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Systemic inflammatory response syndrome after on-pump cardiac surgery in emergency coronary artery bypass grafting: a retrospective trial

L.A. Krichevskiy[1,2,*], A.A. Dvoryadkin[1], D.A. Polyakov[1], E.V. Belyakova[1], D.N. Protsenko[3,4]

[1] S.S. Yudin City Clinical Hospital, Moscow, Russia
[2] Russian Medical Academy of Continuing Professional Education, Moscow, Russia
[3] Moscow Multidisciplinary Clinical Center "Kommunarka", Moscow, Russia
[4] Pirogov Russian National Research Medical University (RNRMU), Moscow, Russia

Abstract

INTRODUCTION: The frequency, spectrum and pathophysiological relationships of systemic inflammatory response syndrome in acute coronary artery bypass grafting is not fully understood. **OBJECTIVE:** To determine the clinical significance of systemic inflammatory response syndrome (SIRS) in emergency coronary artery bypass grafting (CABG) performed with cardiopulmonary bypass. **MATERIALS AND METHODS:** We examined 60 patients (38 men and 22 women, aged 65 ± 9 years) who underwent emergency CABG (3 ± 1 bypass), with cardiopulmonary bypass (CPB) (97 ± 47 min). We retrospectively studied clinical and laboratory data of the perioperative and early postoperative period from emergency and elective coronary bypass surgery. **RESULTS:** In urgently operated patients ($n = 30$) in the early postoperative period, a higher frequency (53.3 and 13.3 %; $p = 0.0022$) of the development of systemic manifestations of the inflammatory response (neutrophilic leukocytosis, fever, postperfusion vasoplegia), as well as respiratory complications (70 and 10 %; $p < 0.001$) was noted. A pathophysiological relationship was established between the manifestations of SIRS and respiratory dysfunction during emergency interventions. **CONCLUSIONS:** SIRS pathophysiologically associated with respiratory dysfunction is characteristic of emergency CABG.

Системный постперфузионный воспалительный ответ при экстренном коронарном шунтировании: ретроспективное исследование

Л.А. Кричевский[1,2,*], А.А. Дворядкин[1], Д.А. Поляков[1], Е.В. Белякова[1], Д.Н. Проценко[3,4]

[1] ГБУЗ города Москвы «Городская клиническая больница им. С.С. Юдина» Департамента здравоохранения города Москвы, Москва, Россия
[2] ФГБОУ ДПО «Российская медицинская академия непрерывного профессионального образования», Москва, Россия
[3] ГБУЗ «Московский многопрофильный клинический центр "Коммунарка"» Департамента здравоохранения города Москвы, Москва, Россия
[4] ФГАОУ ВО «Российский национальный исследовательский медицинский университет им. Н.И. Пирогова», Москва, Россия

Реферат

АКТУАЛЬНОСТЬ: Частота развития, спектр и патофизиологические взаимосвязи основных клинических проявлений системного воспалительного ответа при экстренном аортокоронарном шунтировании (АКШ) не до конца изучены. **ЦЕЛЬ ИССЛЕДОВАНИЯ:** Определить клиническое значение системного воспалительного ответа (СВО) при экстренном АКШ, выполняемом в условиях искусственного кровообращения (ИК). **МАТЕРИАЛЫ И МЕТОДЫ:** Обследовали 60 пациентов (мужчины, $n = 38$, и женщины, $n = 22$; средний возраст 65 ± 9 лет), перенесших экстренное АКШ (3 ± 1 шунт) в условиях ИК (97 ± 47 мин). Ретроспективно изучили клинико-лабораторные данные периоперационного и раннего послеоперационного периода при экстренном и плановом АКШ. **РЕЗУЛЬТАТЫ:** У экстренно оперированных пациентов ($n = 30$) в раннем послеоперационном периоде отметили большую частоту (53,3 и 13,3 %; $p = 0{,}0022$) развития системных проявлений воспалительного ответа (нейтрофильный лейкоцитоз, лихорадка, постперфузионная вазоплегия), а также респираторных осложнений (70 и 10 %; $p < 0{,}001$). Установили патофизиологическую взаимосвязь между проявлениями СВО и респираторной дисфункции при экстренных вмешательствах. **ВЫВОДЫ:** Системный воспалительный

It is during emergency myocardial revascularization that the duration of cardiopulmonary bypass and myocardial ischemia (MI) are predictors of SIRS.

