# Comparison of the clinical application of reactive oxygen species and inflammatory markers in patients with endocarditis

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## Abstract

**Introduction:** Infective endocarditis (IE) is still connected with high operative mortality. Inflammatory markers are commonly used in monitoring patient clinical condition. Respiratory burst and reactive oxygen species (ROS) are the main way of pathogen elimination. Specificity of this process in the aspect of bacterial infection is the key for correlation assessment between ROS and inflammatory markers in patients with IE. In the study, assessment of ROS as a clinical indicator in IE was conducted.

**Material and methods:** During 2007/2008 in the Cardiosurgical Clinic of the Medical University in Lodz there were 20 patients operated on for IE. The examined population consisted of 13 men and 7 women, aged from 23 to 74 years. Inflammatory markers – leukocytosis (WBC), C-reactive protein (CRP), procalcitonin (PCT) and erythrocyte sedimentation rate (ESR) – were assessed preoperatively, on the 3rd, 7th, 12th and 21st day. Simultaneously, with the second venous blood sample chemiluminescence (luminal enhanced whole blood chemiluminescence) was carried out and used to assess ROS production. The results were analyzed statistically.

**Results:** Positive correlation between ESR, CRP and ROS in the preoperative period was confirmed. An increase in ROS and a statistically significant increase in inflammatory markers on the 3rd day were observed. The ROS normalized on the 12th day. Marked individual variability was specific for the inflammatory markers. Despite the significant decrease, not all of them achieved a normal level at the last control point.

**Conclusions:** Assessment of ROS seems to be a universal parameter with possible application in patients with IE.

**Key words:** infective endocarditis, chemiluminescence, respiratory burst.

## Introduction

Reactive oxygen species (ROS) released during the respiratory burst (RB) are the main protection from bacteria. Their impaired production as in staphylococcal endocarditis results in a severe course of the disease [1]. On the other hand, their uncontrolled generation in the ROS-induced ROS-release mechanism (RIRR) plays a negative role [2]. Postoperatively, increased neutrophil activation due to secondary stimuli such as extracorporeal circulation (ECC) called 'priming' can be observed [3]. It is

expressed by postoperative neutrophilia and their increased capacity for aggregation as well as ROS production. Additionally, increasing levels of acute phase proteins during bacterial infection cause further ROS release [4]. Acute phase proteins, used commonly in treatment monitoring, are unspecific components of the immunological response. They take part in opsonization, complement activation and regulation of immunocompetitive cells, mainly leukocyte activation. Erythrocyte sedimentation rate (ESR) alterations in the course of endocarditis are the result of both plasma protein and cellular blood composition changes such as anemia or leukocytosis. So far, proposed schemes of treatment monitoring in patients with infective endocarditis (IE) have proved unsatisfactory due to lack of specificity of the laboratory parameters as well as difficulty in their interpretation. Researchers continue to seek a parameter that will give rapid responses about the indications for operation and effectiveness of treatment, especially in clinically difficult cases.

Aim of the study was establishing the possible clinical application of ROS in patients with IE; comparison with other commonly used inflammatory markers; the hypothetical usage of ROS level as an indicator in monitoring the treatment of patients operated on for IE.

## Material and methods

The assessed population was composed of 20 patients with diagnosed IE, admitted to the Cardiosurgical Clinic of the Medical University in Lodz during 2007/2008 and subjected to the operation of endocardial vegetation removal. Patients were informed about the planned procedures and additional examinations. Written consent was obtained from the patients if the procedures were not considered as part of the standard cardiosurgical management. The study protocol was approved by the ethical committee of our institutions. The diagnosis of IE was established according to modified Duke's criteria [5]. The population consisted of 7 women and 13 men, aged from 23 to 74 years. The average age was 47.8. NYHA class III accounted for 11 patients (55%). A scheduled operation of prosthetic valve implantation was conducted in 18 patients. In one case it was a reimplantation. Two patients were operated on due to life-threatening indications in an active phase of IE. The complete time of ECC ranged from 65 min to 158 min (average 105 min). The cross clamp time varied from 48 min to 132 min, average 81 min. The heart was perfused with a cold crystalloid cardioplegic solution, given antegrade and non-continuously (from 800 to 1600 ml). Patients had venous blood collected and white blood cells (WBC), procalcitonin (PCT), C-reactive protein (CRP) and ESR levels were assessed at the control points: preoperatively and on the 3rd, 7th, 12th and 21st day after the operation. Simultaneously patients had LBCL carried out from 5 ml venous blood samples collected in the morning. On the basis of this examination respiratory burst and ROS production by activated blood granulocytes (PMNs) and monocytes were determined. The test was conducted within 30 min from the blood collection. Nine hundred fourty-seven µl of luminal warmed to 37°C within 60 min was added to 3 µl of blood. Samples were incubated at 37°C for 30 min. Luminescence was measured during 1 min using a 1251 luminometer (Bio-Orbit, Turku, Finland). After adding 50 µl of formyl-methionyl-leucyl-phenylalanine (fMLP) the measurement was continued for the next 7 min. The measurements were repeated 4 times for each patient and the average value was calculated. Resting chemiluminescence was given in aU/$10^4$ phagocytes (PMNs and monocytes present in assessed sample) and fMLP-stimulated total chemiluminescence (tCL) in aU × s/$10^4$ phagocytes. Peak chemiluminescence (pCL) and peak time were also recorded (respectively presented in aU and s).

