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## Original Research Article

# Effect of physical training on indices of platelet aggregation and fibrinogen concentration in patients with chronic heart failure

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## ABSTRACT

**Objective:** The aim of this study was to determine the effect of long-term physical load on the changes in the fibrinogen concentration and platelet aggregation.

**Material and methods:** Platelet aggregation was investigated in 144 patients while fibrinogen concentration in 138 patients with CHF. The patients were divided into the groups of the trained patients and the controls and were investigated as follows: on admission to the hospital (stage 1); after treatment in the hospital (stage 2); after 3 months (stage 3); after 6 months (stage 4); and after 1 year (stage 5). The indices were investigated before and after physical load.

**Results:** It was determined that fibrinogen concentration significantly increased after physical load in all the treatment stages in both groups of the patients ( $P = 0.045$ ). In the course of the treatment, fibrinogen concentration gradually decreased in the group of the trained patients ( $P = 0.02$ ). Platelet aggregation investigated with ADP significantly increased after physical load in all the stages in both groups of the patients and decreased during the different investigation stages in the groups of the untrained ( $P = 0.02$ ) and trained patients. Platelet aggregation investigated with ADR consistently decreased before physical load during the different investigation stages in the groups of the trained (difference is not significant) and untrained patients ( $P = 0.02$ ).

**Conclusions:** Physical training reduces fibrinogen concentration in patients with CHF. It remains unclear whether physical training can have an effect on the decrease in platelet aggregation in patients who have long-term physical training applied.

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## 1. Introduction

It has been proven that adrenalin influences a higher fibrinogen concentration and noradrenalin activates platelet [1]. Exercise training attenuates neurohormonal stimulation [2] and improves quality of life of patients [3]; however, it is not clear which organ systems and which changes in particular have an impact on these processes.

The data of research studies about the importance of physical training on the indices of the hemostasis are controversial. According to some authors, platelet activity does not depend on physical training [4]. Other studies report that moderate exercises reduce platelet activity [5,6]; meanwhile, those of high intensity increase it [5-9]. Some studies have proven that physical training of low [9] and moderate intensity activates platelet [10]. Yet other authors claim that moderate physical load does not affect platelet activity [6]. It is rather complicated to assess and compare these studies since not all the authors provide details about the methods and regimen of the chosen intensity of physical training; they also use different research methods of platelet aggregation. The time period between exercise and investigations was also different, and the results of the studies were influenced by a small number of investigated subjects as well. No scientific studies about the remote effect of physical load on platelet aggregation in patients with chronic heart failure (CHF) have been found.

Fibrinogen is one of the markers of a systemic inflammation, and its level is found to be increased in the blood of the patients with CHF in comparison with healthy subjects [1,11]. It is a risk factor of cardiovascular diseases [12] and one of the factors conditioning the hypercoagulable state [1]. It has been determined that fibrinogen significantly decreases in the blood of patients with CHF if they exercise [12,13]. No significant difference in the fibrinogen concentration has been found when healthy subjects exercising for 6 or 12 weeks were investigated [14]. No data about the influence of long-term physical training on the changes in the fibrinogen concentration in patients with CHF have been found in literature sources.

Thus, the aim of the study was to determine how long-term physical training influenced the changes in the hemostasis indices, i.e., fibrinogen concentration and platelet aggregation.

## 2. Material and methods

Platelet aggregation was investigated in 144 patients and fibrinogen concentration in 138 patients with CHF (class II-IV according to the NYHA (New York Heart Association)). The diagnosis of CHF was made following the guidelines for the diagnostics and treatment of heart failure approved by the European Society of Cardiology [1]. The inclusion criteria were as follows: 18- to 80-year-old patients who agreed to participate in the study; class II-IV heart failure according to the NYHA with ischemic, dilated, or hypertensive cardiomyopathy; left ventricular ejection fraction (LVEF) of <35%;  $\text{VO}_2$  max <20 mL/kg/min; the level of aerobic activity not lower than 3 min as determined by spiroergometry; and patients with a stable clinical state, without inflammation and receiving

adequate treatment with medications. The clinical state was considered stable if there were no changes in the clinical state, functional class according to the NYHA, weight, and used medications during the past 3-4 weeks, nor were there new heart failure symptoms.

