

Monocyte Syk Phosphorylation as a Candidate Biomarker of Vasoplegic Shock After Cardiac Surgery with Cardiopulmonary Bypass: A Proof-of-Concept Observational Study

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Abstract

Background

Vasoplegic shock after cardiac surgery with cardiopulmonary bypass (CPB) is a frequent complication associated with significant morbidity and mortality. The aim of this study was to identify candidate biomarkers of vasoplegic shock on the first postoperative day (POD 1) following cardiac surgery with CPB among three effector proteins of Fc receptor signalling: spleen tyrosine kinase (Syk), phospholipase C gamma (PLC-G) and Src homology 2 domain-containing phosphatase 1 (SHP-1), in monocytes and neutrophils.

Methods

Patients undergoing cardiac surgery with scheduled CPB without autoimmune disease or preoperative infection were included. The expression of phosphorylated Syk, PLC-G and SHP-1 in monocytes and neutrophils was measured by flow cytometry prior to (T0) and after (T1) CPB on PODs 1, 3 and 7. Associations between norepinephrine (NOR) use on POD 1 and protein fluorescence at T1 or T1/T0 ratios were assessed.

Results

Of the 23 patients analysed, four (17%) had NOR on POD 1. NOR on POD 1 was not associated with protein expression at T1. The T1/T0 ratio of Syk in monocytes was lower in patients without NOR on POD 1 ($p = 0.032$). The area under the ROC curve was 0.85 [0.60-1.00]; a threshold of 0.47 provided a sensitivity of 100% (95% CI 40–100) and a specificity of 74% (95% CI 49–91). This association did not remain significant after Bonferroni correction for the six comparisons performed (adjusted $p = 0.19$).

Conclusions

In this exploratory study, monocyte Syk phosphorylation status may represent a candidate biomarker of vasoplegic shock following cardiac surgery with CPB, warranting validation in an independent cohort.

1. Background

Despite the progress made in recent years, cardiac surgery with cardiopulmonary bypass (CPB) is still associated with significant morbidity and mortality rates [1]. Enhanced recovery after surgery protocols have been implemented in many surgical specialties, including cardiac surgery [2]. These programmes reduce postoperative complications, length of stay, and costs [3, 4]. However, the presence of postoperative shock contraindicates some early rehabilitation measures and limits their benefits.

One of the main causes of postoperative shock following cardiac surgery with CPB is vasoplegic shock, which can be associated with organ failure, such as acute kidney injury. This results in a significant inflammatory response generated by the surgical stimulus and the CPB itself [5]. Blood perfusion in the

CPB circuit leads to the activation of immune cells [6]. Neutrophils and monocytes are the primary effectors of this inflammatory response. Monocyte activation results in the secretion of cytokines, and neutrophil activation leads to the extracellular release of cytotoxic molecules and reactive oxygen species that lyse the extracellular matrix and epithelial cell junctions, resulting in increased vascular permeability, microthrombi formation, and parenchymal cell injury [7]. The main immunoreceptors of both monocytes and neutrophils are the receptors for the constant region of antibodies, the Fc receptors (FcRs). Activation of FcRs, through the recognition of their ligands, triggers signalling cascades leading to modulation of the inflammatory response [8]. Depending on the ligand and on the strength of receptor engagement, they transduce either an activating signal through the immunoreceptor tyrosine-based activation motif (ITAM) in its activating configuration (ITAMa), mediated by phosphorylation of spleen tyrosine kinase (Syk) which in turn phosphorylates phospholipase C gamma (PLC-G), or an inhibitory signal (ITAMi) mediated by phosphorylation of Src homology 2 domain-containing phosphatase 1 (SHP-1).

A deeper understanding of the activation of these phagocytic cells could help clinicians better understand the inflammatory response and its complications after cardiac surgery. Many predictive biomarkers have been described in cardiac surgery [9–11]. These markers, however, either reflect established organ injury or measure the circulating concentration of inflammatory mediators; to the best of our knowledge, no study has assessed the intracellular phosphorylation status of the FcR signalling pathway in circulating monocytes and neutrophils as an early perioperative marker in adult cardiac surgery. Measuring the activation state of the effector cells themselves, rather than the mediators they release, may capture the individual intensity of the immune response to CPB more directly. The aim of this study was to identify candidate biomarkers of vasoplegic shock on the first postoperative day (POD 1) following cardiac surgery with CPB that could be used in daily practice and could help physicians select patients for early rehabilitation measures or for early haemodynamic optimisation measures.