ответ, патофизиологически ассоциированный с респираторной дисфункцией, характерен для экстренного коронарного шунтирования. Именно при экстренной реваскуляризации миокарда длительность ИК и ишемии миокарда является предиктором СВО.

KEYWORDS: cardiac surgical procedures, cardiopulmonary bypass, systemic inflammatory response syndrome

КЛЮЧЕВЫЕ СЛОВА: кардиохирургия, искусственное кровообращение, синдром системного воспалительного ответа

* *For correspondence:* Lev A. Krichevskiy — Dr. Med. Sci., Intensivist, Chief of the Department of Anesthesiology and Reanimatology No 2, City clinical hospital named after S.S. Yudin, Head of the Department of Anesthesiology and Reanimatology named after Professor E.A. Damir, Russian Medical Academy of Continuing Professional Education, Moscow, Russia; e-mail: levkrich72@gmail.com

* *Для корреспонденции:* Кричевский Лев Анатольевич — д-р мед. наук, профессор, заведующий отделением анестезиологии и реаниматологии № 2, городская клиническая больница им. С.С. Юдина, заведующий кафедрой анестезиологии и реаниматологии имени профессора Е.А. Дамир ФГБОУ ДПО «Российская медицинская академия непрерывного профессионального образования», Москва, Россия; e-mail: levkrich72@gmail.com

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Introduction

Depending on the criteria taken into account, the systematic inflammatory response syndrome (SIRS) complicates 5–50 % of all cardiopulmonary bypass (CPB) procedures used in cardiac surgeries [1]. SIRS is an expected consequence of CPB associated with several pathogenetic factors: blood contact with synthetic surface of extracorporeal circuit [2]; myocardial ischemia and subsequent reperfusion of myocardium and lungs [3, 4]; activation of neutrophils and other immune cells [5]; use of heparin and protamine [6], etc. SIRS clinical manifestations are well-known and, as a rule, it all comes to a combination of vasoplegic syndrome, fever, metabolic disorders (hyperlactatemia, hyperglycemia, etc.) as well as an increase in inflammatory markers level [7]. In the majority of cases, postperfusion SIRS has no prognostic significance, since etiological factor itself is finite [8], however it is associated with a certain aggravation of the early post-surgery period even under favorable clinical course [9]. At the same time, in a number of cases SIRS may have a persistent, rather severe clinical course, which directly affects surgical outcome [10].

Surgical treatment of acute coronary syndrome performed with CPB in itself can be certainly considered as SIRS trigger [11]. Inability to perform standard preoperative preparation and examination, foci of chronic infection sanitation [12], presence of another comorbid disorder (chronic obstructive pulmonary disease [COPD], multifocal atherosclerosis, diabetes, etc.), stay in intensive care unit (ICU) and inevitable contact with hospital flora before surgical intervention, and, finally, actual ischemic myocardial injury [13] may be the key factors conductive to it in the given situation.

Objective

Determine clinical significance of SIRS in emergency CABG performed with CPB.

Materials and methods

On the basis of City Clinical Hospital named after S.S Yudin, 60 patients (38 men and 22 women) aged 65 ± 9 years, who underwent elective (n = 30) and emergency (n = 30) cardiac surgical treatment with CPB (97 ± 47) and cold blood cardioplegia (aortic cross-clamp time 58 ± 35) were retrospectively examined. Criteria for including patients in the main group (emergency patients): 1) presence of acute coronary syndrome (ACS); 2) impossibility of endovascular intervention; 3) performing emergency coronary bypass grafting with CPB. The control group included patients without ACS, who underwent elective coronary bypass grafting with CPB. Patients were simultaneously recruited into groups starting from February 1, 2018. The study did not involve patients with obvious signs of acute infection or exacerbation of chronic infection disease, immunodeficiency or septic states as well as cancer.

