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Joanna Sikora[1, 2], Michał Cyrankiewicz[3], Tomasz Wybranowski[3], Blanka Ziomkowska[3], Michał Kasprzak[1], Magdalena Krintus[4], Grażyna Odrowąż-Sypniewska[4], Beata Augustyńska[2], Stefan Kruszewski[3], Jacek Kubica[1]

[1]Department of Cardiology and Internal Medicine
[2]Department of Biochemistry
[3]Department of Biophysics
[4]Department of Laboratory Medicine
Nicolaus Copernicus University, Collegium Medicum in Bydgoszcz, Poland

Fluorescence lifetime of collagen degradation products in plasma of patients with left ventricular remodeling

Corresponding author:

Joanna Sikora
Department of Cardiology
and Internal Medicine
Nicolaus Copernicus University,
Collegium Medicum
Skłodowskiej-Curie Street No. 9
85–094 Bydgoszcz, Poland
Phone: +48 525 854 023
E-mail: joanna.sikora@cm.umk.pl

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ABSTRACT

Background. The concentration of collagen degradation products in plasma may reflect the process of left ventricular remodeling in patients after acute myocardial infarction. The aim of this study was to confirm that mean fluorescence lifetime of plasma is decreased in patients with left ventricular systolic dysfunction.

Patients, materials and methods. The study group consisted of patients treated with primary percutaneous coronary intervention for acute myocardial infarction admitted to the Department of Cardiology and Internal Medicine at the University Hospital in Bydgoszcz. The overall group comprised of 65 patients. From each patient 8 mL of blood was taken to obtain plasma that was used for further examination. The time-resolved spectrometer Life Spec II with the sub-nanosecond pulsed 360 nm EPLED® diode was used in order to measure fluorescence lifetime of samples.

Results. Significant differences were observed in mean fluorescence lifetime of plasma between groups of patients divided according to brain natriuretic peptide levels. Statistical analysis showed that the increase in brain natriuretic peptide level is an independent factor resulting in the decrease in mean fluorescence lifetime.

Conclusions. It seems that plasma concentration of collagen degradation products is closely related to brain natriuretic peptide level. However, this experiment confirmed that plasma of patients with potential high probability of developing left ventricular remodeling is characterized by the decrease in mean fluorescence lifetime.

Key words: left ventricular remodeling, collagen degradation products, fluorescence

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Introduction

The improved effectiveness of reperfusion therapy with percutaneous coronary intervention (PCI) or thrombolysis in individuals with acute myocardial infarction (MI) resulted in short-term mortality reduction. This, however, leads to increased prevalence of patients with left ventricular systolic dysfunction (LVSD) and/or heart failure (HF) due to left ventricular remodeling (LVR) in the long-term follow-up [1, 2]. The mortality and morbidity in patients with LVSD and/or HF after MI is high [3–5]. To implement preventive treatment, it is of supreme importance to distinguish patients with increased risk of LVSD and HF development.

Degradation of cardiac collagen and its re-synthesis plays an essential role in remodeling of the left ventricle following MI and in the consecutive development of HF. Therefore, markers of collagen turnover are tested as biomarkers to determine the ongoing heart remodeling [6]. Zannad et al. [7] reported that high serum level of procollagen type III amino-terminal propeptide in patients with HF was associated with poor outcome. On the other hand, the benefit from spironolactone was associated with higher levels of collagen synthesis markers.

Fluorescence spectroscopy is an important and widely used technique in physical sciences. Fluorescence lifetime (FLT) can be sensitive to a great variety

of internal factors defined by the fluorophore structure and external factors. A combination of environmental sensitivity and parametric independence renders FLT as a separate yet complementary method to traditional fluorescence intensity measurements [8]. The time resolution can be obtained with time-correlated single photon counting (TCSPC) [9] which consists in the idea that the distribution for emission of a single photon after an excitation event yields the actual intensity of all the photons emitted as the result of excitation [10].