2. Patients and methods

2.1. Study design

This prospective, monocentric, proof-of-concept observational study was performed according to current guidelines in a tertiary care teaching hospital performing more than 1,000 annual cardiac surgical procedures with CPB.

Between June 1st and September 30th, 2019, all patients hospitalised for cardiac surgery with CPB scheduled on a Tuesday morning were eligible. For reasons of technical feasibility related to the sampling schedule, only two patients per week could be included on Tuesday mornings. This allowed each blood sample to be processed immediately after collection on working days. The non-inclusion criteria were preoperative infection, long-term immunosuppressive therapy (corticosteroids), patients lacking decision-making capacity, minors, and patient refusal to participate in the study. Patients in whom immunological markers were not assessed at the end of CPB were also excluded; this occurred

exclusively because of the unavailability of flow cytometry reagents on the day of surgery, an event unrelated to patient characteristics or to the postoperative course (Fig. 1).

The interval between data collection and manuscript submission resulted from several compounding factors: disruption caused by the COVID-19 pandemic, a one-year editorial process at Scientific Reports, and a subsequent delay caused by the unwitting submission of this work to a fraudulent website impersonating BMC Surgery, which was identified and required resolution before a legitimate resubmission could be pursued.

2.2. Objectives

Vasoplegic shock was defined, in line with current expert consensus, as a mean arterial pressure below 65 mmHg despite adequate fluid resuscitation and in the absence of a low cardiac index on echocardiography, requiring vasopressor support. Because continuous haemodynamic and echocardiographic variables were not recorded prospectively in this pilot study, the need for norepinephrine (NOR) on POD 1 was used as an operational surrogate for this definition: in our unit NOR is prescribed according to a written protocol applying exactly these criteria (see 2.4.3), so that NOR exposure on POD 1 identifies patients meeting the haemodynamic definition of vasoplegia beyond the immediate post-CPB period. The primary endpoint was therefore to identify a marker measured at the end of surgery capable of predicting the need for NOR on POD 1, among three proteins mediating monocyte and neutrophil FcR signalling: SHP-1, Syk, and PLC-G. Secondary endpoints were to evaluate the evolution of the phosphorylation of SHP-1, Syk, and PLC-G during the first 7 PODs. Circulating cytokine concentrations were also measured in this cohort; these data address a distinct research question and will be reported separately.

2.3. Data collection

2.3.1. Clinical data

Clinical data were prospectively collected on PODs 0, 1, 3 and 7.

2.3.2. Biological data

Blood collections scheduled for the study were as follows. The first blood sample (T0) was collected after anaesthetic induction and before any surgical stimulus. It was used to evaluate the baseline value of each marker. Blood samples were then obtained at the end of CPB (T1), on the morning of POD 1 (T2), on the morning of POD 3 (T3), and finally on the morning of POD 7 (T4). T0 and T1 blood samples were collected during the pre- and post-CPB biological analyses, respectively. T2, T3, and T4 blood samples were collected between 6 and 7 a.m. during the morning blood tests performed as part of standard patient management.

Samples were then sent to the immunology laboratory for analysis by flow cytometry. All manipulations were performed on whole blood. Monocytes and neutrophils were identified by flow cytometry via FSC/SSC (forward scatter/side scatter) and CD14/CD16. After permeabilisation, labelling of intracellular

proteins was performed using fluorescent antibodies specific to the phosphorylated forms of the three proteins studied: pSHP-1S591, pSykY525, and pPLC-GY759 (see supplementary material). These phosphorylations activate Syk and PLC-G, whereas they inhibit SHP-1. The levels of phosphorylation were expressed as mean fluorescence intensity.

2.4. Patient management

2.4.1. Anaesthesia management

Anaesthetic management was standardised and independent of the type of surgery performed. Patient monitoring included measurements of invasive arterial pressure, central venous pressure, depth of anaesthesia by bispectral index (BIS), and the use of transoesophageal echocardiography. Induction and maintenance were performed with propofol and sufentanil administered by target-controlled infusion. The hypnotic component of anaesthesia was titrated to maintain BIS values between 40 and 60. Muscular relaxation was achieved by repeated boluses of atracurium. Tranexamic acid was administered after induction by bolus and continuous infusion. No locoregional analgesia was performed. Transfusion of labile blood products was conducted according to protocol.