Intravenous injection of midazolam 0.05–0.08 mg/kg, propofol 0.5–2 mg/kg, fentanyl 2.5–3.5 mcg/kg and rocuronium bromide 1 mg/kg were used to induce general anesthesia of all operated patients. Anesthesia was maintained by means of sevoflurane 0.5–1.0 of minimum alveolar concentration, whereas propofol (3–4 mg/kg/h) was used during CPB. Fentanyl was injected intravenously by infusion at a dose of 3–4 mcg/kg/h, and was also added fractionally at the traumatic stages of surgery at a dose of 2–4 mcg/kg. Myoplegia was maintained by fractional intravenous injection of rocuronium bromide.

CPB was always performed in the normothermy mode with a perfusion index of 2.4 l/min/m^2 by means of Jostra-20 device (Maquet). Balanced crystalloid (700 ml) and colloidal solutions (500 ml gelatin solution), 4 % sodium bicarbonate solution (100 ml) were used for primary filling of CPB line. Cold blood cardioplegia was used in all cases to protect the myocardium during aortic cross-clamp. Systematic heparinization was performed in an amount of 300 units/kg to achieve the targeted activated coagulation time > 450 s.

The criteria of perioperative SIRS involved one or more of the following factors developed within 24 hours after surgery: 1) leukocytes level increase > 20 × 10^9/L; 2) body temperature rise > 38.0 °C; 3) development of vasoplegia requiring vasoconstrictor therapy with norepinephrine for more than 24 hours.

Assessment of general clinical and laboratory data as well as central hemodynamics parameters in both groups was carried out: 1) initially — before surgical intervention; 2) immediately after completion of surgery and transportation to ICU. Additional attention was paid to the identification of perioperative SIRS signs that are systemic and may affect the respiratory system. For these reasons, combinations (combined endpoints) of the corresponding symptoms were additionally taken into account in study groups. There were cases, when perioperative SIRS was combined with signs of lung inflammatory process/respiratory dysfunction.

Vasoactive and inotropic indices were used to assess the severity of inotropic and vasopressor therapy at all stages of study. When calculating inotropic index, commonly-accepted formula was used: dopamine dosage (mcg/kg/min) + dobutamine (mcg/kg/min) + epinephrine 100×(mcg/kg/min), when calculating vasoactive index: dopamine dosage (mcg/kg/min) + dobutamine (mcg/kg/min) + epinephrine 100×(mcg/kg/min) + norepinephrine 100×(mcg/kg/min).

Statistical analysis was performed with the benefit of commercial programs — Microsoft Excel and Medcalc. Kolmogorov-Smirnov method was used to determine the shape of distribution. In case of normal distribution, data was presented as (M ± σ), Student's t-test was used to compare the data; in the event of abnormal distribution, data was presented as Me (Q1; Q3), Mann-Whitney test was used to compare the data. Pearson correlation analysis (correlation coefficient R) was carried out to determine the relationship between studied numerical parameters. ROC curves (receiver operating characteristic) analysis with calculation of area under the curve — AUC ROC (area under the ROC curve) and cut-off threshold (cut-off) was used to assess the prognostic effect of expected predictors on the occurrence of predicted event. In addition, Kaplan-Meyer curves were plotted to illustrate the influence of studied factor on the rate of occurrence of event. Fisher's criterion was used to intergroup frequency comparison. The differences and relationships between parameters were considered as valid at $p < 0.05$.