According to the results of our previous unpublished *in vitro* study, the increase inplasma concentration of type III collagen degradation products (CDPs) resulted in the decrease in mean FLT (mFLT) of plasma. The aim of this study was to confirm our findings *in vivo* assessing mFLT of plasma in patients with LVSD.

Materials and methods

Study group

The study population consisted of 65 consecutive patients treated with primary PCI for acute MI, admitted to the Department of Cardiology and Internal Medicine at the University Hospital No. 1 in Bydgoszcz. Each patient received a thorough information regarding the study and gave a written consent. Study population characteristics are displayed in Table 1. The study protocol has been approved by the Ethical Committee of Nicolaus Copernicus University. Blood samples (8 mL) for time resolved fluorescence spectroscopy (TRFS) examination were taken three days after admission at 8.00 a.m. An additional blood sample was sent to Diagnostic Laboratory in the University Hospital No. 1 in Bydgoszcz where plasma concentration of brain natriuretic peptide (BNP) was measured on Architect *ci*8200 analyzer (Abbott Diagnostics, Wiesbaden, Germany). Other laboratory parameters were assayed using standardized tests. A standard echocardiography measurement was performed in all patients. Patients were divided into two groups according to qualifications based on echocardiography results and plasma concentrations of BNP. These two criteria were applied separately (Tab. 1).

Time-resolved fluorescence spectroscopy

The time-resolved spectrofluorimeter Life Spec II (Edinburgh Instruments Ltd, United Kingdom) with the sub-nanosecond pulsed EPLED® diode emitting light of the wavelength λ = 360 nm was used in order to measure FLT of samples. The spectrofluorimeter was equipped with electronically cooled photomultiplier Hamamatsu R928 connected with TCC900 PC Card, which incorporates all the electronic modules required for TCSPC. The measurements were carried out with the use of quartz 3.5 × 10 mm cuvettes at room temperature. Exposure time of samples amounted to 300 seconds. Collagen was excited by light of the wavelength λ = 360 nm, showing strong emission at λ = 450 nm. Measurements at this excitation wavelength allow the decrease in the contribution of different components, especially tryptophan-rich proteins, which have the maximum absorption at λ = 270–290 nm [11].

Statistical analysis

The preliminary step of the analysis was the Shapiro-Wilk test of normality of the distribution of all measured parameters inside each patient group selected according to the specified criteria. Due to the non-normality of the most analysed variables, the Mann-Whitney-Wilcoxon (MWW) unpaired rank sum tests were used for the comparisons between two groups. Therefore, if the variables were normally distributed, p-values achieved in Student's t-test were given. The dependence between mFLT and clinical characteristics of patients was determined by Spearman's rank correlation coefficients (ρ values). Categorical variables were expressed as a number of patients presenting the given feature in the analysed group, including mFLT of plasma, gel electrophoresis of proteins results, lipid profile, echocardiography results and biochemical parameters. Differences were considered as significant at $p < 0.05$. P values between 0.05 and 0.10 were considered as a trend towards significance. In order to establish independent factors which have an influence on the mFLT of plasma, the analysis of multiple regression was obtained. The statistical analysis was carried out using the MATLAB® tools and confirmed with the use of other statistical packages (Statistica®, SPSS®).

Results

We applied the TRFS method in search of the characteristic plasma fluorescence resulting in the combination of plasma proteins (including products of collagen degradation) specific for heart dysfunction defined on the basis of left ventricular ejection fraction (LVEF) assessed by echocardiography or plasma concentration of BNP in patients hospitalized for acute MI (Tab. 1). The analysis showed that BNP concentrations were significantly higher in patients with lower LVEF. As one could expect, patients grouped according to the LVEF exhibit significant differences in other (but not all) echocardiographic parameters. However, a statistically important difference among the mean triglycerides concentrations was also observed. It is interesting that higher triglyceride levels occurred in patients with LVEF > 40%. On the other hand, when concentration of BNP was applied as a grouping criterion, significant differences were found in left ventricular end-diastolic

