Changes in the Nrf2/Keap1 Ratio and PON1 Concentration in Plasma of Patients Undergoing the Left Main Coronary Artery Stenting

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Nuclear factor erythroid 2-related factor2 (Nrf2), together with its inhibitor Kelch-like ECH-associated protein 1 (Keap1), is a crucial regulator of cellular redox response. Nrf2 binds to the antioxidant response element (ARE) present in the DNA sequence of a broad group of antioxidant compounds, including paraoxonase (PON1), inducing their transcription. This study was to answer the question of the effect of temporary ischemia/oxidative stress resulting from the left main stenting via percutaneous coronary intervention (LMPCI) performed in the patients included in this study on the cellular redox balance, which is guarded by the Nrf2/Keap1 interaction. We expected a reflection of the redox imbalance due to reactive oxygen species (ROS) in the change in PON1 concentration observed in the following stages of the study, as well as in total antioxidant capacity (TAC) levels. Our results showed the mobilization of cellular Nrf2/Keap1 team right after the procedure (pre-LMPCI median: 2.532, range: 0.07-11.88; post-LMPCI median: 3.735, range: 0.1545-16.18; 24 h-LMPCI median: 5.596, range: 0.02-49.18), which suggest being the result of oxidative stress that accompanies percutaneous coronary intervention (PCI). The course of Keap1 and Nrf2 concentrations at all stages of the experiment appeared to show that Keap1 shadowed the Nrf2 to switch off its activity after Nrf2 induced the mobilization of the antioxidant response. We observed an increase in PON1 concentration (pre-LMPCI median: 179.3, range: 49.76-6120; post-LMPCI median: 215.7, range: 3.80-2771) and a decrease in the TAC level immediately after PCI (pre-LMPCI: 1.008 ± 0.271, post-LMPCI: 0.8030 ± 0.27). This study design allowed for the first time to analyze the chronology of mechanisms and the relationship between selected parameters reflecting the redox state in patients’ plasma. We may conclude that ischemia induced by the PCI was the source of imbalance in the Nrf2/Keap1 ratio via oxidative stress, and this leads to an increase in PON1 concentration first and, in the next step, the TAC mobilization.

1. Introduction

Nuclear factor erythroid 2-related factor2 (Nrf2) is a transcription factor managing the phase II response to oxidative stress by inducing the variety of antioxidant enzymes. It also modulates the expression of genes controlling the inflammatory and immune system response [1–3]. Under stress conditions, Nrf2 has dissociated from its Kelch-like ECH-associated protein 1 inhibitor (Keap1) and translocated into the nucleus [1–3]. Nrf2 promoting mechanism involves binding to the antioxidant response element (ARE) in the promoter region of several adaptive genes such as glutathione-S-transferase (GST), γ-glutamyl cysteine, heme oxygenase 1 (HO-1), and paraoxonase-1 (PON1) [4–6]. PON1 is an HDL-associated serum enzyme dependent on Ca2+ ions synthesized in the liver. The PON1 antioxidant capacity is associated with...
preventing low-density lipoprotein (LDL) oxidation, and it is also known as an acute phase protein [7, 8]. Thus, it plays a crucial role in reducing the initiation and progression of atherosclerosis by hydrolyzing activity similar to that of phospholipase A2 towards oxidatively modified phospholipids [9]. Although PON1 is studied to exhibit the activity towards a variety of substrates like phenylacetate, paraoxon, or homocysteine thiolactone, almost nothing is known regarding the PON1 substrate in the atherosclerotic tissue [9, 10]. The mechanism explaining the transcriptional regulation of PON1 is not yet completely understood. However, it is noted that three putative Nrf2 binding sites are present in the promoter region of PON1 [6, 11].