Results

Archived data of patients who underwent elective (group 1) and emergency (group 2) CABG surgery was analyzed. In the emergency group (group 2) 3 patients (10 %) were operated having acute myocardial infarction (AMI) with ST segment elevation, 8 patients (27 %) — having AMI without ST elevation and 19 patients (63 %) – having unstable angina with a high risk of lethality (Global Registry of Acute Coronary Events (GRACE) — a scale for assessing the risk of lethality and development of myocardial infarction > 6 %). At the same time, 6 patients (20 %) of emergency group were operated within 48 hours after the development of myocardial infarction, 24 patients (80 %) — within 3–7 days. Initial state parameters of patients who underwent surgery did not differ in two study groups, except for troponin level, which was significantly higher before emergency coronary artery bypass grafting (CABG) ($p < 0.0001$) compared to the group of elective patients. The surgical intervention risk, expressed in points according to the EuroSCORE scale, was also higher in the group of emergency patients ($p = 0.014$), obviously reflecting the urgency of surgical intervention (Table 1).

A comparative analysis of clinical and laboratory data of the early post-surgery period in study groups has shown significantly higher numbers of neutrophilic leukocytes in the

Table 1. Clinical and laboratory results of the initial state patients and operations performed in the group of elective and emergency coronary artery bypass grafting (CABG)

Parameters	Coronary bypass surgery		*p*
	Group 1 (*n* = 30), elective	Group 2 (*n* = 30), emergency	
EuroSCORE, points	3.3 ± 1.1	7.2 ± 2.6	0.014
Age, years	66 ± 8	64 ± 9	0.495
LVEF, %	51 ± 9	49 ± 11	0.314
Bypassed arteries, *n*	3 ± 1	3 ± 1	0.857
CPB, min	89 (75; 104)	91 (64; 110)	0.716
MI, min	50 (45; 59)	45 (38; 64)	0.205
Hemoglobin, g/l	124 ± 16	121 ± 20	0.582
Hematocrit index, %	37 ± 5	36 ± 6	0.415
Leukocytes, $\times 10^9$/L	6 (5.2; 7.2)	6.5 (4.7; 8)	0.121
Troponin prior to surgery, ng/ml	0.02 (0.01; 0.05)	0.38 (0.2; 1.5)	< 0.0001
Lactate, mmol/L	1 ± 0.3	1.2 ± 0.3	0.113

Data is presented as M ± σ, Me (Q1; Q3).
CPB — cardiopulmonary bypass; EuroSCORE (European System for Cardiac Operative Risk Evaluation) — a scale for assessing the risk of cardiac surgery; LVEF — left ventricular ejection fraction; MI — myocardial ischemia.

Table 2. Hemodynamic and laboratory parameters after transfer from the operating room to the intensive care unit

Parameters	Coronary bypass surgery		*p*
	Group 1 (*n* = 30), elective	Group 2 (*n* = 30), emergency	
MAP, mm Hg	83 ± 6	82 ± 8	0.538
MPAP., mm Hg	15 ± 3	16 ± 2	0.221
HR, min^{-1}	78 ± 13	89 ± 14	0.002
CVP, mm Hg	7 ± 2	8 ± 1	0.201
CI, $l/min/m^2$	3.2 ± 0.5	3.0 ± 0.5	0.349
II, points	0 (0; 3)	3 (0.8; 5.1)	0.003
VI, points	0 (0; 3)	4 (1.8; 14.5)	0.003
SVRI, $dyne/s/sm^{-5}m^2$	1873 (1697; 2119)	1823 (1683; 2080)	0.331
Hemoglobin, g/l	106 ± 17	106 ± 15	0.846
Hematocrit index, %	32 ± 5	32 ± 4	0.880
Leukocytes, $\times 10^9$/L	11.9 (9.3; 14.9)	13.2 (10.2; 18.7)	0.044
Ph (potentia hydrogenii)	7.41 ± 0.05	7.37 ± 0.08	0.021
Lactate, mmol/L	1.5 (1.3; 1.9)	2 (1.5; 2.9)	0.022
SaO_2, %	98.9 ± 0.4	98.6 ± 0.7	0.011
PaO_2/FiO_2, mm Hg	405 ± 97	350 ± 77	0.016
Patients with leukocytosis >20 × 10^9/L, *n* (%)	1	5	0.195