The patients were randomly divided into 2 groups, i.e., intervention group and controls, at a ratio of 1:1. The patients in both groups were given optimal treatment following the guidelines for the diagnostics and treatment of heart failure approved by the European Society of Cardiology [15]. The aerobic physical training method was applied to the patients in the intervention group, i.e., the intensity of physical load was 10% lower than their anaerobic threshold registered during spiroergometry. During aerobic physical exercise, the load was gradually increased by prolonging the duration of exercise and later by increasing load intensity. Everyday physical activity of 30 min was recommended for the patients in the control group as well.

The patients were investigated in the following treatment stages: on admission to the hospital (1); after the treatment in the hospital (2); after 3 months (3); after 6 months (4); and after 1 year (5). Except for the first stage, the indices were analyzed before and after physical load. During the first stage in the hospital, the patients in the intervention group had physical training for 5-10 min twice a day, i.e., in the morning and afternoon, until they were discharged from the hospital. During the second stage, ambulant physical training for 10-30 min twice a week in a clinic and 3 times a week at home was continued. Later, the patients continued individual home training programs. When the diaries prepared for this study and filled out by the patients were checked during different study periods, it was observed that 90% of the patients adhered to the program. The mean training duration was 32 min a day.

Hematological parameters (hematocrit and complete blood count), platelet aggregation and fibrinogen concentration of every study participant were analyzed during all five stages of the study. Blood for hematocrit and complete blood count testing was taken from the forearm vein into 4.5-mL vacuum tubes with EDTA (ethylene-diamine-tetra-acetic acid) and was put into hematological analyser COULTER LH 780 (USA, Brea, CA). Before inclusion in the study, CRP levels of every patient were tested. C-reactive protein concentrations were quantified using "Synchron" analyzer based on turbidimetry (Beckman Coulter, USA, Brea, CA). Patients with CRP levels exceeding 7.5 mg/L were not included in the study due to the presence of inflammation.

In order to investigate platelet aggregation, blood was taken from the forearm vein into 5-mL vacuum tubes with 3.8% sodium citrate. In order to prepare the platelet-rich plasma blood was centrifuged at 1000 rpm ( $100 \times g$ ) for 15 min at room temperature. Platelet-poor plasma was obtained when the rest of blood was centrifuged at 3000 rpm ( $1000 \times g$ ) for 30 min. Platelet aggregation was investigated in platelet-rich plasma using the aggregometer (Chrono-Log, USA) by the standard Born method [16]. ADP (3.8 mmol/L, Chrono-log P/N 384), collagen (2  $\mu$ mol/L, Chrono-log P/N 385) and adrenalin (ADR, 4.5 mmol/L) were used for aggregation induction. Spontaneous aggregation (SP) was registered without using an inductor.

Fibrinogen concentration was investigated by the Clauss method using a semiautomatic analyzer Bios-4 (France) and