Ischemic heart disease is mainly caused by atherosclerosis in coronary arteries. Stenosis in the artery leads to limitations in the blood flow and impairment in the heart blood supply. The clinical symptoms include angina with the severity depending on the extent of the ischemia. The left main coronary artery (LMCA) is particularly essential since the blood supply provided by the vessel is large. Significant coronary artery (CA) disease is defined as stenosis over 50% and is observed in 5-7% of patients undergoing coronary angiography [12]. Revascularization is recommended in all patients with LMCA stenosis ≥ 50% rather than medical therapy only [13] due to poor prognosis and high mortality risk ranging 40-50% in 3-4 year follow-up [12]. The main goal of percutaneous coronary intervention (PCI)—to restore the optimal blood supply in the ischemic region—may result in the additional negative effect of oxidative stress phenomenon [14, 15]. Especially, alternate phases of ischemia and reperfusion during coronary angioplasty may potentially lead to impairment in the myocardial function [16]. Therefore, this study aimed at investigating the effect of the oxidative stress accompanying the left main coronary artery PCI on the relation between Nrf2/Keap1 status and PON1 concentration.

2. Materials and Methods

2.1. Material. The study group consisted of 29 consecutive patients with symptomatic coronary artery disease and ≥50% stenosis of LMCA treated with LM angioplasty in the I Department of Cardiology Poznan University of Medical Science in the years 2017 and 2018. Clinical characteristics are presented in Table 1. The exclusion criteria included severe kidney disease with creatinine clearance less than 15 ml/min or under dialysis therapy, severe valvular disease, the presence of diabetes mellitus, any known contraindication for antplatelet therapy or severe blood coagulation disorders and/or active bleeding, and large surgery during last 15 days. All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Poznan University of Medical Science nr 1224/16 from 01.12.2016. After the routine laboratory evaluation, blood samples of 29 patients were eligible for further analysis.

Coronary angioplasty was performed by a standard percutaneous radial or transfemoral access. The angioplasty strategy was performed according to the operator’s preference with the aim of complete coverage of the diseased segment. Heparin 100 U/kg was used intravenously before PCI. Before and after the procedure, all patients received dual antiplatelet therapy according to current guidelines. The blood samples were collected into lithium heparin tubes before (pre-LMPCI), few minutes after the procedure (post-LMPCI), and on the following day (24 h-LMPCI), after centrifugation aliquoted, and frozen in -80°C until analyzed.

2.2. Methods. Nrf2 was measured by the commercially available RayBio Human NRF2 ELISA KIT (Ray Biotech Life USA). Briefly, standards and samples were pipetted into the antibody specific for human Nrf2 coated wells. Nrf2 present in a sample was bound to the wells by the immobilized antibody. After following the steps including washing unbound antibody, pipetting the HRP-conjugated streptavidin, and the addition of TMB substrate, the development of blue color was observed in proportion to the amount of the Nrf2 bound. The stop solution changed the blue color to yellow, and the absorbance was measured at 450 nm.

Keap1 (Kelch-like ECH-associated protein 1) was assayed according to the procedure provided by the LifeSpan BioSciences ELISA kit. Briefly, this assay is based on the sandwich ELISA principle. Standards and samples were added to target specific capture antibody precoated wells. Then, a biotin–conjugated detection antibody was added to bind the captured antigen. After the washing procedure, the avidin–HRP conjugate was added to bind biotin; the unbound amount was removed with the washing procedure. Addition of tetramethylbenzidine TMB substrate results with

<table>
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<tr>
<th>Table 1: Clinical characteristics of patients.</th>
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<tr>
<td>Clinical data</td>
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<tr>
<td>Female</td>
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<tr>
<td>Male</td>
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<tr>
<td>Mean age</td>
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<tr>
<td>Arterial hypertension</td>
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<tr>
<td>Atrial fibrillation</td>
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<td>Previous myocardial infarction</td>
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<td>Previous PCI</td>
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<tr>
<td>Previous CABG</td>
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<tr>
<td>Hypercholesterolaemia</td>
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<tr>
<td>Chronic kidney disease</td>
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<tr>
<td>Mean GFR (ml/min)</td>
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<tr>
<td>Mean left ventricle ejection fraction (%)</td>
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<tr>
<td>Coronary lesions in other arteries</td>
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<tr>
<td>Mean body mass index [kg/m²]</td>
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<tr>
<td>Mean hemoglobin level before the procedure [10^12/l]</td>
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<tr>
<td>Mean leucocyte count before the procedure [10^9/l]</td>
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PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; GFR: glomerular filtration rate.
blue color development, which changes to yellow immediately after the stop solution was added, and the absorbance was measured at 450 nm.