Data is presented as M ± σ, Me (Q1; Q3).
CI — cardiac index; CVP — central venous pressure; HR — heart rate; II — inotropic index; MAP — mean arterial pressure; MPAP — mean pulmonary artery pressure; PaO_2/FiO_2 — the ratio of the partial pressure of oxygen in arterial blood to the fraction of inhaled O_2; SVRI — systemic vascular resistance index; SaO_2 — arterial blood saturation; VI — vasoactive index.

group of emergency patients ($p = 0.044$), more prominent features of respiratory dysfunction characterized by a decrease in the ratio of oxygen partial pressure in arterial blood to the fraction of inhaled oxygen (PaO_2/FiO_2) ($p = 0.016$), as well as acid-base imbalance and lactate acidosis ($p = 0.022$) in the given group (Table 2). There were more prominent features of postperfusion cardiovascular insufficiency requiring longer inotropic and vasopressor support ($p = 0.015$) in the group of emergency patients (Table 3).

It was revealed that the duration of emergency patients' stay both in ICU ($p = 0.047$) and in the hospital ($p = 0.033$) in general was significantly higher (compared to the group of elective patients) focusing on inotropic, vasoconstrictor and respiratory support (Table 3).

Further analysis of early post-surgery data revealed that SIRS symptoms and respiratory disorders were more common in the group of emergency patients both individually and in combination with each other (Table 4).

Thus, the SIRS is more common for early post-surgery period of emergency patients compared to elective patients, and is characterized by neutrophilic leukocytosis, fever and postperfusion vasoplegia as well as respiratory disorders, which require longer respiratory support. Diagnostics of common combination of systematic and respiratory manifestations of inflammatory response in the group of emergency patients became a prerequisite for further analysis. It was revealed during the study that after emergency surgeries, severe respiratory disorders (requiring LV for more than 8 hours, $n = 9$) were found only in case of SIRS presence ($n = 16$), whereas other emergency patients without SIRS ($n = 14$) did not have these disorders (with SIRS — 56 %, without SIRS — 0 %, respectively; $p < 0.01$). It was also found that there were

Table 3. Comparative analysis of the early postoperative period in the groups of emergency and elective coronary artery bypass grafting, *n* (%)

Parameters	Coronary bypass surgery		*p*
	Group 1 (*n* = 30), elective	Group 2 (*n* = 30), emergency	
LV, h	5 (3.2; 8.3)	6 (3.5; 12)	0.095
Inotropic and vasopressor therapy, h	3 (0; 9)	10 (2.5; 36)	0.015
Need for norepinephrine infusion > 24 h	2 (6.6 %)	9 (30 %)	0.012
Temperature (maximum t on the first day), °C	37.2 (36.8; 37.4)	37.6 (36.9; 37.8)	0.047
Patients with fever >38 °C on the first post-surgery day, *n* (%)	3	7	0.299
Duration of stay in ICU, days	1 (1; 2)	2 (1; 6)	0.047
Cases of rehospitalization in ICU, *n*	1 (3.3 %)	3 (10 %)	0.612
Duration of hospitalization, days	11 ± 3	14 ± 7	0.033
Perioperative myocardial infarction, *n*	0 (0 %)	1 (3 %)	1
Lethality, *n*	0 (0 %)	2 (7 %)	0.237

Data is presented as M ± σ, Me (Q1; Q3), *n* (%).
LV — lung ventilation.

Table 4. Combined criteria (endpoints) of systemic and/or respiratory inflammatory process after elective and emergency coronary bypass surgery, *n* (%)

Endpoints	Coronary bypass surgery		*p*
	Group 1 (*n* = 30), elective	Group 2 (*n* = 30), emergency	
Respiratory disorders*	3 (10 %)	21 (70 %)	< 0.001
Severe respiratory disorders**	1 (3.3 %)	9 (30 %)	0.012
Systematic inflammatory response#	4 (14 %)	16 (54 %)	0.0022
Respiratory disorders and SIRS##	2 (7 %)	12 (40 %)	0.004

* One or more signs: pneumonia, atelectasis, effusion in the pleural cavity of more than 500 ml, exacerbation of chronic obstructive pulmonary disease. ** Respiratory disorders that required postoperative LV for more than 8 hours. # One or more signs: vasoplegia > 24 hours; fever > 38 °C; neutrophilic leukocytosis > 20×10^9/L.
Combination of (*) and (#).

moderate dependencies of PaO_2/FiO_2 index on the level of blood fibrinogen immediately after surgery in the group of emergency patients (Figure 1) and peak blood temperature during the first post-surgery day (Figure 2). Similar correlations were absent in the group of elective surgeries.