Table 1. Clinical characteristics of the study population divided into groups according to EF and BNP

	LVEF > 40%			LVEF ≤ 40%			p	BNP < 200 pg/mL			BNP ≥ 200 pg/mL			p
	N	M	p (SW)	N	M	p (SW)		N	M	p (SW)	N	M	p (SW)	
Albumin [g/dL]	41	3.68	0.004	23	3.55	0.585	0.127	34	3.86	0.678	30	3.38	0.038	0.000
α1 glob [g/dL]	41	0.34	0.000	23	0.33	0.221	0.806	34	0.31	0.263	30	0.36	0.000	0.027
α2 glob [g/dL]	41	0.78	0.471	23	0.79	0.001	0.850	34	0.79	0.000	30	0.78	0.798	0.623
β1 glob [g/dL]	41	0.42	0.030	23	0.41	0.059	0.556	34	0.43	0.112	30	0.40	0.032	0.057
β2 glob [g/dL]	41	0.38	0.000	23	0.37	0.835	0.769	34	0.38	0.000	30	0.37	0.854	0.920
γ glob [g/dL]	41	0.95	0.000	23	1.07	0.002	0.081	34	0.97	0.129	30	1.02	0.000	0.861
Total protein [g/dL]	41	6.55	0.203	23	6.53	0.793	0.899*	34	6.74	0.249	30	6.32	0.078	0.012*
BNP [pg/mL]	41	263.78	0.000	23	1268.23	0.000	0.017	34	85.36	0.575	30	1236.06	0.000	0.000
CK MB [U/L]	11	23.91	0.001	12	23.58	0.565	1.000	12	22.42	0.001	11	25.18	0.702	0.478
CK [U/L]	32	140.72	0.000	14	172.79	0.002	0.659	25	137.00	0.000	21	166.52	0.002	0.467
CRP [mg/L]	41	24.03	0.000	23	30.10	0.000	0.433	34	19.46	0.000	30	33.86	0.000	0.019
Ttrop I [ng/mL]	41	3.31	0.000	23	4.97	0.000	0.900	34	3.49	0.000	30	4.38	0.000	0.276
LVESd [mm]	24	34.54	0.314	13	46.77	0.184	0.000*	18	37.11	0.156	18	40.67	0.126	0.259*
LVEDd [mm]	38	47.03	0.406	21	55.62	0.620	0.000*	30	47.83	0.087	28	52.32	0.875	0.024*
LA [mm]	40	40.23	0.283	21	43.10	0.837	0.036*	31	40.94	0.451	29	41.66	0.605	0.590*
Aorta [mm]	38	32.53	0.645	20	34.40	0.233	0.027*	29	32.86	0.624	28	33.43	0.335	0.496*
RVEDd [mm]	36	26.08	0.221	21	27.86	0.012	0.215	28	25.96	0.814	28	27.61	0.005	0.276
IVSd [mm]	38	12.55	0.012	21	12.81	0.047	0.723	30	12.43	0.005	28	12.86	0.168	0.306
PWd [mm]	38	11.66	0.009	21	11.76	0.087	0.581	30	11.67	0.012	28	11.71	0.026	0.673
LVMI [g/m2]	22	134.46	0.345	11	166.64	0.731	0.012*	24	139.46	0.254	9	160.44	0.562	0.134*
LVM [g]	31	250.36	0.847	17	347.35	0.779	0.000*	28	267.32	0.443	19	307.16	0.328	0.115*
LVEF (%)	41	47.88	0.000	22	31.68	0.024	0.000	33	44.52	0.030	29	39.34	0.299	0.071
TC [mg/dL]	35	197.63	0.120	17	185.06	0.974	0.520*	27	209.59	0.059	25	176.16	0.542	0.090
HDL-C [mg/dL]	35	45.00	0.525	17	45.59	0.776	0.875*	27	44.81	0.006	25	45.60	0.813	0.389
LDL-C [mg/dL]	29	116.41	0.090	17	122.00	0.335	0.918	22	132.86	0.281	24	105.29	0.136	0.080*
TG [mg/dL]	34	136.44	0.000	16	86.63	0.033	0.027	25	140.68	0.000	25	100.32	0.096	0.273
Age	42	67.50	0.844	23	69.22	0.136	0.564*	34	65.26	0.922	30	71.60	0.034	0.009