PON1 was measured following the protocol provided by the ABNOVA PON1 (Human) ELISA Kit. Briefly, the reaction is based on a solid phase immunoassay, and after adding the standards and the samples to the wells, the biotinylated antibody was added. Following the procedure, the absorbance of the yellow product was measured at 450 nm; the absorbance of the product is linearly proportional to the PON1 concentration in the sample.

Total antioxidative capacity of plasma (TAC) was measured according to the colorimetric test by Omnignostica Forshungs GmbH. Briefly, the determination of the TAC is based on the reaction of peroxides with peroxidase followed by a color reaction of the TMB. After the addition of the stop solution, the color of the sample turns from blue to yellow, and the intensity of it was measured at 450 nm.

2.3. Statistical Analysis. Data were statistically analyzed with Graph Pad Prism Version 8.3.1 (GraphPad Software, San Diego, USA). Data were presented as mean ± SD (standard deviation) when passed the normality test and median and interquartile range if they did not meet the Gaussian distribution criteria. The statistically significant differences between the treated groups were analyzed by the Friedman test for parameters that did not pass the normality test. Dunn’s posttest was used to compare the difference in the sum of ranks between the studied group. Since the Friedman test first ranks the values in each matched set and then sums the ranks in each group, the figures in Results and Comparisons of Parameters represent the ranks of a parameter as a y-axis. Repeated measure ANOVA was used for normal distribution parameters. For a further analysis of differences between the groups, Holm-Sidak’s multiple comparisons test was used for non-Gaussian and matched parameters. Correlations between the parameters were analyzed with the Spearman or Pearson test. Statistical significance was set at p < 0.005.

3. Results and Comparisons of Parameters

Nrf2 concentration was found to increase right after the procedure of post-LMPCI (median: 151.9 pg/ml; range: 12.69-462.4) in comparison with the basal state (median: 82.67 pg/ml; range: 6.070-538.4) when compared to the previous state (pre-LMPCI) and then a significant increase in the following step (24 h-LMPCI) of the experiment (Figure 2). The Nrf2/Keap1 ratio was also evaluated by Friedman’s test (Figure 3), showing the dynamic increase due to the PCI and significantly increased (p = 0.0313) the day after the procedure (pre-LMPCI median: 2.532 range: 0.07-11.88 pg/ml; post-LMPCI median: 3.735 range: 0.1545-16.18 pg/ml; 24 h-LMPCI median: 5.596 range: 0.02-49.18 pg/ml). The PON1 concentration demonstrated a similar run, as observed in Nrf2 and Keap1 described above. Namely, in the first stage of the experiment, the increase in PON1 concentration was observed (pre-LMPCI median: 179.3 range: 49.76-6120 pg/ml; post-LMPCI median: 215.7 range: 3.80-2771 pg/ml) and then decreases within the 24 hours after the PCI procedure (median:154.9 range: 3.325-2615 pg/ml) (p = 0.0032) (Figure 4). Again, we observed the response of antioxidant enzyme PON1 to oxidative stress induced by the ischemia during PCI.

3.1. Correlations between Parameters. Either concentrations of Nrf2 or Nrf2/Keap1 ratio values correlated negatively with PON1 concentration, as well as right after the procedure step (post-LMPCI), and the day after the PCI. The following day after the procedure, the inversely dependent correlation was found between concentrations of Keap1 and Nrf2. The exact values of the coefficients of correlations are presented in Table 2.
4. Discussion