Further, the possible effect of postperfusion SIRS on the rate of post-surgery activation was analyzed in the group of emergency patients and such dependence was revealed. Significantly different rate of tracheal extubation ($p = 0.0036$) after emergency myocardial revascularization (group 2) depending on post-surgery blood neutrophil level of greater or less than 13.5×10^9/L is shown in the form of Kaplan-Meyer curves (Figure 3).

Further, an in-depth analysis of group 2 ($n = 30$) revealed that the subgroup of patients with post-surgery SIRS symptoms ($n = 16$) had significantly higher CPB and MI duration ($p < 0.05$) compared to the subgroup of patients without SIRS symptoms ($n = 14$) (Table 5).

Subsequent analysis of ROC curves showed that CPB and MI duration of more than 40 minutes and 73 minutes, respectively, was a significant predictor of SIRS development in the group of emergency patients (Figure 4 and 5).

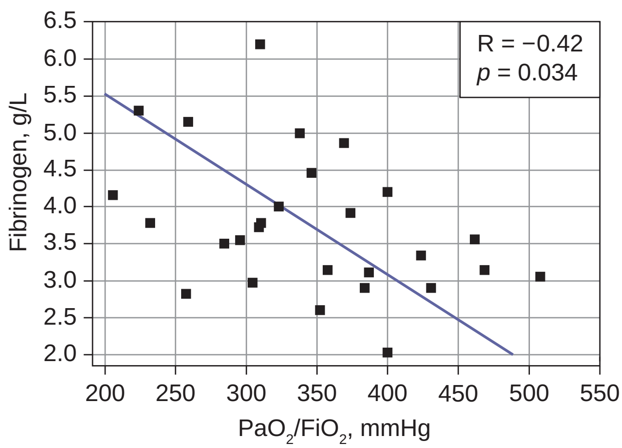

Fig. 1. Moderate significant inverse correlation between fibrinogen level and PaO_2/FiO_2 index immediately after emergency CABG (group 2)

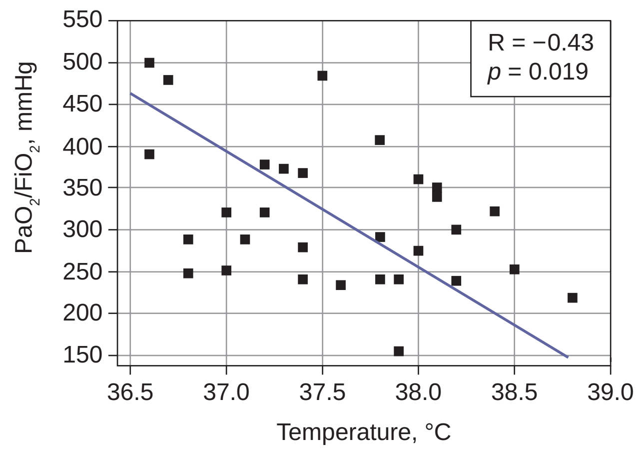

Fig. 2. Moderate significant inverse correlation between the PaO_2/FiO_2 index immediately after emergency CABG (group 2) and peak body temperature on the first postoperative day