*Student's t-test was applied, because of the normal distribution

α1 glob — α1 globulins; α2 glob — α2 globulins; β1 glob — β1 globulins; β2 glob — β2 globulins; γ glob — γ globulins; BNP — brain natriuretic peptide; CK MB — creatine kinase MB isoform; CK — creatine kinase; CRP — C-reactive protein; Trop I — troponin I; BMI — body mass index; BSA — body surface area; LVESd — left ventricular end-systolic diameter; LVEDd — left ventricular end-diastolic diameter; LA — left atrium; RVEDd — right ventricular end-diastolic diameter; IVSd — intraventricular septum diastolic diameter; PWd — posterior wall diastolic diameter; LVMI — left ventricular mass index; LVM — left ventricular mass; LVEF — left ventricle ejection fraction; TC — total cholesterol; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; TG — triglycerides; N — number of results included in the measurements; M — mediana; p(SW) — results from Shapiro-Wilk test

Table 2. Mean FLT in patients divided into groups according to EF and BNP

	LVEF > 40%			LVEF ≤ 40%			p	BNP < 200 pg/mL			BNP ≥ 200 pg/mL			p
	N	M	p (SW)	N	M	p (SW)		N	M	p (SW)	N	M	P (SW)	
Mean FLT [ns]	42	6.78	0.003	23	6.43	0.832	0.071	34	6.85	0.012	30	6.46	0.252	0.091
Mean FLT (diluted) [ns]	42	7.31	0.009	23	6.97	0.200	0.300	34	7.40	0.001	30	6.98	0.915	0.031

*=Student's t-test was applied. because of the normal distribution

Mean FLT — mean fluorescence lifetime of plasma; mean FLT (diluted — mean fluorescence lifetime of diluted plasma (2:50); BNP — brain natriuretic peptide; LVEF — left ventricle ejection fraction; N — number of results included in the measurements; M —mediana; p(SW) — results from Shapiro-Wilk test

diameters (LVEDd) and plasma concentrations of albumin, α1 globulin, total protein and C-reactive protein (CRP).

Patients with lower LVEF as well as those with higher concentration of BNP were characterized with a tendency to have shorter plasma mFLT. A statistically important difference was obtained for diluted plasma and BNP level taken as a discriminating variable (Tab. 2).