The present study revealed the changes and relations between the parameters chosen for the evaluation of the redox mechanism mediated by the Nrf2/Keap1 pathway accompanying the procedure of the left main stenting (LMPCI). The PCI treatment performed during this study is considered as a model of ischemia, leading to a cascade of reactions induced by reactive oxygen species (ROS). There is a poor number of studies that evaluate the redox status of the plasma mirrored by the concentration of Nrf2 and Keap1 [17–19]. Based on the available literature, it can be concluded that the presence of the Nrf2 factor and its inhibitor Keap1 in the plasma is associated with their leakage from the cell that is destroyed by chronic inflammation and oxidative stress. The damaged cell membrane of the vascular endothelial cells loses its integrity due to the peroxidation of the lipids that make it up [17, 18]. To the best of our knowledge, Sireesh et al. presented for the first time the correlation of circulatory levels of Nrf2 with both oxidative stress and inflammatory cytokines in DM patients [19]. Sireesh observed that circulating Nrf2 levels measured using ELISA as well as the expression of Nrf2 measured in PBMC of study subjects using western blot and mRNA levels of Nrf2 using RT-PCR were significantly lower in the study group compared to control [19]. These results indicate that both the intracellular Nrf2 pool and the circulating one show the same trend and sense in terms of the antioxidant mechanism. However, most of the available literature data are focused on the cellular and nuclear concentration of those parameters [20–24]. The technique used so far using cell lysates to assess the content of Nrf2 is time-consuming, expensive, and more invasive, thus limiting for many clinical trials [18]. The present study proves that those parameters are successfully measurable in

Table 2: The correlation coefficients for PON1, Nrf2, Keap1 concentration, and Nrf2/Keap1 ratio studied in the following stages of the experiment (p < 0.05).

<table>
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<th>Experiment stage</th>
<th>r</th>
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<tr>
<td>PON1</td>
<td>0.4023 Post-LMPCI</td>
</tr>
<tr>
<td>Nrf2</td>
<td>-0.3734 24 h-LMPCI</td>
</tr>
<tr>
<td>Keap1</td>
<td>0.3713 Post-LMPCI</td>
</tr>
<tr>
<td>Nrf2/Keap1</td>
<td>-0.4301 24 h-LMPCI</td>
</tr>
<tr>
<td>Nrf2</td>
<td>-0.54102 Post-LMPCI</td>
</tr>
<tr>
<td>Keap1</td>
<td>-0.54102 24 h-LMPCI</td>
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</table>

Figure 2: The TAC level (mmol/l) observed in the following stages of the experiment presented as mean and SD.

Figure 3: The Nrf2/Keap1 (pg/ml) ratio level which is presented as ranks in the following stages of the experiment presented as median with range.

Figure 4: PON1 concentration (pg/ml) presented as ranks in the following stages of the experiment presented as median with range.
plasma. This aspect may be an advantage in providing more facilitated insight into the induction pathway of antioxidant mechanisms, which may serve as an introduction to more advanced intracellular analysis. Keap1 and Nrf2 create the central cellular sensor that mediates oxidative stress signals to the induction of phase II detoxifying enzyme genes and antioxidative protein genes. On exposure to oxidative stress or electrophiles, Nrf2 is released from repression mediated by Keap1 and translocated to the nucleus [3, 25–27]. Keap1 is a crucial factor in regulating the redox response of the cell [27]. It has a dual function which covers first: being a molecular sensor due to cysteine residues in Keap1, sensitive for redox imbalance, and then plays a role of a molecular switch turning the molecular mechanism of Nrf2 on and off according to the intracellular redox condition [28]. Under basal conditions, the switch is in off position, and Nrf2 is continuously targeted for degradation and ubiquitination by Keap1 functioning as an E3 ubiquitin ligase [26–28].

In consequence, there is a minimal level of Nrf2 in the cell. The switch is turned on under oxidative stress conditions when the Keap1 ubiquitin ligase activity is inhibited, resulting in an increased level of Nrf2. Unbound Nrf2 is translocated to the nucleus and binds to ARE to activate downstream genes [28]. The expression of II phase enzymes restores intracellular redox homeostasis, what is the signal to switch off the Nrf2/Keap1 pathway again. This time, Keap1 is translocated into the nucleus to dissociate Nrf2 from ARE, and the Nrf2/Keap1 complex is traveling outside the nucleus [28]. In the cytosol, the complex binds to the core of Cul3 ubiquitin ligase, and Nrf2 undergoes degradation, the switch turns off [27, 28]. In the presented study, we observed a negative correlation between Keap1 and Nrf2 in the early postprocedural period, and especially the day after the PCI procedure, what we understand as the reflection of the affinity of Keap1 to Nrf2 in the postinduction phase switching off the Nrf2 activity (Figure 5(a)). When the progress of Keap1 and Nrf2 levels during the presented study stages are analyzed, we observe that both represent a similar character, with an increase in the post-LMPCI stage and a decrease in the 24-LMPCI step (Figure 5(b)). However, the analysis of their relationship in the post-PCI and the day after the stage shows that those parameters correspond to each other in an inversely dependent manner. In our understanding, the results show that the status of the Nrf2/Keap1 ratio is influenced by the ischemia during the PCI procedure. Namely, the time of the PCI procedure induces the oxidative stress-mediated Nrf2 pathway, and after mobilization of the cellular antioxidant response, Keap1 shuttles the Nrf2 for cytosol degradation (Figures 5(a) and 5(b)).