### Statistical analysis

Data were analyzed statistically. Values were expressed as mean with standard deviation and median with range. Spearman test was used to determined the correlation between ROS production and particular inflammatory markers. The differences between chosen dependent variables were analyzed by the Wilcoxon test. ANOVA Friedman test with appropriate 'post-hoc' tests was used for assessing the parameters' variability with time.

## Results

Only one case of endocarditis was related to a prosthetic valve. Preoperatively, *Staphylococcus* as an etiological factor was estimated in 50% of positive blood cultures. Fifty-five percent of all preoperative cultures were negative.

In the study a variable connection between the particular assessed inflammatory markers and ROS generation was found. A positive correlation was found only between ROS and preoperative levels of CRP and ESR (level of significance $p < 0.05$). Leukocytosis correlated positively with tCL at the initial control point and with peak time on the 7th postoperative day. Surprisingly, there was no correlation between ROS and PCT.

Although ROS level increased on the 3rd postoperative day, it was not statistically significant. However, during the 21-day observation rCL, tCL and pCL started to decrease from the 3rd day. On the 21st day it reached the value before the operation. On the 12th day a statistically significant ($p < 0.05$)

decrease was noted. The difference between the level of ROS on the 7th day and at subsequent check points was statistically significant ($p < 0.05$). The comparison between preoperative and postoperative peak time showed a statistically significant increase ($p < 0.05$).

The analysis of WBC, CRP, ESR and PCT revealed the highest increase of their values on the 3rd day. At the subsequent control points a gradual decrease of their levels was observed. For all these parameters the differences were statistically significant ($p < 0.05$ for PCT and WBC, $p < 0.02$ for ESR, $p < 0.0001$ for CRP). Furthermore, individual variability of the particular inflammatory parameters' normalization in the examined population was estimated. A statistically significant positive correlation between the preoperative values of CRP and remaining inflammatory markers was noted (Table I).

## Discussion

The cardiosurgical operation of a patient with IE is a model example of a slight balance between contrary immunological mechanisms. Simultaneously, as a result of surgery and ECC usage, the systemic inflammatory response syndrome (SIRS) develops and stimulates the compensatory antiinflammatory response syndrome (CARS). Additionally, the presence of a restricted bacterial focus modifies the patient's response to the surgical trauma.

In comparison to the preoperative values, neutrophilia and lymphopenia, which tend to normalize within the next few days, can be observed [6]. The postoperative lymphopenia, caused by surgery-induced lymphocyte apoptosis, is mainly responsible for the increased organism susceptibility to infection. It is especially significant in patients with IE [7].

Fransen *et al.* [8] assessed PMN activation by evaluating the level of bactericidal permeability increasing protein (BPI) in patients subjected to CABG with or without ECC. Only in the first group did BPI remain elevated and the increase occurred during the aortic cross clamping. On the other hand, Tarnok *et al.* [9] recorded decreased activation of neutrophils during cardiosurgical operations in children. It was proven by decreased expression of the adhesive molecules (LFA-1, Mac-1) and reduced respiratory burst, both basal and PMA-stimulated (PMA – phorbol-12-myristate-13-acetate). The researchers explained this effect by selective filtration of PMNs with increased adhesion capacity and their maintenance in the cardiopulmonary bypass (CPB) device or lung capillaries. Our experience and results confirm that the surgical procedure induces neutrophil activation, oxidative burst in phagocytes and ROS generation. However, a rapid decrease of ROS in the early postoperative period (rCL, tCL, pCL) is a sign of an effective cardiosurgical intervention and uncomplicated recovery. Appropriate antibiotic therapy was also proven to enhance the respiratory burst of neutrophils impaired during general infections in neonates [10]. Consequently, the antibiotic therapy in our patients was effective.