Table 3. Correlations between mean FLT of plasma and clinical parameters

Clinical parameters	Mean FLT [ns]	Mean FLT (diluted) [ns]
Albumin [g/dL]	p = 0.387 p = 0.002	p = 0.319 p = 0.010
α1 glob [g/dL]	p = –0.185 p = 0.144	p = –0.161 p = 0.205
α2 glob [g/dL]	p = 0.210 p = 0.096	p = 0.226 p = 0.073
β1 glob [g/dL]	p = 0.363 p = 0.003	p = 0.297 p = 0.017
β2 glob [g/dL]	p = –0.096 p = 0.439	p = –0.139 p = 0.275
γ glob [g/dL]	p = –0.136 p = 0.284	p = –0.176 p = 0.165
Total protein [g/dL]	p = 0.231 p = 0.067	p = 0.181 p = 0.153
BNP [pg/mL]	p = –0.406 p = 0.001	p = –0.376 p = 0.002
CK MB [U/L]	p = –0.257 p = 0.237	p = –0.119 p = 0.587
CK [U/L]	p = 0.177 p = 0.239	p = 0.157 p = 0.299
CRP [mg/L]	p = –0.274 p = 0.029	p = –0.185 p = 0.145
Trop I [ng/mL]	p = 0.121 p = 0.341	p = 0.183 p = 0.147
LVESd [mm]	p = –0.199 p = 0.212	p = –0.206 p = 0.195
LVEDd [mm]	p = –0.160 p = 0.211	p = –0.186 p = 0.145
RVEDd [mm]	p = –0.215 p = 0.095	p = –0.149 p = 0.251
IVSd [mm]	p = 0.132 p = 0.302	p = 0.236 p = 0.062
PWd [mm]	p = 0.031 p = 0.808	p = 0.157 p = 0.219
LVMI [g/m^2]	p = –0.066 p = 0.707	p = –0.130 p = 0.455
LVM [g]	p = –0.47 p = 0.742	p = –0.004 p = 0.977
LVEF (%)	p = 0.327 p = 0.007	p = 0.261 p = 0.033
TC [mg/dL]	p = 0.404 p = 0.003	p = 0.425 p = 0.002
HDL-C [mg/dL]	p = –0.009 p = 0.952	p = –0.035 p = 0.805
LDL-C [mg/dL]	p = 0.303 p = 0.040	p = 0.353 p = 0.016
TG [mg/dL]	p = 0.392 p = 0.005	p = 0.313 p = 0.027

Mean FLT — mean fluorescence lifetime of plasma; mean FLT (diluted) — mean fluorescence lifetime of diluted plasma (2:50); α1 glob — α1 globulins; α2 glob — α2 globulins; β1 glob — β1 globulins; β2 glob — β2 globulins; γ glob — γ globulins; BNP — brain natriuretic peptide; CK MB — creatine kinase MB isoform; CK — creatine kinase; CRP — C-reactive protein; trop I — troponin I; LVESd — left ventricular end-systolic diameter; LVEDd — left ventricular end-diastolic diameter; LA — left atrium; RVEDd — right ventricular end-diastolic diameter; IVSd — intraventricular septum diastolic diameter; PWd — posterior wall diastolic diameter; LVMI — left ventricular mass index; LVM — left ventricular mass; LVEF — left ventricle ejection fraction; TC — total cholesterol; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; TG — triglycerides

The analysis of correlations between mFLT and clinical parameters was performed in all patients (Tab. 3). Significant correlations for albumin, β1 globulin, BNP, body mass index (BMI), body surface area (BSA), LVEF, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG) were found in both plasma and diluted plasma. However, for CRP the correlation with mFLT was revealed only in plasma.

In the context of our research, it is crucial to point out the moderate negative correlation between mFLT and BNP values (Fig. 1). In the case of mFLT obtained for diluted plasma, the correlation with BNP level slightly decreases but the trend remains the same — the increase in BNP concentration is associated with the decrease in mFLT.

According to the analysis of multiple regression, concentrations of β1 globulins, troponin I and BNP are the only independent factors affecting the mFLT that reach statistical significance. The optimal regression model for mFLT of plasma can be expressed by the following equation:

$$\text{Mean FLT} = 4{,}596 \times \beta\ 4{,}596\ \text{sman}\left[\frac{\text{g}}{\text{dL}}\right] + 0{,}028 \times \text{troponim I}\left[\frac{\text{ng}}{\text{mL}}\right] - 0{,}0002 \times \text{BNP}\left[\frac{\text{pg}}{\text{mL}}\right] + 4{,}784$$

The p-values of these variables were $p_{\beta 1g}$ = 0,0009, p_{tI} = 0,0438, p_{BNP} = 0,0121, respectively. The coefficient of determination (R^2) of the model was 0,419; p = 0,00006. This model explains 42% of variability of the mFLT of plasma.

