_{max}]) and immediately after occlusion (hyperemic response [HR_{max}]). Additionally, plasma levels of asymmetric dimethylarginine (ADMA) and endothelin-1 (ET-1) were measured to assess the association between biochemical markers and microvascular function evaluated in vivo by FMSF.*

Results: *A significant inverse correlation was found between ADMA levels and hyperemic response ($r = –0.534$, $p = 0.003$), while ET-1 levels were inversely related to the ischemic response ($r = –0.575$, $p = 0.001$). Both IR and HR were found lowest in patients with advanced CAD and diabetes. When the repeatability of the method was tested, the intraclass correlation coefficient for IR_{max} and HR_{max} were 0.985 ($p < 0.001$) and 0.914 ($p < 0.001$), respectively. Moreover, in Bland and Altman analysis, both variables IR_{max} and HR_{max} showed good agreement in repeated measurements.*

Conclusions: *In this pilot study, it was demonstrated that NADH fluorescence measured by FMSF device in CAD patients was associated with established plasma endothelial markers, and that both ischemic and hyperemic response were blunted in patients with advanced disease and diabetes. Furthermore, FMSF device showed excellent repeatability and good agreement for repeated measurements. However, further study is warranted to confirm these results in a larger patient cohort.* (Cardiol J 2018; 25, 1: 120–127)

Key words: endothelium, endothelial plasma markers, microcirculation, flow mediated skin fluorescence, NADH fluorescence, brachial artery occlusion, coronary artery disease

Introduction

Cardiovascular disease (CVD), and notably coronary artery disease (CAD), remains the leading cause of mortality in industrialized countries. Endothelial dysfunction is one of the earliest vascular manifestations of CVD [1]. Actually, the endothelium plays an important role in the maintenance of vascular structure, control of vascular tonus, homeostasis, and inflammation. Thus, functional

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Received: 26.06.2017 Accepted: 19.07.2017

and structural integrity of the endothelium is essential for preventing the initiation and progression of atherosclerosis [2].

As previously mentioned, endothelium-derived mediators play an essential role in vascular homeostasis. Among them, nitric oxide (NO) a potent endogenous vasodilator which is released in response to shear stress. Therefore, NO is mainly responsible for flow-mediated dilatation (FMD). Additionally, NO inhibits platelet aggregation and controls processes of vascular inflammation. The endogenous competitive inhibitor of NO synthase, asymmetric dimethylarginine (ADMA), has been shown to decrease both the production and bioavailability of NO. Therefore, elevated plasma concentrations of ADMA have been considered to be an indicator of endothelial dysfunction and a risk factor for CVD [3].

There is a large body of evidence that endothelin-1 (ET-1) plays a crucial role in vascular inflammation and subsequent atherosclerosis progression. Additionally, ET-1 is a potent vasoconstrictor and mitogen produced in response to hypoxia and vessel wall stress. It is known to play an important role in endothelial dysfunction. Of note, elevated plasma levels of ET-1 have been reported in wide range of cardiovascular disorders [4].

Taken together, accumulating evidence suggests that endothelial control of vascular tonus is mainly regulated by NO and ET-1, which antagonize the effects of each other. Both mediators are released in response to shear-stress and influence endothelium-dependent vasodilatation [5].

Most studies have focused on assessment of endothelial function in conduit arteries using the FMD technique. However, microvascular dysfunction may precede endothelial impairment in large arteries and clinical manifestations. Conventionally, microvascular endothelial function can be studied using non-invasive laser Doppler techniques or more recent laser speckle contrast imaging coupled with brachial artery occlusion. Such an approach enables the assessment of endothelium-dependent hyperemic response [6]. On the other hand, it does not provide information regarding the vascular and tissue response which occur during ischemia.

Currently however, it is possible to assess the changes in tissue biochemistry in vivo using the measurements of reduced form of nicotinamide adenine dinucleotide (NADH) fluorescence signal intensity. Of note, NADH fluorescence has been used in vitro as a test for mitochondrial function [7]. Additionally, it has been proven that the decrease in oxyhemoglobin levels during arterial occlusion is associated with an increase in NADH fluorescence in human epidermal cells. Indeed, the epidermis is particularly sensitive to hypoxia [8]. The newly-developed flow mediated skin fluorescence (FMSF) device enables measurement of the changes in cutaneous NADH fluorescence over time in response to brachial artery occlusion. In addition to endothelium-dependent hyperemic response, FMSF allows the assessment of ischemic response which may reflect tissue sensitivity to hypoxia [9].