**Table 1 – Clinical characteristics of patients and control subjects.**

Clinical variable	Untrained patients with CHF	Trained patients with CHF	P
	(n = 72)	(n = 72)	
Age, years	68 (11.96)	76 (9.46)	0.0001
Men, n (%)	60 (83)	66 (88)	NS
Women, n (%)	12 (17)	10 (12)	NS
Smoking, n (%)	25 (35)	11 (15)	NS
Body mass index, kg/m <sup>2</sup>	27.40 (4.18)	27.87 (4.58)	NS
Systolic blood pressure, mm Hg	114.79 (17.50)	115.35 (17.76)	NS
Diastolic blood pressure, mm Hg	77.79 (11.06)	77.72 (11.42)	NS
Heart rate, beats per min	78.74 (12.75)	86.65 (16.46)	0.002
Left ventricular ejection fraction, %	21.71 (7.30)	21.35 (7.83)	NS
VO <sub>2</sub> max, mL/kg/min	29.06 (9.50)	27.25 (6.65)	NS
Diuretics, n (%)	59 (82)	63 (88)	NS
Beta-blockers, n (%)	60 (83)	65 (90)	NS
ACE inhibitors, n (%)	58 (81)	64 (89)	NS
Anticoagulants, n (%)	28 (39)	34(47)	NS
Nitrates, n (%)	7 (10)	4 (6)	NS
Digoxin, n (%)	15 (21)	12 (17)	NS
Fibrinogen concentration, g/L	3.84 (1.09)	4.15 (0.98)	NS
ADP-treated platelet aggregation before treatment	62.84 (20.76)	58.65 (23.17)	NS
ADR-treated platelet aggregation before treatment	64.35 (24.05)	59.30 (26.90)	NS
Spontaneous platelet aggregation	7.23 (4.98)	6.52 (4.19)	NS
Collagen-treated platelet aggregation before treatment	64 (24.82)	62.19 (26.74)	NS

Values are mean (standard deviation) unless otherwise indicated. NS, not significant.

Diagnostika Stago reagents [17,18]. The quality of the investigations was assessed based on the criteria of the internal quality control system. Data validity was periodically assessed by the World Health Organisation Collaborating Centre for the care of Patients with Bleeding and Clotting Disorders in United Kingdom. A permission of the Regional Biomedical Research Ethics Committee to perform a biomedical study was obtained.

Statistic analysis was done by using Excel, SPSS 22.0 for Windows and Statistica 8.0 statistic packages. Values are expressed as mean (SD). Comparisons of measured values between the study groups were done with one-way ANOVA. The relation between measured values of ADP-induced aggregation and age, functional class of CHF, or LVEF and others were examined using linear regression. Statistical significance was set at  $P < 0.05$ .

### 3. Results

The clinical characteristics of patients and control subjects are summarized in Table 1. There were no significant differences in the fibrinogen concentration and platelet aggregation

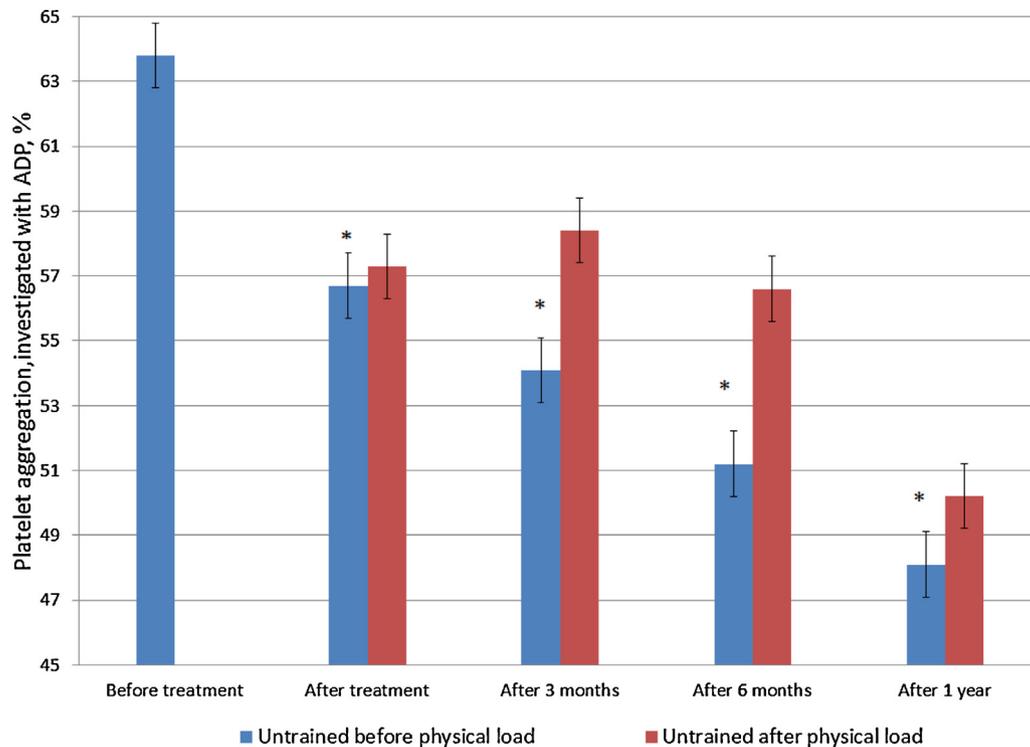
between trained and untrained patients before the treatment. There was no correlation between age and platelet aggregation and fibrinogen concentration.