Although the prolongation of postoperative peak time in comparison to preoperative values was observed on the 3rd day, only the difference with the postoperative values from the 21st day was statistically significant. This may be related to impairment of the respiratory burst, probably in the mechanism of exhaustion. This state may be connected with increased susceptibility to recurrence of the infection. In cases of high risk patients or with worse prognosis, antibiotic therapy modification in this period should be considered.

Monocyte suppression (lack of TNF-α release and HLA-DR expression) may be a result of extensive surgery. Grundmann *et al.* [11] discovered that ex vivo monocyte blockade can be achieved with blood from patients after CABG and returned by adding anti-IL-10 and labetalol. Volk *et al.* [12] eliminated catecholamine and cortisol stimulated IL-10 production by applying the thoracic epidural block (TEB). However, they did not obtain elevation in monocyte activation. Hiesmayr *et al.* [13] observed the increase of IL-10 only in cardiosurgical patients in comparison to patients who underwent thoracic surgery. Sbrana *et al.* [14] found an unspecific increase in adhesion of monocytes and platelets as a result of non-receptor membrane changes, induced by ECC. Alterations in the RB level were not present. They suggested that the detected IL-10, responsible for monocyte suppression, was released by myocardial lymphocytes. The researchers conducted the examinations with blood from the coronary sinus. That proves the local immunosupp-

**Table I.** Range and variability of alterations in ROS presentation relying on the basal and fMLP stimulated oxidative burst

| Time of measurement | | Preoperatively (T1) | 3rd day (T2) | 7th day (T3) | 12th day (T4) | 21st day (T5) |
|---|---|---|---|---|---|---|
| Average ± SD | rCL | 1.18 ±0.85 | 1.75 ±1.85 | 1.39 ±1.24 | 0.78 ±0.011 | 0.89 ±0.20 |
| | pCL | 6.56 ±7.69 | 10.61 ±12.3 | 8.46 ±10.50 | 2.31 ±1.45 | 2.89 ±3.12 |
| Min-max | rCL | 0.60-3.10 | 0.70-7.10 | 0.68-5.33 | 0.67-1.05 | 0.62-1.35 |
| | pCL | 1.29-22.68 | 1.21-22.41 | 1.29-25.29 | 1.20-6.05 | 0.89-12.68 |

*T2, T3, T4, T5 measurements in the postoperative period*

ression. Simultaneously, lack of immunological response suppression, connected with a leukocyte activation decrease, is an unfavorable prognostic factor [15].

Documentary data showed the role of IL-6, whose alterations seemed to correlate more specifically with the clinical response to therapy [16]. On the other hand, ECC induces an unspecific increase of IL-6 with maximal values between postoperative hours 6 and 24 [17]. The superiority of ROS relies on its availability.

Studies were also carried out to assess the role of lipopolysaccharide-binding protein (LBP) in the course of endocarditis. Some results are promising. Wollmer *et al.* [18] noted high specificity and sensitivity (> 90%) of this marker. Simultaneously, they estimated the synchrony of LBP and CRP alterations. They confirmed the clinical value of CRP in patients with IE. The LBP showed superiority to CRP only in patients with recurrence of IE during the in-hospital antibiotic therapy. The increase of LBP was observed 3 days prior to the increase of the CRP. According to our results, CRP does not seem to be specific enough for the assessment of a patient with IE and does not show superiority to ESR or WBC. Despite effective therapy it does not normalize in some patients (the median value on the 21$^{st}$ day was 9.3 mg/l). Other researchers did not confirm the diagnostic and prognostic value of LBP, which could be caused by the application of other methods for measurements, as Wollmer suggested. The LBP level was also markedly modified by the surgery. The immediate postoperative period (24-72 h) did not differ in patients with IE or valvular heart disease. In contrast, Ostrowki *et al.* [19] observed even 3-fold postoperative (on the 3$^{rd}$ day) increase in patients with IE in comparison to patients operated on for valvular diseases. In view of the aforementioned results of Tarnok, postoperative RB stimulation in patients with IE may be related to the release of bacterial antigens. It cannot be excluded that in patients with infection the hyperreactive immune system reacts more extensively to the surgical procedure.