It has recently been shown that the inter-day reproducibility of the newly-developed FMSF device is excellent both in healthy volunteers and CAD patients. Moreover, it was demonstrated that both ischemic and hyperemic response differentiated between healthy subjects and patients with CAD suggesting microvascular dysfunction in those patients [10]. Therefore, given its relatively low cost and ease of use, FMSF seems a promising tool for the assessment of microvascular endothelial function in CVDs.

Thus, the aim of this pilot study was to investigate the relationship between FMSF parameters and two established plasma endothelial biomarkers ADMA and ET-1. Additionally, the aim in this research was to assess the repeatability and agreement for repeated measurements by FMSF device.

Methods

Study population

This study enrolled 28 consecutive patients with stable CAD recruited from the cardiology outpatient clinic. All participants were over 18 years of age and were included between November 2016 and May 2017. The diagnosis of CAD was based on European Society of Cardiology guidelines [11] and angiographically confirmed (> 50% stenosis at least in 1 major artery based on coronary angiography). This study included patients with a history of acute coronary syndrome or with prior percutaneous coronary intervention. All participants had remained in stable condition for at least 3 months prior to inclusion to the study and no alterations of pharmacotherapy had been introduced over that period. Patients with cancer, history of substance abuse and/or with respiratory, kidney or hepatic failure were excluded from the study.

The study conforms to the principles outlined in the Declaration of Helsinki. The study protocol was approved in June 2016 by the Independent Ethics Committee at the Medical University of Gdansk (IRB no. 667). All subjects gave written informed consent prior to participation.

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Study design

This was an open-label, single-center study. Blood samples for biochemical measurements were collected in the morning, prior to microvascular function assessment. Subjects were placed in a temperature-controlled room (24 ± 1°C). After a 15-min acclimatization period, baseline NADH fluorescence intensity was recorded for 3 min on the forearm. Then, blood flow in the brachial artery was occluded for 3 min by inflating a cuff placed on the left upper arm to 50 mm Hg above systolic blood pressure. During the occlusion period, the NADH fluorescence was continuously measured in the same area of the forearm. The cuff was then released and the decrease in fluorescence was recorded until return to baseline values.

FMSF measurements

Flow mediated skin fluorescence is a noninvasive optical technique to study microcirculation based on measurements of skin fluorescence intensity. FMSF was quantified using AngioTester (SN-2016-009M, Angionica, Lodz, Poland).

Excitation of the forearm with ultraviolet (UV) light at 340 nm results in the emission of a NADH fluorescence signal from the skin tissue cells. The level of NADH fluorescence corresponds to the balance of mitochondrial oxidation-reduction processes occurring in the tissue, reflected by the balance between the oxidized form of the coenzyme (NAD^+) and its reduced form (NADH). Indeed, NADH fluorescence is the strongest component of the fluorescence emitted from human skin. The intensity of the signal also changes as a function of time in response to blockage and release of blood flow in the brachial artery. The emitted fluorescence light of NADH at 460 nm is detected by receiver diode and corresponds to the activity of microcirculation [9].

The maximal penetration of the exciting light (340 nm) is about 0.3 to 0.5 mm, but over 90% of the NADH excitation occurs at a depth of 0.1 mm. Therefore, a substantial fraction of the exciting light is absorbed by the epidermidis. To allow for this, in FMSF, the diameter of the probe (detection window) is relatively large, 20 mm, which gives approximately 100 mm^3 volume of the investigated tissue [9].

Technical description of FMSF device

The FMSF device consists of three main parts: a light source, system of filters, and detector. The UV diode emits light at 340 nm wavelength and a small amount of blue light to show that the diode is working (Marktech Optoelectronics MTE340H21-UV, Peak Wavelength 340 nm, Spectral Line Half Width 9 nm). Blue light is cut through the band pass filter (Hoya U340) which allows the transmission of only UV light at 340 nm and blocks the visible light. Then the light beam passes through a quartz window, which has excellent transmission to the skin (over 90%).