It was determined that the fibrinogen concentration significantly increased after physical load during all the study periods in both groups of the investigated patients (Table 2). The hematocrit (Ht) values after physical load significantly increased ( $P < 0.0001$ ). However, fibrinogen concentration did not depend upon the difference between Ht before and after physical load ( $P < 0.0001$ ). The fibrinogen concentration gradually decreased ( $P = 0.02$ ) in the group of the trained patients during the course of the treatment. In the control group (untrained patients), there was a tendency for fibrinogen concentration to decrease until the third observation month; later, it returned to the level before the treatment. Changes in the fibrinogen concentration during the course of the treatment in the control group were insignificant ( $P > 0.05$ ). No correlations between the fibrinogen concentration and age, medication use, body mass index, blood pressure, heart rate and hematological parameters were found.

The changes in the indices of platelet aggregation, investigated with different reagents, before and after physical load during different treatment stages differed. Platelet

**Table 2 – Changes in the fibrinogen concentration before and after physical load in the groups of trained and untrained patients during different treatment stages.**

Treatment stage	Fibrinogen concentration, g/L					
	Untrained		P	Trained		P
	Before physical load	After physical load		Before physical load	After physical load	
After treatment	3.70 (0.32)	3.84 (0.27)	0.021	4.00 (0.42)	4.18 (0.55)	0.033
After 3 months	3.54 (0.28)	3.64 (0.17)	0.012	3.65 (0.34)	3.80 (0.46)	0.031
After 6 months	3.59 (0.39)	3.78 (0.49)	0.013	3.72 (0.49)	3.93 (0.35)	0.004
After 1 year	3.77 (0.42)	3.98 (0.35)	0.002	3.63 (0.59)	3.85 (0.32)	0.007



**Fig. 1 – Changes in intensity of platelet aggregation (%) investigated with ADP during different treatment stages before and after physical load in the group of the untrained patients. \*A significant difference of platelet aggregation before physical load in comparison with the value before the treatment.**

aggregation investigated with ADP significantly increased after physical load during all the study periods in the groups of the trained and untrained patients ( $P < 0.001$  and  $P = 0.045$ , respectively) (Figs. 1 and 2). Platelet aggregation investigated with ADP decreased during different study periods in the group of the untrained patients before physical load ( $P < 0.02$ ) (Fig. 1). In the group of trained patients it decreased until the third month ( $P = 0.04$ ) (Fig. 2). Platelet aggregation investigated with ADR in untrained patients statistically significantly increased after physical load only after 6 months ( $P < 0.005$ ). During the other study periods, the changes after physical load were insignificant. Platelet aggregation investigated with ADR during different treatment stages consistently decreased before physical load in the groups of the untrained patients ( $P < 0.02$ ) (Fig. 3). In the group of the trained patients platelet aggregation investigated with ADR significantly decreased before physical load until the third month ( $P = 0.037$ ). During the others study periods, the changes before physical load in comparison with the value before the treatment were insignificant (Fig. 4). Changes of platelet aggregation, investigated with ADR, after physical load in the group of trained patients, were insignificant ( $P > 0.05$ ).

There were no significant changes in platelet aggregation investigated with collagen determined during different treatment stages or before and after physical load.