The number of studies focusing on the course of changes in PON1 concentrations before, during, and shortly after the revascularization procedure or other surgical intervention is limited. Those studies in most cases are based on a small group of patients, and activity was analyzed more often than the concentration of PON1 [29–32]. Wysocka et al. observed a significant increase in the PON1 activity in a group of patients undergoing coronary artery bypass grafting (CABG) [30]. This observation is in line with the suggestions of other authors that the activity of PON1 increases shortly after surgery and then falls to a level close to the baseline [32, 33]. Referring to Wysocka’s research and other authors, percutaneous angioplasty is a less invasive procedure in comparison to Wysocka’s research and other authors, percutaneous angioplasty is a less invasive procedure in comparison with CABG, where the direct damage of myocardium is associated with oxidative stress and inflammatory reactions [34, 35]. However, the moderate production of ROS due to
less invasive PCI procedure may correspond with the induction of PON1 transcription, one of the second phase antioxidant enzymes that contain ARE sequence recognized by Nrf2 [36]. The evaluation of PON1 and Nrf2 concentrations during the experiment showed the same tendency, namely, the increase of both after LMPCI followed by the decrease observed the next day after PCI. An interesting finding was noted during correlation analysis of PON1 and Nrf2 in post-LMPCI and 24 h-LMPCI. Namely, the parameters remained inversely correlated with each other (Figure 6(a)). To understand this interesting relationship, we purposely involved in the analysis the positive correlation between Keap1 and PON1 observed the next day after the procedure (Figure 6(b)). Therefore, the positive correlation between the Keap1 and PON1 reflects the switch-off time for Nrf2 when its concentration after mobilization of the antioxidant response is silenced. Nrf2 withdrawing by Keap1 leaves the activated PON1 in the circulation. Hence, the day after surgery, we observe a positive correlation between PON1 and Keap1. (c) Spearman correlation between PON1 and Nrf2/Keap1 during the perioperative LMPCI procedure.

Further analysis of the Nrf2/Keap1 ratio during the experiment shows a significant correlation that is in line with the narrative of the hypothesis established for the aim of the present study (Figure 6(c)). The PON1 antioxidant activity is due to its hydrolysis of ROS-modified unsaturated fatty acid residues in phospholipid molecules [37, 38]. The different types of activities are influenced by the polymorphic forms of promoting and coding region of the PON1 gene [10]. Depending on the phenotype, the rates of hydrolyzing the PON1 substrate may vary [39–42]. The evaluation of concentration of PON1 instead of its activity avoids the troublesome resulting from the phenotype-dependent character of the PON1 activity. Analysis of the PON1 level also gives the opportunity to focus on the function of the acute phase protein, which is also attributed to PON1. The dynamic course of the PON1 concentration observed during the present study may reflect the nature of the acute phase protein more than its antioxidant character. Wysocka et al. described the potential impact of the PON1 activity and polymorphism analysis as a valuable marker of overall cardiovascular risk [30]. In their other study, the dynamic change in the PON1 activity during the perioperative

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**Figure 6:** (a) Spearman correlation between PON1 and Nrf2 during the perioperative LMPCI procedure. The negative correlation is suggested to be related to Keap1 involvement in Nrf2 degradation after the procedure. (b) Spearman correlation between PON1 and Keap1 during the perioperative LMPCI procedure. The positive correlation between the Keap1 and PON1 reflects the switch-off time for Nrf2 when its concentration after mobilization of the antioxidant response is silenced. Nrf2 withdrawing by Keap1 leaves the activated PON1 in the circulation. Hence, the day after surgery, we observe a positive correlation between PON1 and Keap1. (c) Spearman correlation between PON1 and Nrf2/Keap1 during the perioperative LMPCI procedure.
treatment in patients undergoing CABG surgery is revealed, which encourages PON1 changes to be considered as a reflection of the progress of oxidative stress and inflammation in one [31].