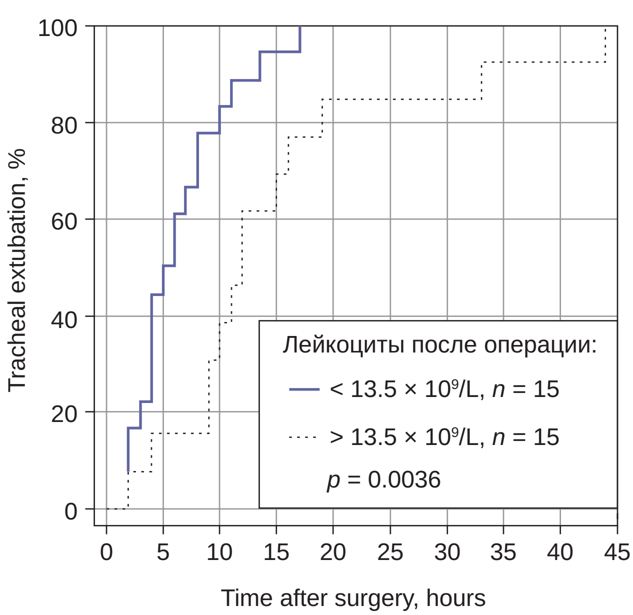

Fig. 3. Kaplan-Meier analysis of the rate of postoperative tracheal extubation after emergency CABG (group 2) depending on the level of neutrophilic leukocytosis immediately after surgery

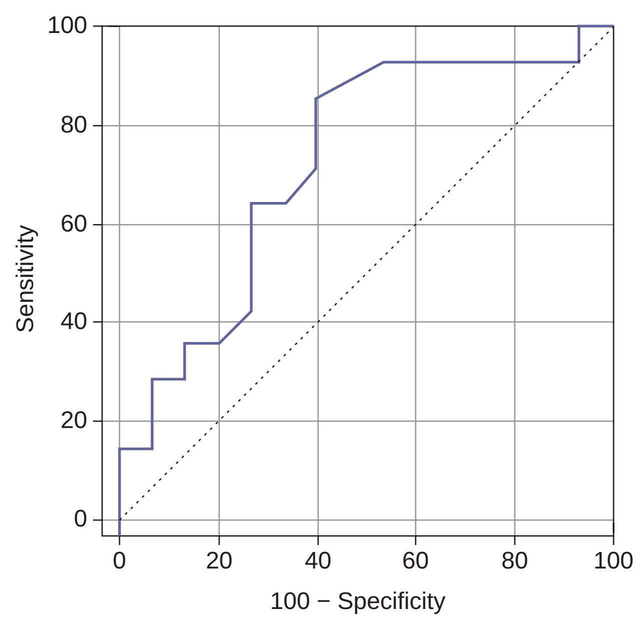

Fig. 4. ROC-curve of the dependence of development of SIRS in the early postoperative period on the duration of MI. AUC ROC = 0,724 (95 % CI: 0,527–0,872; p = 0,024). Cut-off = 40 min (sensitivity — 85,7 %, specificity — 60 %)

Table 5. Comparative analysis of a group of emergency patients ($n = 30$)

Parameter	Patients with SIRS ($n = 16$)	Patients without SIRS ($n = 14$)	p
CPB, min	102 (81; 129)	71 (59; 88)	0.018
MI, min	54 (43; 73)	40 (36; 45)	0.049
EF, %	51 (45; 58)	57 (47; 62)	0.235
Age, years	64 (53; 75)	64 (61; 69)	0.821
Troponin level prior to surgery, ng/ml	0.2 (0.08; 0.9)	0.4 (0.1; 1.4)	0.44
Leukocytes prior to surgery, ×10⁹/L	6.9 (4.6; 9)	6.7 (5; 8)	0.879

Data is presented as M ± σ, Me (Q1; Q3), *n* (%).
CPB — cardiopulmonary bypass; EF — ejection fraction; MI — myocardial ischemia.