Spontaneous platelet aggregation after physical load after the treatment in the hospital ( $P = 0.0185$ ) and after 6 months significantly decreased ( $P = 0.035$ ) in the group of the untrained patients. During the other study periods, the change in spontaneous platelet aggregation in the group of the untrained

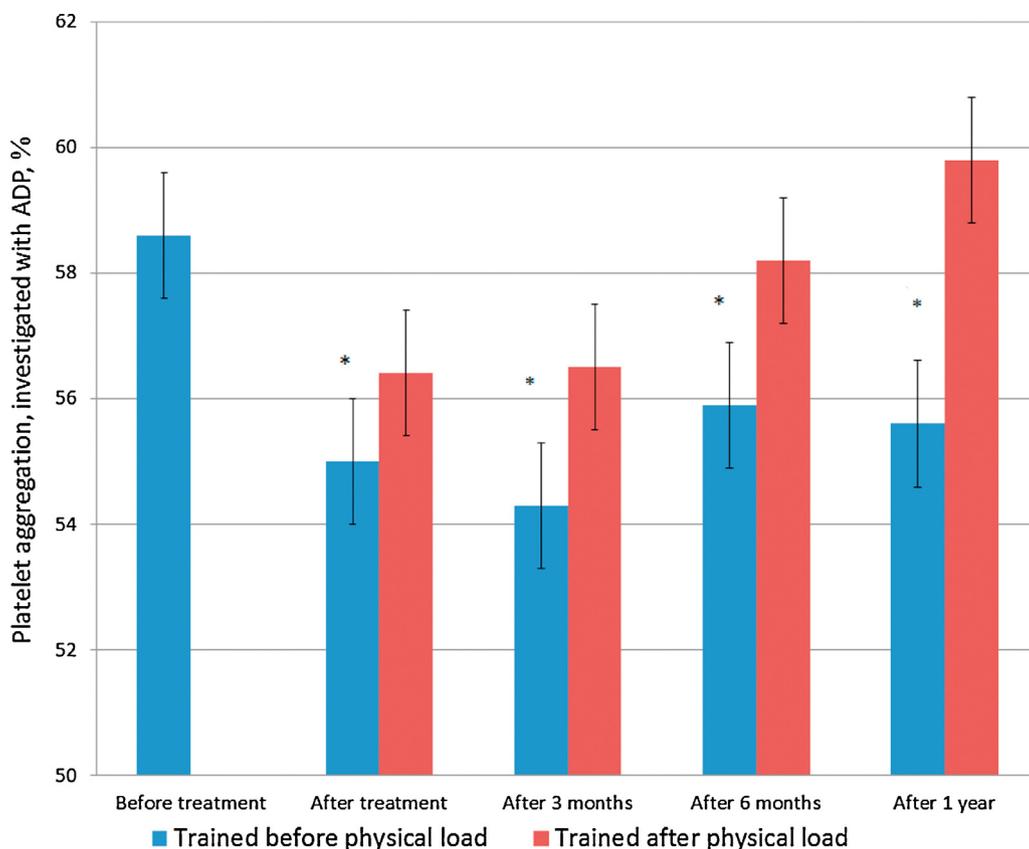
patients was not statistically significant ( $P = 0.204$  after 3 months and  $P = 0.433$  after 1 year). In the group of the trained patients, no significant changes either before and after physical load or during different observation stages were found.

There were no significant differences in the fibrinogen concentration and platelet aggregation between smoker and non-smoker subgroups of control and trained group participants. Our study showed that pharmacological chronic heart failure treatment had no influence on platelet aggregation and fibrinogen concentration. The study only included patients who did not receive antiaggregants. Oral anticoagulants were used by 39% of the control group patients, and 47% of the trained patients. Anticoagulants used by the patients did not affect fibrinogen concentration.