The emitted fluorescence light of NADH at 460 nm is detected by the receiver diode (OSI Optoelectronics UV-035EQ). There are 2 filters in front of the detector which block the possibility of reaching the UV detector reflected from the hand or measuring head components. The first filter is made of material Thermoset ADC (CR-39®, Edmund Optics), the second is an interference 460 nm filter (Full Width-Half Max FWHM 10 nm, Minimum Transmission [%] > 50, Edmund Optics).

Biochemical measurements of ADMA and ET-1

Blood samples for the specified biomarkers were collected on the day of FMSF examination between 8 a.m. and 10 a.m., after at least 8 h of fasting. Plasma was obtained and stored at –70°C until assaying. Both markers were measured with an enzyme-linked immunosorbent assay (ELISA) according to manufacturer instructions. ELISA kit for measurement of ADMA was purchased from BioVendor (Brno, Czech Republic), while ET-1 concentration was determined using ELISA kit from Phoenix Pharmaceuticals Inc. (Burlingame, CA, USA).

Data analysis

Data were digitized, stored on a computer, and analyzed off-line with signal processing software (AngioTester Software, Angionica, Lodz, Poland). Two different parameters were measured: the ischemic response (IR_{max}) defined as the ratio (in %) relative to baseline (before occlusion) maximal increase in NADH fluorescence intensity observed during cuff occlusion and the hyperemic response (HR_{max}) expressed (in %) as relative to baseline (after occlusion) maximal decrease in NADH fluorescence intensity after cuff release (Fig. 1).

Statistical analysis

Quantitative data are expressed as the mean and standard deviation. The Pearson correlation test was used to assess the relationship between FMSF variables and endothelial biochemical markers. To evaluate the reliability of repeated measurements, intraclass correlation coefficients (ICC) were calculated and the Bland-Altman plots were applied. ICC values of < 0.40, 0.40–0.75 and

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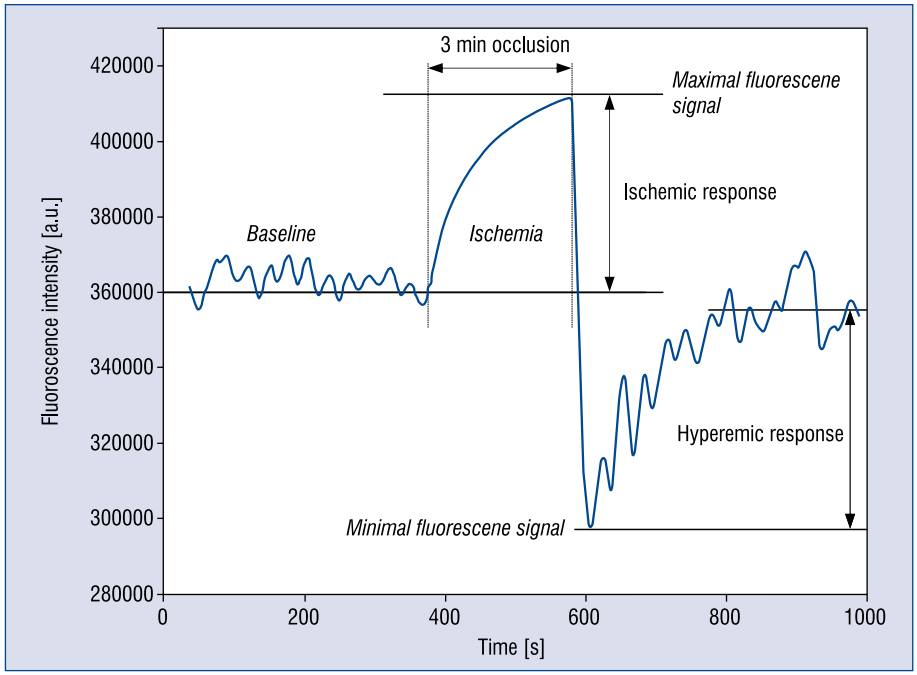

Figure 1. The exemplary image of NADH fluorescence trace in response to blockage and release of blood flow in the brachial artery. The ischemic response (IR_{max}) is relative to baseline maximal increase in NADH fluorescence intensity observed during cuff occlusion and the hyperemic response (HR_{max}) is relative to maximal decrease in NADH fluorescence intensity after cuff release.