The choice of TAC for this study resulted from its potential to provide the concept of overall physiological antioxidant efficiency corresponding to various aspects of plasma redox interactions. Plasma redox status arises from the total action of reducing and oxidizing equivalents. TAC brings the concept of knowledge of synergy and interaction between different antioxidants with different activities, and this accumulation provides more efficient protection against free radical injury than any antioxidant alone [43, 44]. Since TAC measures the amount of a given free radical scavenged by a test solution, it is a resourceful parameter monitoring the plasma redox status of patients undergoing PCI. The analysis of TAC results brings the inside in dynamic changes of redox status that may be observed in the following stages of our study. The decrease in the antioxidant capacity right after the PCI procedure shows how quickly the “antioxidant cocktail buffer” was depleted due to the induced oxidative stress. The stage after 24 h is the time of restoring of the redox balance due to the TAC increase. The evaluation of the TAC progress brings the conclusion that ischemia-induced during PCI procedure is the source of free radicals. Therefore, we should expect the effects on the status of Nrf2/Keap1. Indeed, the post-LMPCI stage shows the Nrf2/Keap1 ratio increased; however, the next day, the ratio reached the concentration below the basal level. It seems that those two parameters, describing the plasma redox status, represent the opposite run when the effect of the PCI procedure is analyzed. Again, in our opinion, this is due to the role of the Keap1 inhibitor, which at this stage of our experiment is designed to turn off the Nrf2 activity, transporting it to the cytoplasm for degradation. Therefore, at this stage, the Nrf2/Keap1 ratio increases compared to previous steps, which is the result of reducing the amount of Nrf2.

In contrast, the TAC level in the 24 h-LMPCI stage reflects the plasma antioxidant mobilization. The results that we observed for TAC are consistent with what we know from the Hadjinioklaou study, where the authors found a sharp initial decrease followed by a tendency for partial recovery after six hours, not reaching the preoperative levels [35]. The observation of a reduction in TAC during CABG, shown by Gonenc, also confirm the hypothesis that activated neutrophils, xanthine oxidase of endothelial cells, and damaged heart mitochondria lead to an imbalance in the redox potential of the plasma due to production of ROS [34]. Our study is burdened with certain limitations: first, a small study group resulting from the qualification procedure and assessment of the patients’ condition. We did not decide to divide the study group into smaller groups to avoid statistically unreliable results.

5. Conclusions

This study design allowed for the first time to analyze the chronology of mechanisms and the relationship between selected parameters reflecting the redox state in patients’ plasma. Therefore, we may conclude that ischemia induced by the PCI was the source of imbalance in the Nrf2/Keap1 ratio via oxidative stress and inflammation, which leads to the increase in PON1 concentration first and the TAC mobilization in the next step. PON1 concentration turned out to be a very sensitive biomarker of oxidative stress and acute phase resulting from PCI-induced ischemia, measurable just a few minutes after the end of the procedure. On the other hand, because of the complex nature of this parameter, we believe that TAC mobilized the antioxidant activity of patients’ plasma only the next day after surgery. Considering the research conducted on the use of the Nrf2/Keap1 pathway as a promising therapeutic target in the development of atherosclerosis, we believe that our study will bring a new perspective on its short-term interaction ischemia with PON1 and TAC in plasma. There is no doubt that a better understanding of the Nrf2/Keap1 mechanisms governing redox potential of patient’s plasma creates the possibility of future modulation to reduce the risk of myocardial damage during heart surgery and other procedures accompanied by induced oxidative stress.

Data Availability

Data available on request. Contact to the corresponding author Magdalena P. Kasprzak, magdarut@ump.edu.pl.

Conflicts of Interest

The authors declare no conflict of interest.

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