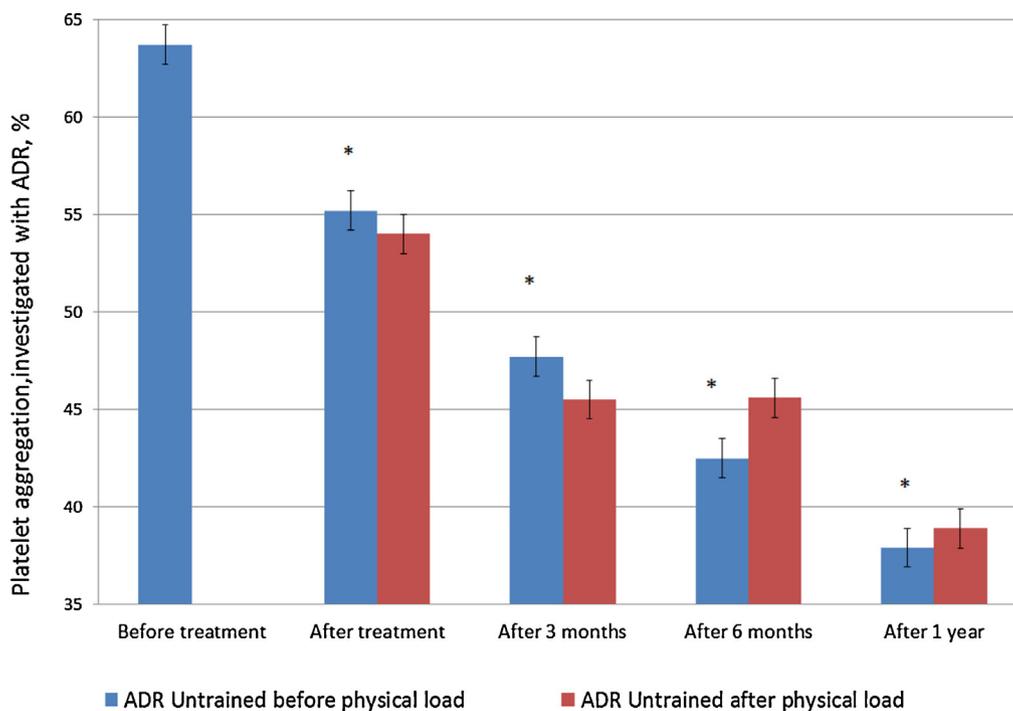
However, fibrinogen concentration and platelet aggregation indices depended neither on the cause of the development of CHF nor on the hematological parameters (hematocrit and complete blood count). Platelet aggregation investigated with ADP and ADR and fibrinogen concentration demonstrated a weak correlation with the NYHA class ( $r = 0.18$ ,  $P = 0.048$ ;  $r = 0.238$ ,  $P = 0.026$ ; and  $r = -0.205$ ,  $P = 0.043$ , respectively). There were no correlations between age and fibrinogen concentration and platelet aggregation.

#### 4. Discussion

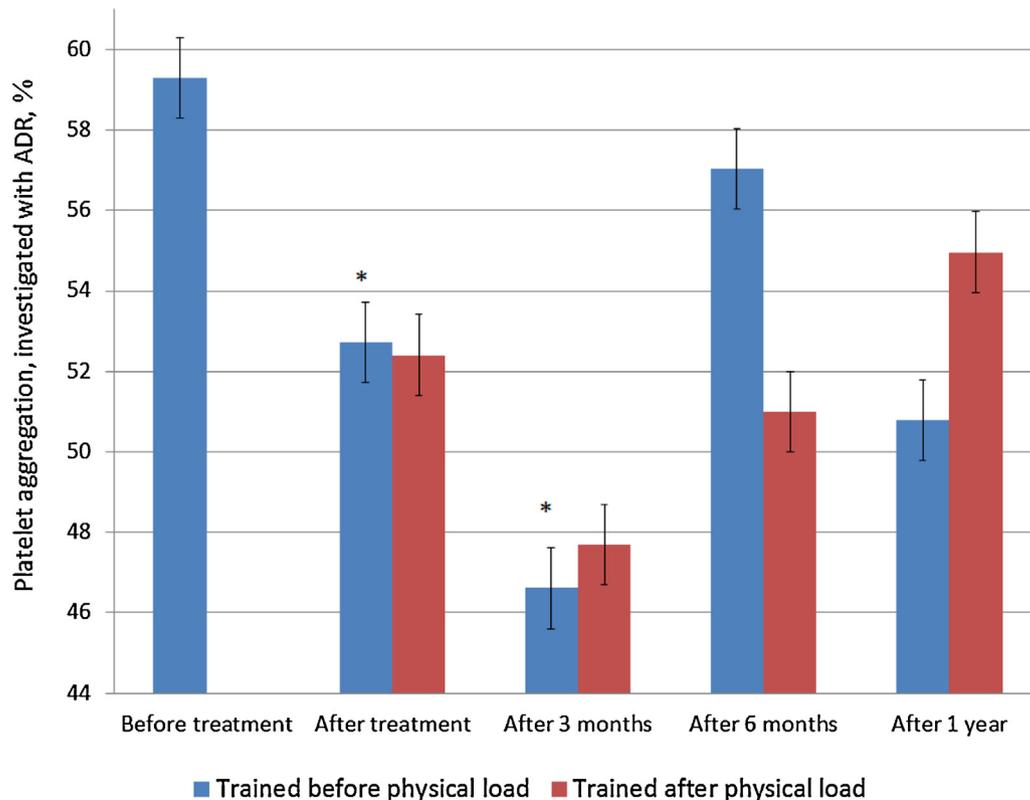
The results of researchers investigating the importance of training on platelet aggregation are different. Comparison of the impact physical training has on platelet aggregation with