> 0.75 represent poor, fair to good and excellent agreement, respectively. Differences between mean values in independent groups were examined by parametric Welch t-test and complemented by nonparametric Mann-Whitney U test. Normality assumption of data set was checked by the Shapiro-Wilk test. A p-value of < 0.05 was considered statistically significant. All statistical analyses were performed using Statistica version 12.0 (StatSoft, Tulsa, OK, USA).

Results

Patients characteristics

In this pilot study, stable CAD patients were enrolled. The demographic and clinical characteristics of the study group are summarized in Table 1. All participants completed the protocol.

Plasma biomarkers and FMSF parameters

Mean plasma levels of ET-1 and ADMA were 0.3 ± 0.1 ng/mL, and 0.64 ± 0.1 μmol/L, respectively. Mean values of IR_{max} and HR_{max} were 8.2 ± ± 4.6 and 11.8 ± 5.0, respectively. In a subset of patients with left ventricular (LV) dysfunction when compared to patients with preserved LV function, a trend was noted for lower IR_{max} (6.6 ± 3.2 vs. 9.6 ± ± 5.2, respectively, p = 0.075) and reduced HR_{max} (10.9 ± 6.3 vs. 12.5 ± 3.4, respectively, p = 0.181).

Table 1. Clinical characteristics of coronary artery disease patients (n = 28).

Male/female [n/n]	20/8
Age [years]	64.4 ± 7.5
Body mass index [kg/m^2]	28.5 ± 4.8
Systolic blood pressure [mm Hg]	141.3 ± 16.8
Diastolic blood pressure [mm Hg]	80.4 ± 9.9
Pulse wave velocity [m/s]	9.3 ± 2.2
Heart rate [bpm]	66.3 ± 7.4
Hypertension	25 (90%)
Diabetes mellitus	15 (53%)
Chronic heart failure	13 (47%)
Left ventricular ejection fraction [%]	51.7 ± 9.7
B-type natriuretic peptide [pg/mL]	106.7 ± 188.1
Creatinine [mg/dL]	0.98 ± 0.2
Total cholesterol [mg/dL]	157 ± 32
LDL cholesterol [mg/dL]	88 ± 28
HDL cholesterol [mg/dL]	46 ± 10

HDL — high density lipoprotein; LDL — low density lipoprotein

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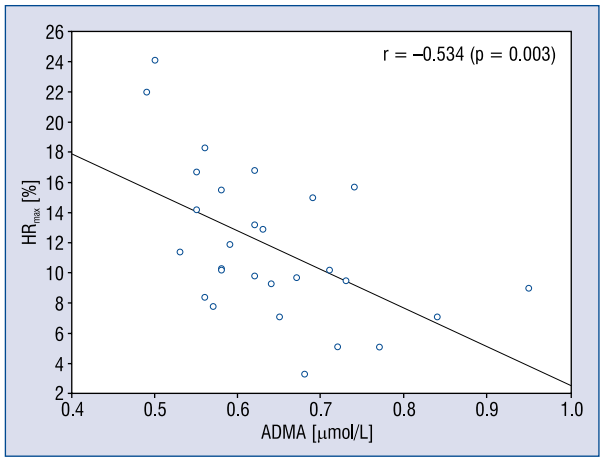

Figure 2. Correlation analysis between asymmetric dimethylarginine (ADMA) plasma levels and hyperemic response (HR_{max}) in coronary artery disease subjects.

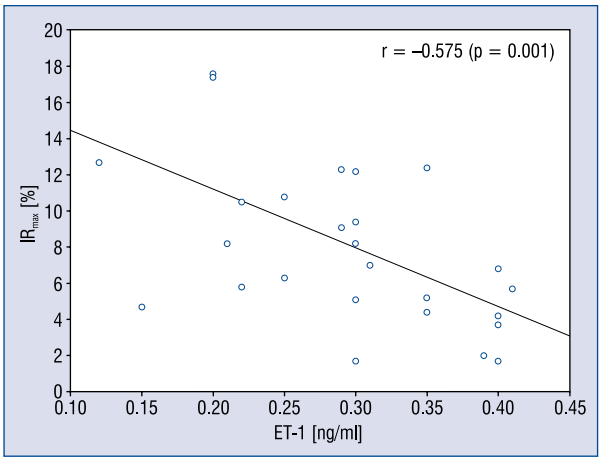

Figure 3. Correlation analysis between endothelin-1 (ET-1) plasma levels and ischemic response (IR_{max}) in coronary artery disease subjects.