2.4.2. Cardiopulmonary bypass management

CPB was performed in normothermia and with myocardial protection by intermittent antegrade or retrograde warm blood cardioplegia. Venous cannulation was atrio-cava or of both vena cava and arterial cannulation at the ascending thoracic aorta. A bolus of 300 IU/kg unfractionated heparin was administered before the initiation of CPB for an ACT (activated clotting time) target of > 400 seconds. At the end of the procedure, dose-for-dose protamine antagonization was performed to achieve an ACT below 120% of the basal value. Phenylephrine boli were administered to maintain a mean arterial pressure between 60 and 80 mmHg before and during CPB. Venous line oxygen saturation > 80% was targeted. Norepinephrine (NOR) vasopressor support was instituted intraoperatively in case of repeated use of phenylephrine. Inotropic support was initiated according to anaesthetist or intensivist discretion. Non-heparin-bonded circuits were used. Intraoperative corticosteroids were not administered to any patient, as they are not part of the institutional protocol for cardiac surgery with CPB in our centre. Haemofiltration during CPB was not performed systematically. Fluid therapy was at the discretion of the perfusionist to allow the delivery of a flow consistent with the theoretical cardiac output calculated according to the patient's weight and height.

2.4.3. Postoperative care management

All patients were admitted to the cardiac surgery intensive care unit (ICU) immediately after surgery. NOR was administered when the mean arterial pressure was below 65 mmHg despite adequate fluid resuscitation. Propofol sedation initiated in the operating room was continued in the ICU and then stopped for extubation. Extubation took place between 4 and 6 hours after admission unless the patient had immediate postoperative respiratory, haemodynamic, or haemorrhagic complications that contraindicated it. Preventive anticoagulation with unfractionated heparin was started after 6 hours in

the absence of bleeding complications. Postoperative analgesia was according to protocol: paracetamol and nefopam intravenously followed by oral administration and morphine subcutaneously after initial intravenous titration. Insulin therapy was administered intravenously for the first 24 hours and then subcutaneously. All patients received motor and respiratory physiotherapy the day after surgery. Drains were removed at the 36th hour after the surgery.

2.5. Ethics approval

The written and signed consent of the patients was collected after providing them with oral and written information the day prior to surgery. The protocol received favourable approval from the institutional review board “Comité de protection des personnes Est I” (ID-RCB: 2018-A00216-49). The collected data were declared to the Commission Nationale de l’Informatique et des Libertés (CNIL, declaration number 2191694v0).

2.6. Sample Size calculation

No formal sample size calculation was performed, as this study was exploratory in nature. A target of 30 patients was set to allow for meaningful univariate statistical analyses

2.7. Statistical analysis

Continuous variables are expressed as median values with interquartile ranges [IQRs] and were compared using the Mann–Whitney U test or the Kruskal–Wallis test, as appropriate. Categorical variables are expressed as counts and percentages and were compared using Fisher’s exact test or the chi-square test, as appropriate. Patients were separated into two groups according to NOR prescription on POD 1 and the level of the Syk T1/T0 ratio in monocytes. Receiver operating characteristic (ROC) curves were generated to explore the sensitivity and specificity of the markers in predicting NOR prescription on POD 1, and the Youden index was calculated to determine the optimal threshold value. This threshold was derived from and evaluated in the same dataset, no independent validation cohort being available; the resulting performance estimates are therefore optimistic. Because six protein ratios (three proteins in two cell types) were compared with the primary endpoint, Bonferroni- and Benjamini-Hochberg-adjusted p-values are reported alongside the unadjusted values (Supplementary Table 1). Sensitivity, specificity and predictive values are reported with exact Clopper-Pearson 95% confidence intervals. With only four events, conventional multivariable logistic regression was not interpretable; the robustness of the association was therefore explored using three complementary approaches: partial Spearman correlations between the monocyte Syk ratio and NOR requirement, adjusted for EuroSCORE II, CPB duration and procedure type; stratified Wilcoxon-Mann-Whitney tests using the same variables as strata; and Firth penalised logistic regression, which is appropriate when the number of events is small. These analyses are exploratory and are reported to assess the robustness of the primary signal, not to establish independence. Statistical and graphical analyses were performed using R software v4.0.3 (<https://www.rproject.org>). A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