**Fig. 2 – Changes in platelet aggregation investigated with ADP during different treatment stages before and after physical load in the group of the trained patients. \*A significant difference of platelet aggregation before physical load in comparison with the value before the treatment.**



**Fig. 3 – Changes in platelet aggregation investigated with ADR before and after physical load in the group of the untrained patients. \*A significant difference of platelet aggregation before physical load in comparison with the value before the treatment.**



**Fig. 4 – Changes in platelet aggregation investigated with ADR before and after physical load in the group of the trained patients. \*A significant difference of platelet aggregation before physical load in comparison with the value before the treatment.**

the literature data is complicated since not all the reports elaborate on the extent of physical load and methods of its choice; they use different training and platelet aggregation research methods, analyze both healthy subjects and patients with different (not only cardiovascular) diseases; the period between exercise and performed investigations is different, and the results are also undoubtedly affected by a small number of the investigated cases. The patients investigated in our particular study performed individualized physical exercises according to the tolerated physical load.

Some researchers have found a statistically significantly increased platelet aggregation immediately after physical load in patients with ischemic heart disease [9]. The data of our research confirmed that it also applied to patients with CHF. The researchers explain this change [9] by an interaction between hemodynamic factors and atherosclerosis-affected endothelium, which is difficult to agree with as platelet aggregation should, in such a case, intensify after physical load only in those CHF patients whose cause of CHF is ischemic heart disease or arterial hypertension. Meanwhile, the data of our research demonstrated that intensified platelet aggregation after physical load did not depend on the cause of CHF. The endothelium synthesizes and secretes vasorelaxing and antiplatelet factors, which are known to increase with exercise [19] since there is an increase in blood shear stress on the endothelium [19]. However, during physical training, platelet are directly activated by blood shear stress [4,20], due to which they express more CD41 [21], and there is an increased

catecholamine concentration via  $\alpha_2$  adrenoreceptors on the surface of platelet [8] and an increased concentration of reactive oxygen species [22]. The activation of platelet during physical load has also been confirmed by the fact that GPIIb/IIIa receptor expression increases after physical load [21]. It has been claimed that, when reactive oxygen species increase during intensive physical load, lipid peroxidation is activated, due to which there is an increase in the oxidized low-density lipoproteins [23], which affect specific platelet receptors and suppress the ability of platelet to synthesize NO [24]. These factors activate platelets. Thus, it is logic that platelet aggregation increases after physical load not only in patients [4,6,7,19], but also in healthy subjects [9]. Besides, when physical load gradually increases, mechanisms inhibiting uncontrolled enhancement of platelet aggregation start working [6]. Thus, our data correspond to the data of the researchers who find activated platelets after low-grade physical exercises [9].