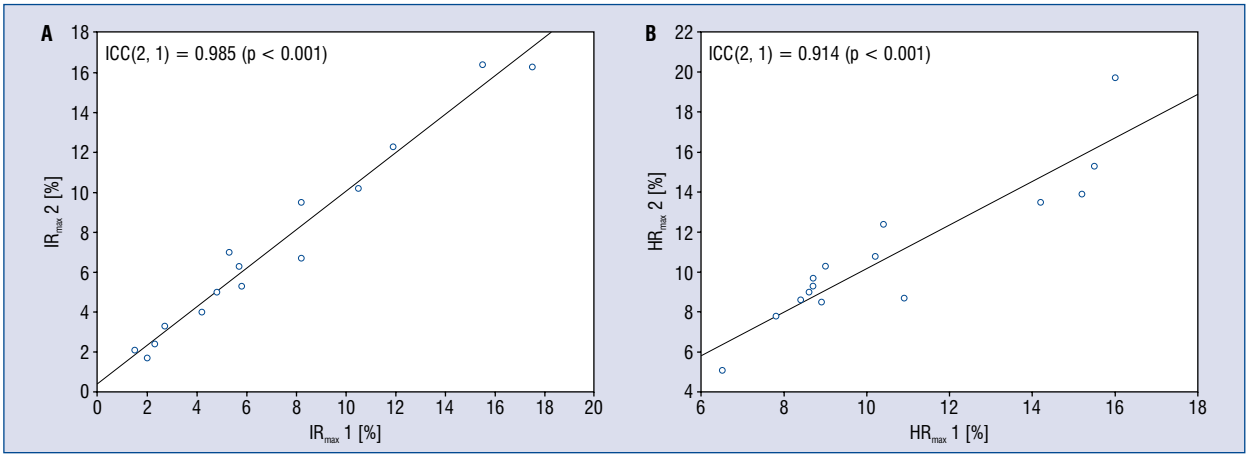

Figure 4. Repeatability of ischemic response (IR_{max}) and hyperemic response (HR_{max}). Correlation analysis across consecutive measurements of IR_{max} (**A**) and HR_{max} (**B**). The intraclass correlation coefficient (ICC) was slightly better for IR_{max} than HR_{max}.

Similar trends were noted in the diabetic vs. non-diabetic patients for lower IR_{max} (7.1 ± 4.9 vs. 9.5 vs. 3.8, respectively, p = 0.087) and for reduced HR_{max} (10.3 ± 4.3 vs. 13.5 ± 5.2, respectively, p < 0.05). In patients with LV dysfunction and diabetes, as compared with diabetic CAD patients with preserved LV function, both IR_{max} (4.2 ± 1.7 vs. 8.6 ± 3.5, respectively, p < 0.05) and HR_{max} (5.6 ± 1.7 vs. 12.6 ± 3.1, respectively, p < 0.001) were markedly reduced.

Correlation analyses

As shown in Figure 2, in CAD patients, a significant inverse correlation between plasma ADMA levels and hyperemic response was observed (r = –0.534, p = 0.003). In contrast, no such relationships were found for ADMA concentrations and ischemic response (r = 0.028, p = 0.889). Furthermore, ET-1 levels were strongly and inversely associated with the ischemic response (r = –0.575, p = 0.001) (Fig. 3). Whereas, no correlation was observed between ET-1 and hyperemic response (r = 0.048, p = 0.810).