Between June 1st and September 30th, 2019, 33 patients were eligible, of whom 23 were included and analysed. Ten patients were not analysed: four declined to participate and six had no marker assessment at the end of CPB because of reagent unavailability (Fig. 1). Of these, four patients (17%) received NOR on POD 1 (Fig. 1). These patients were less likely to have undergone coronary artery bypass graft surgery (CABG) (25% vs. 79%, $p = 0.008$), had longer aortic cross-clamping and CPB durations (82 min [79–118] vs. 40 min [33–47] and 106 min [100–167] vs. 49 min [39–57], respectively, both $p = 0.003$), and had longer ICU stays (16 days [8.5–27] vs. 3 [2–3.5], $p = 0.004$). Notably, these patients showed more biological abnormalities on POD 1, with higher creatinine and lactate levels and lower platelet counts and haemoglobin levels (Table 1).

Table 1

Characteristics of the study population according to norepinephrine infusion on the first postoperative day

Variables	All patients (n = 23, 100%)	Patients without NOR on POD 1 (n = 19, 83%)	Patients with NOR on POD 1 (n = 4, 17%)	p
Clinical characteristics				
Age (years)	68 [56–73]	68 [58–73]	54 [36–73]	0.52
Male gender	17 (74)	14 (74)	3 (75)	1.00
Body mass index	27 [23–29]	27 [25–30]	23 [22–23]	0.02
Hypertension	15 (65)	13 (68)	2 (50)	0.59
Dyslipidaemia	11 (48)	11 (58)	0	0.09
Diabetes	7 (30)	7 (37)	0	0.27
LEAOD	2 (9)	2 (11)	0	1.00
LVEF < 50%	4 (17)	3 (16)	1 (25)	1.00
ACE inhibitor	12 (52)	11 (58)	1 (25)	0.32
Statin	14 (61)	13 (68)	1 (25)	0.26
Beta blocker	19 (83)	17 (90)	2 (50)	0.12
EuroSCORE II	1.4 [1.1–3.5]	1.2 [1.0–2.0]	7.4 [6.4–9.5]	0.005
Surgery				
Prior cardiac surgery	2 (9)	0	2 (50)	0.02
CABG	16 (70)	15 (79)	1 (25)	0.008
Valvular surgery	7 (30)	4 (21)	3 (75)	0.07
Aortic valve replacement	5 (22)	3 (16)	2 (50)	0.19
Mitral valve replacement	2 (9)	1 (5)	1 (25)	0.32
Aortic surgery	1 (4)	0	1 (25)	0.17
Continuous variables are expressed as the median and interquartile range [IQR] and were compared using the Mann–Whitney U test. Categorical variables are expressed as n (%) and were compared with Fisher's exact test.				
NOR: norepinephrine; POD: postoperative day; LEAOD: lower extremity arterial occlusive disease; LVEF: left ventricular ejection fraction; ACE: angiotensin-converting enzyme; CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; AKI: acute kidney injury; AST: aspartate-aminotransferase; ICU: intensive care unit				

Variables	All patients (n = 23, 100%)	Patients without NOR on POD 1 (n = 19, 83%)	Patients with NOR on POD 1 (n = 4, 17%)	p
Clinical characteristics				
Aortic cross-clamping duration (minutes)	43 [35–53]	40 [33–47]	82 [79–118]	0.003
CPB duration (minutes)	50 [41–72]	49 [39–57]	106 [100–167]	0.003
Transfusion	6 (26.1)	3 (16)	3 (75)	0.04
Postoperative data				
Catecholamines at the end of CPB	14 (61)	10 (53)	4 (100)	0.13
Norepinephrine alone	9 (39)	8 (42)	1 (25)	1.0
Dobutamine alone	1 (4)	0	1 (25)	0.17
Norepinephrine and dobutamine	4 (17)	2 (11)	2 (50)	0.12
Surgical site bleeding (mL)	805 [585–1135]	850 [565–1155]	660 [645–745]	0.47
Mechanical ventilation on POD 1	1 (4)	0	1 (25)	0.17
Postoperative atrial fibrillation	4 (17)	3 (16)	1 (25)	1.00
Postoperative AKI	3 (13)	1 (5)	2 (50)	0.07
ICU length of stay (days)	3.0 [2.0–5.0]	3.0 [2.0–3.5]	16.0 [8.5–27.0]	0.004
Blood parameters on POD 1				
Leukocyte count (G/L)	11.1 [9.7–13.0]	11.4 [10.3–13.2]	9.7 [8.2–10.6]	0.19
Platelet count (G/L)	173 [158–222]	186 [162–228]	149 [127–162]	0.039
Continuous variables are expressed as the median and interquartile range [IQR] and were compared using the Mann–Whitney U test. Categorical variables are expressed as n (%) and were compared with Fisher's exact test.				
NOR: norepinephrine; POD: postoperative day; LEAOD: lower extremity arterial occlusive disease; LVEF: left ventricular ejection fraction; ACE: angiotensin-converting enzyme; CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; AKI: acute kidney injury; AST: aspartate-aminotransferase; ICU: intensive care unit				