Discussion

According to our research, TRFS is a promising method for plasma assessment which allows screening for different diseases, including those with concomitant increase in CDPs concentration. Iraqi et al. [12] demonstrated usefulness of CDPs assessment in short- and long-term follow-up after MI. The combination of increased concentrations of CDPs and BNP was associated with all-cause mortality and the composite end point of cardiovascular death or HF hospitalization, with hazard ratios of 2.49 (p = 0.039) and 3.03 (p = 0.002), respectively. Moreover, during follow-up the concentration of CPDs was consistently lower in patients treated with eplerenone. The long-term kinetics of biomarkers of collagen synthesis and degradation suggests that extracellular matrix (ECM) remodeling is an active process in patients with acute MI with left ventricular dysfunction and congestive HF [12].

The BNP is secreted by the left ventricle in response to mechanical wall stress and is involved in cardiac remodeling [13]. It has been suggested that BNP level may have an essential role in screening for LVSD in patients after acute MI [14, 15]. The concentration of

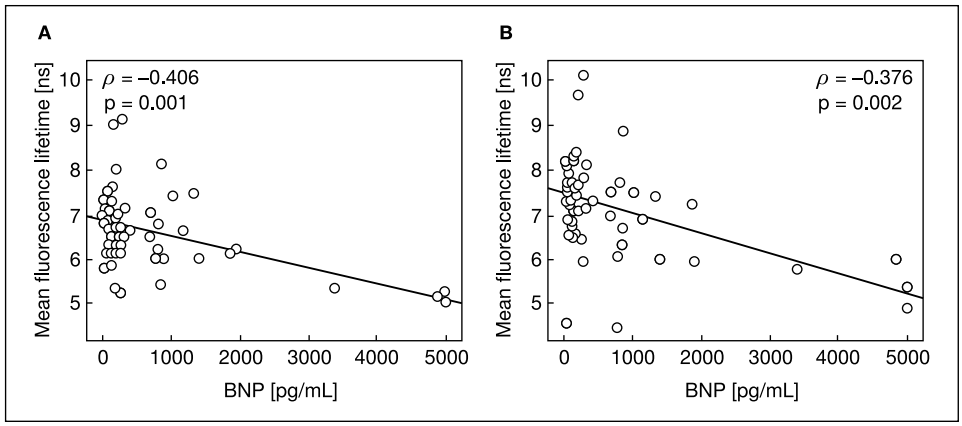

Figure 1. Correlations between mean FLT [ns] and BNP [pg/mL] in plasma (A) and diluted plasma (B)

plasma BNP increases in proportion to the size of the infract, after acute MI [16–18]. Xueyan et al. [19] observed the significant negative correlation between LVEF and BNP level. They also presented the significant difference of BNP concentration in patients with severe HF between baseline and after treatment. Wang et al. [20] suggested that high serum concentrations of BNP are associated with poor outcomes.

We observed significant differences in mFLT of plasma between groups of patients divided according to BNP levels. Moderate negative correlation was also revealed between concentration of BNP and mFLT of plasma in patients after MI. A multiple regression analysis confirmed that the increase in BNP level is an independent factor resulting in the decrease in mFLT. The data obtained from this observational study are in line with the results of our previously performed *in vitro* experiment showing the decrease in mFLT with increasing concentrations of type III CDPs (unpublished data). Both of these studies suggest that plasma of patients with potential high probability of developing LVR is characterized by the decrease in mFLT.

Study limitations

Some other factors, except for BNP, may have an influence on mFLT. Therefore, additional methods should be applied to distinguish patients with the increased level of CDPs. In further studies, it is essential to eliminate the majority of unnecessary particles from plasma just before the final measurement. Probably, the special membranes with specific diameter, such as those eliminating albumins, will be the simplest method. Albumin, which is the main protein in the human blood plasma, [21] has a molecular weight much bigger than CDPs and elimination of this protein removes about 50% of the human plasma proteins. It is crucial to continue further investigation in this field.

Conclusion

Having taken into account the experimental data, we assumed that plasma concentration of CPDs is closely related to BNP level. This experiment confirmed that plasma of patients with potential high probability of developing LVR is characterized by the decrease in mFLT.

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