Repeatability of FMSF measurements

As presented in the Figure 4A and 4B, the intraclass correlation coefficient for repeated measurements was 0.985 for IR_{max} (p < 0.001) and for HR_{max} was 0.914 (p < 0.001). Bland and Altman plots for repeated IR_{max} and HR_{max} measurements

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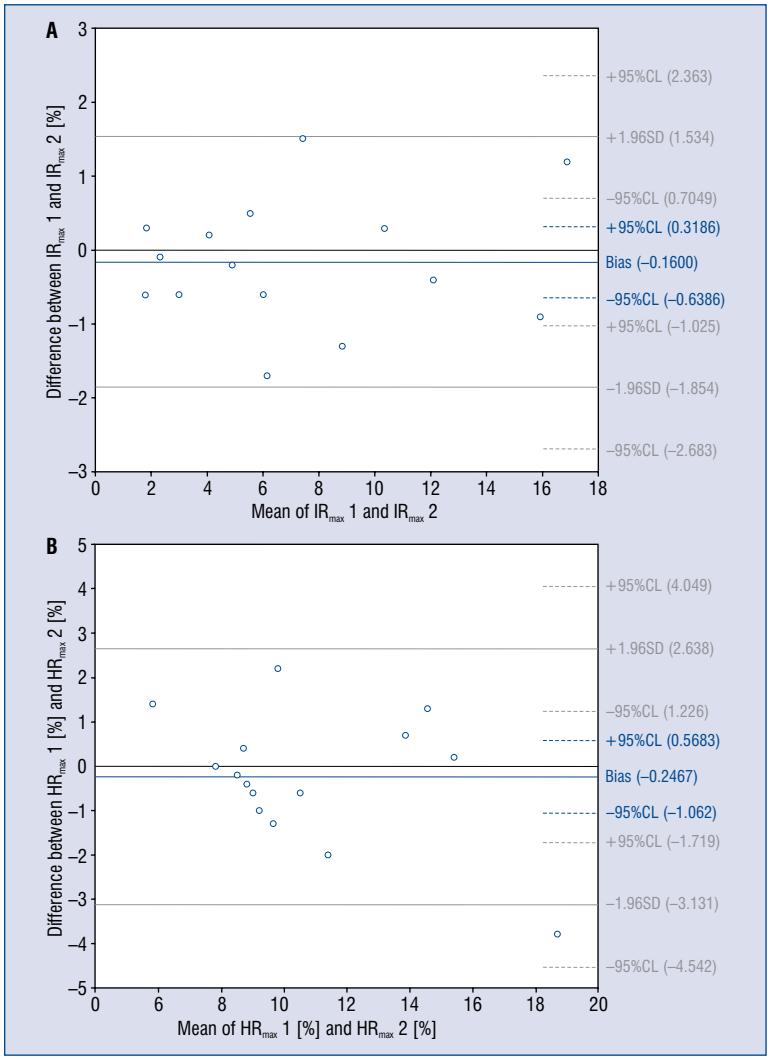

Figure 5. Bland and Altman plots for consecutive measurements of ischemic response (IR_{max}) (**A**) and hyperemic response (HR_{max}) (**B**). Both variables IR_{max} and HR_{max} showed a good agreement for repeated measurements; CL — confidence limits; SD — standard deviation.

are presented in Figure 5. Although, both variables IR_{max} and HR_{max} showed a good agreement for repeated measurements, the bias (–0.1600) and limits of agreement (–1.854; 1.534) for repeated IR_{max} (Fig. 5A) were slightly better than the bias (–0.2467) and limits of agreement (–3.131; 2.638) for repeated HR_{max} (Fig. 5B).

Discussion

The key finding of this pilot study is that both FMSF indices, IR_{max} and HR_{max}, significantly inversely correlated with ET-1 and ADMA, respectively. ADMA, the endogenous inhibitor of NO synthase, is inversely related to hyperemic response measured by FMSF. As an endothelium-derived NO is released in response to the increase of sheer stress, an important regulator of FMD. In the current study, CAD patients with high ADMA plasma levels presented low values of hyperemic response, which is most likely due to the reduced NO bioavailability. Such data are consistent with a previously published report which showed that elevated ADMA levels are associated with impaired hyperemic response in essential hypertension [12]. Similarly, in another study using FMD, endothelium-dependent vasodilatation was inversely related to ADMA concentrations in patients with hypercholesterolemia [13]. Indeed, a large body of evidence suggests ADMA to be associated with endothelial dysfunction. Additionally, an elevated plasma level of ADMA may predict adverse cardiovascular events in patients with CAD and chronic heart failure [14].