Our data demonstrated that an increase in platelet activity after physical load did not depend on the platelet count, hematocrit, fibrinogen concentration, and used medications, which corresponds to the reports of other researchers [21].

No scientific studies have been found to address the long-term effect of physical load on platelet aggregation in patients with CHF. Only one source analyzed the long-term effect of physical training on healthy subjects. The authors determined that intense exercise for 6 weeks significantly decreased platelet aggregation [22], which corresponds to our results.

Literature sources note that the quality of life of CHF patients who do exercise improves [2]; however, the biochemical mechanisms of action have not been clarified yet. It has been found out that regular exercise improves the endothelium function with time, i.e., it produces more NO, which conditions vasodilation and facilitates cardiac performance [19]. Besides, a repeated increase in blood shear stress and an increase in the concentration of oxidants encourage an increase in anti-inflammatory enzymes and antioxidants [25], which results in the improved endothelial function [26]. It has been proven that patients with ischemic heart disease or atherosclerosis have an increase in the prostacyclin level in the serum [27]. Both prostacyclin and NO suppress platelets [4]. It has also been proven that there is a decrease in one of the markers of platelet activation, i.e., P-selectin, in the blood of CHF patients who regularly exercise [11]. These facts can explain a long-term impact of exercise on platelet aggregation.

Fibrinogen is one of the markers of a systemic inflammation, and CHF patients have more fibrinogen in the blood than healthy subjects [1,11]. It is a risk factor of cardiovascular diseases [12] and one of the factors determining the hypercoagulable state [1]. It has been found out that there is a statistically significant decrease in fibrinogen in the blood of those patients with coronary heart disease and CHF who exercise [12,13]. These changes have been reported not to depend on body weight or on medications used [13], which corresponds to the data obtained in our research with the CHF patients who do exercise. It is being clarified what determines such changes. With healthy subjects under investigation, no significant difference in fibrinogen concentration when exercising for 6 or 12 weeks has been determined [14]. Researchers think that such results can be caused by smoking and an insufficient duration of exercise or insufficient physical load during exercise.

We found no significant differences between smoker and non-smoker subgroups of control and trained group patients with regard to fibrinogen concentration and platelet aggregation values despite available evidence proposing that carbon monoxide-containing cigarette fumes increase smokers' blood fibrinogen levels, whereas nicotine activates platelets [28]. Insignificance of the difference might have been determined by insufficient sample size after distribution of study participants into subgroups. Literature sources provide data about a moderate correlation between the leukocyte count and fibrinogen concentration ( $r = 0.35\text{--}0.45$ ,  $P < 0.01$ ) and a weak correlation between fibrinogen concentration and body mass index ( $r = -0.33$ ,  $P < 0.001$ ) when healthy subjects are studied [12]. Such dependence is explained by the fact that body fat, especially in the abdominal area, directly influences an increase in the concentration of inflammatory markers in blood due to intensified cytokine synthesis. No significant correlations between these indices were determined in our study.

## 5. Conclusions

Fibrinogen concentration significantly increases after physical load in the groups of the trained and untrained subjects. In the group of the trained patients, fibrinogen concentration

statistically significantly gradually decreases with time. These changes do not depend on the age, medications used, body mass index, blood pressure, heart rate, or hematological parameters. Thus, it can be claimed that physical training decreases fibrinogen concentration in patients with CHF.

A significant increase in platelet aggregation investigated with ADP after physical load in the groups of the trained and untrained subjects was found. In the group of the untrained patients, platelet aggregation gradually and significantly decreased during different treatment and observation stages. In the group of the trained patients, there was a significant decrease of platelet aggregation, investigated with ADP, until the third month. Platelet aggregation, investigated with ADP, during different treatment stages consistently significantly decreased before physical load in the untrained patients. Thus, it is not clear whether physical training can have an impact on the decrease in platelet aggregation in the course of treatment.

## Conflict of interest

The authors state no conflict of interest.

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