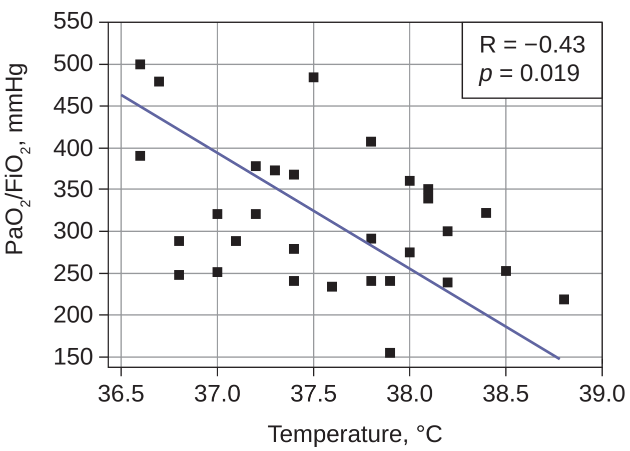

Fig. 5. ROC-curve of the dependence of development of SIRS in the early postoperative period on the duration of CPB. AUC ROC = 0,693 (95 % CI: 0,506–0,843; p = 0,049). Cut-off = 73 min (sensitivity — 88 %, specificity — 56 %)

Discussion

CABG surgeries have become the focus of our attention due to their insatiable demand and high risk [14]. Perioperative myocardial injury as an obvious adverse factor has been studied comprehensively earlier [4]. The role of ischemic myocardial injury, which occurs immediately before emergency surgical intervention is understudied. It is well-known that acute ischemia and myocardial infarction are independent SIRS triggers causing activation of inflammatory cascades and synthesis of various inflammatory mediators such as interleukins-1, -6, tumor necrosis factor α, nuclear factor κB, metalloproteinases-1, -9, etc., and inflammatory response associated with ischemic/reperfusion myocardial injury — an independent predictor of shock, multiple organ failure and lethality [11]. However, the direct pathophysiological significance of SIRS in emergency coronary bypass grafting remains in the background, despite its relevance.

The initial assumption of an increased SIRS risk in the event of emergency CABG was primarily associated with acute coronary syndrome and ischemic myocardial injury as well as subsequent reperfusion in perioperative period; possible disorders of central hemodynamics in the given category of patients before and during surgery [11, 15]. The results obtained at the retrospective stage of this study fully confirmed the original hypothesis. Indeed, the manifestations and symptoms of inflammatory syndrome have a significant impact on a clinical scenario and prognosis in the early stages after emergency CABG. At the same time, emergency nature of cardiac surgery is not specifically considered in the literature as a risk factor of SIRS [2]. Obviously, it may occur due to the fact that researchers pay their attention exclusively to the actual myocardial damage and acute cardiac failure in the given clinical situation [11]. At the same time, practical significance of inflammatory response in emergency cardiac surgery remains in the background. Thus, one may talk of scientific novelty of these findings.

The data obtained suggests that the duration of CPB and MI play a crucial role in the SIRS development after emergency CABG. In addition, a pathophysiological relationship between SIRS and severity of respiratory dysfunction was revealed in the early postperfusion period among the given category of patients. This dependence may indicate both pathogenetic role of lung ischemia-reperfusion in SIRS development, and their damage as a result of inflammatory response. From a scientific and practical point of view, this data forces us to pay attention to measures of lung protection and rehabilitation in post-surgery period complicated by postperfusion SIRS [16, 17]. Methods aimed at SIRS prevention with CPB are being actively developed, including the use of both pharmacological measures and various mechanical devices, which effectiveness has not been proved yet, and accessibility of those is very limited [18]. Within the framework of this study, we did not use any specific measures to prevent postperfusion SIRS due to the lack of commonly-accepted recommended protocols [18].

Conclusion

Emergency CABG surgeries have an increased risk of SIRS development compared to elective surgeries. At the same time, inflammatory response is associated with respiratory disorders, which are actually involved in the clinical and pathophysiological scenarios of SIRS in the given clinical situation. In addition, CPB and MI duration is a significant predictor of SIRS development specifically in the event of emergency myocardial revasculization surgery.

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Author's ORCID:

Krichevskiy L.A. — 0000-0001-8886-7175
Dvoryadkin A.A. — 0000-0002-1595-8663
Polyakov D.A. — 0000-0002-0334-4138
Belyakova E.V. — 0009-0003-7196-0535
Protsenko D.N. — 0000-0002-5166-3280

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