Additionally, this pilot study showed, for the first time, that plasma ET-1 levels were strongly and inversely associated with the ischemic re-

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sponse as measured by the novel FMSF device. With the FMSF technique, lack of oxygen during arterial occlusion is associated with an increase in NADH fluorescence intensity. Indeed, NADH is a major mitochondrial component which plays a key role in cellular energy metabolism [8]. Therefore, the measurement of ischemic response provides insight into mitochondrial function, and its amplitude may reflect tissue sensitivity to hypoxia. Importantly, accumulating evidence suggests that mitochondria are probably the most important sensors of oxygen level in the cells. Therefore, mitochondrial dysfunction may lead to a decrease in the oxygen consumption rate. In line with the present results, it has been previously shown in an animal model that mitochondrial dysfunction increases expression of ET-1 [15].

Additionally, there is compelling evidence for a link between the pathogenesis of CVD and increased mitochondrial dysfunction [16]. Therefore, the possibility of monitoring the oxygen-dependent processes in the mitochondria is crucial in understanding the pathophysiology of CVDs such as CAD [17]. In the presented pilot study, mitochondrial function was evaluated *in vivo* in humans by measuring an ischemic response via NADH fluorescence recording. It was shown that CAD patients with high ET-1 plasma levels presented low values of ischemic response suggesting their low sensitivity to intermittent hypoxia. It has been reported that plasma levels of ET-1 are elevated in patients with atherosclerosis. Indeed, ET-1 is a potent vasoconstrictor produced in response to hypoxia and high levels of ET-1 which have been also been associated with microvascular dysfunction [4]. Additionally, it was demonstrated that active vasoconstriction of large arteries during reduced blood flow is mediated by endothelin receptor activation and can exacerbate ischemia [5]. Thus, in patients with CAD immediate response to hypoxia seems blunted, which results in limited increase of NADH fluorescence intensity leading to lower ischemic response in FMSF examination.

While analyzing these preliminary results, it should be noticed that there are several important factors which could influence FMSF ischemic and hyperemic responses. In this pilot study, a trend was found towards reduced IR_{max} and HR_{max} parameters in type 2 diabetes compared to those without diabetes. Furthermore, the IR_{max} and HR_{max} parameters were also blunted in CAD patients with LV dysfunction compared to CAD patients with preserved LV function. Moreover, the IR_{max} and HR_{max} were markedly reduced in individuals with LV dysfunction combined with diabetes suggesting that microvascular endothelial function is impaired due to advanced diseases and comorbidities known to affect the endothelium.

Lastly, as FSMF device is a new measurement tool, its performance was also evaluated. As previously demonstrated, the inter-day reproducibility of the FMSF device is excellent [10]. In this study, an assessment was made of inter-observer agreement using the same device in the same subject under identical conditions. Using Bland and Altman plots, it was shown that both ischemic and hyperemic responses presented high concordance for repeated measurements, with slightly better agreement for ischemic response. Similarly, the ICC values suggested slightly better inter-observer agreement for ischemic response than hyperemic response values.

As FMSF technique is noninvasive, reproducibility is easy to perform and can be particularly useful in clinical trials on endothelial function. It may also be a promising tool for the evaluation of novel cardiovascular drugs.

Limitations of the study

This study has several limitations. First, the study group was relatively small, but sufficient from a statistical point of view for reaching the conclusions. Thus, further research with larger sample sizes is strongly needed. Secondly, results were not confirmed by any other technique measuring microvascular endothelial function. While all microvascular techniques quantify blood flow, the FMSF device, according to available literature, is the first method to measure metabolic changes which directly depend on local perfusion. Further mechanistic studies are needed to explain the regulation mechanisms of these changes.

Conclusions

In conclusion, this pilot study demonstrated that in patients with CAD, NADH fluorescence measured by the FMSF device is associated with established plasma endothelial markers and that both ischemic and hyperemic response were blunted in patients with advanced disease and diabetes. This suggests that FMSF is a useful tool for the assessment of endothelial function. Furthermore, FMSF device showed excellent repeatability and good agreement for repeated measurements. However, further study is warranted to confirm these results in a larger patient cohort.

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Acknowledgements

This work was supported by the European Union from the resources of the European Regional Development Fund under the Smart Growth Operational Program, Grant No. POIR.01.01.01-00-0540/15. Dr. Marcin Hellmann received a scientific scholarship from the Polish Ministry of Science and Higher Education for the years 2016–2019.

Conflict of interest: None declared

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