An important issue, demanding an individual clinical approach, is population variability in the response to ECC, reflected by the variable antioxidative capacity (AOC) of the plasma [20]. Unavoidable tissue hypoxia during the operation with subsequent reperfusion increases the production of inflammatory cytokines and ROS [21]. Bugajski *et al.* [22] observed that hypoxic myocardial cells produce a factor stimulating plasma neutrophils. It was indirectly confirmed to be endothelin 1. The average time of aortic cross clamping lasting 81 min allowed us to reduce the ROS alterations modified by hypoxia. Documentary data show that 4-h mild or acute hypoxia markedly affects the ROS value and induces cardioblast apoptosis [23]. In each patient we noted increased ROS generation and analogical time variability, which is a huge advantage in comparison to highly individualized inflammatory markers. A further advantage is its faster normalization in comparison to inflammatory markers (the median on the 12$^{th}$ day vs. the 21$^{st}$ day for WBC, ESR, PCT or CRP). What is more, the ROS content in patients' blood, reflecting the oxidative stress, inflammation advancement or correlating with lipid metabolism, does not undergo such sudden alterations [24]. It would be reasonable to assess ROS only preoperatively, on the 3$^{rd}$ and 12$^{th}$ postoperative day.

Although operative mortality has decreased (30% in the 1970s), it continues to be high and ranges from 7.5% to 10% [25]. In our practice it also reached 10%. Based on the authors' experience and knowledge, only acute mitral and aortic insufficiency in the course of endocarditis demands urgent surgical intervention due to no possibility for compensatory mechanism development and the life-threatening state. According to the newest guidelines, heart failure, uncontrolled infection and prevention of peripheral emboli are the indications for surgery (emergent or urgent) [26].

Surprisingly, no correlation between ROS and PCT was noted. As PCT is a principal marker assessing the bacteremia advancement [27], it should have correlated with ROS and RB, stimulated by the bacterial infection. Probably, the lack of correlation between these parameters is a result of various and sudden kinetics of their alterations. Some authors [17] suggested not determining the absolute values of PCT but following the dynamics of its variability. In our study, comparing the median values from the 7$^{th}$ vs. the 12$^{th}$ postoperative day, we observed a 3-fold decrease of PCT. It should be kept in mind that PCT increases moderately during extensive surgery [27]. This marker, which should achieve normal limits within 2 days on condition of proper antibiotic therapy, is regarded as being more specific and sensitive than CRP, leukocytosis or IL-6 [17, 27]. Our analysis has not confirmed its superiority in patients with IE [28].

The outcomes of our study show the compatibility between ESR, CRP and LBCL variability over time. They also prove the uselessness of the common control of the above two parameters in patients with IE, as was also confirmed by other researchers. They proved mild compatibility between them (67%) and the superiority of CRP in inflammatory diseases [29]. The correlation between ROS and CRP is not so obvious in the aspect of the mentioned CRP regulative role of leukocyte activation in the infection. This protein takes part in the inhibition of neutrophil chemotaxis and has a slight chemotactic activity on monocytes. Furthermore, it inhibits ROS production, even stimulated by fMLP, which is interpreted as its protective effect on tissues, defending them against oxidative stress [30].

On the other hand, it is known to have a negative role in the induction of ROS production by the endothelial progenitor cells, resulting in their increased tendency to apoptosis [31]. The choice of ROS examination seems to be more appropriate also in the view of unspecific CRP, whose increase is observed in burns, myocardial infarction, acute pancreas inflammation, pregnancy, neoplasms, obesity and renal dysfunction [32, 33]. Other studies also confirmed the connection between ROS decrease and patient clinical improvement [19]. The positive correlation between the increase of ROS and the inflammatory markers, found in this study, is indirect evidence of their clinical impact.

The clinical utility of new tests (FORT) assessing the content of ROS in patients' blood was found in myocardial infarction [34]. Their application in patients with endocarditis would be a fast indicator of disease progression.

It should be emphasized that the choice of monitoring parameter depends on the way of treatment: conservative or surgical. It should be included in assessment of inflammatory markers or cytokines. In our opinion ROS level could be a universal indicator, which does not exclude the individualized approach in each episode of IE. The ROS may have a particular implication in high-risk patients, especially when the assays of inflammatory markers are confusing.

Our study has some important limitations. They mainly concern the small number of enrolled patients, which could have disturbed the statistical assessment. However, the number of patients operated on annually for endocarditis in our clinic is 20-30 patients. The purpose of this research was to assess only the most commonly used biochemical markers. These selected markers were also taken into consideration in our previous study [28].

In conclusion, ROS level assessment in patients with IE seems to have wider clinical implications than monitoring inflammatory markers such as WBC, CRP, PCT or ESR. The ROS decrease within the complex treatment of patients with endocarditis was confirmed. Further studies are needed to evaluate the specificity of ROS examination in patients with IE to exclude the marked influence of respiratory hypoxia, obesity, diabetes and other factors inducing RB and also other ways of ROS generation. The contribution of tissue trauma seems to have reduced the impact on the RB and ROS level. FORT application could ensure a rapid, non-invasive, simple and economical indicator in monitoring patients with IE.

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