Variables	All patients (n = 23, 100%)	Patients without NOR on POD 1 (n = 19, 83%)	Patients with NOR on POD 1 (n = 4, 17%)	<i>p</i>
Clinical characteristics				
Haemoglobin (g/dL)	11.6 [10.6–12.2]	11.7 [11.2–12.4]	8.9 [8.3–10.1]	0.028
Blood lactate level (mmol/L)	1.3 [1.1–1.7]	1.3 [1.1–1.5]	2.0 [1.7–3.5]	0.025
Creatinine level (μmol/L)	77 [64–114]	73 [59–95]	129 [114–160]	0.021
Potassium (mmol/L)	4.5 [4.0–4.9]	4.3 [3.9–4.7]	5.0 [4.9–5.1]	0.039
Troponin (μg/L)	3 [2–6]	3 [2–4]	21 [16–191]	< 0.001
AST (UI/L)	36 [29–57]	34 [28–42]	83 [59–262]	0.06
Continuous variables are expressed as the median and interquartile range [IQR] and were compared using the Mann–Whitney U test. Categorical variables are expressed as n (%) and were compared with Fisher's exact test.				
NOR: norepinephrine; POD: postoperative day; LEAOD: lower extremity arterial occlusive disease; LVEF: left ventricular ejection fraction; ACE: angiotensin-converting enzyme; CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; AKI: acute kidney injury; AST: aspartate-aminotransferase; ICU: intensive care unit				

3.2. Descriptive evolution of phosphoprotein fluorescence intensity

The temporal evolution of fluorescence intensity of the three proteins studied differed markedly between neutrophils and monocytes. First, the fluorescence intensity in the basal (induction, T0) state was spread across a wide range, with the maximum intensity for each protein being at least 10-fold higher than the minimum intensity (Fig. 2). Second, the median fluorescence in monocytes was at least ten times higher than in neutrophils. Third, no general pattern could be identified with respect to the evolution of phosphorylation during the first postoperative week. Nevertheless, at the end of CPB (T1), the fluorescence of SHP-1 and PLC-G in neutrophils and of Syk and PLC-G in monocytes showed a significant reduction in phosphorylation compared to T0. This decrease in phosphorylation in neutrophils and monocytes suggests a reduction in the activation of these cells.

3.3. Identification of a marker of norepinephrine requirement on POD 1

Absolute fluorescence intensities of the three proteins studied at T1 in both monocytes and neutrophils were not significantly different between patients receiving NOR on POD 1 and those not receiving NOR (Fig. 3). Of the six protein ratios studied in both neutrophils and monocytes, only the Syk ratio in monocytes differed depending on NOR prescription on POD 1. Indeed, the T1/T0 fluorescence Syk ratio

in monocytes was lower in patients not receiving NOR on POD 1 than in those receiving NOR, with respective values of 0.22 [0.11–0.45] and 0.64 [0.58–1.01] ($p = 0.032$; Bonferroni- and Benjamini-Hochberg-adjusted $p = 0.19$) (Fig. 4). None of the five remaining ratios approached significance (all unadjusted p greater than 0.24, Supplementary Table 1). None of these ratios was correlated with CPB duration (Fig. 5).

This Syk ratio in monocytes was correlated with the SHP-1 ratio in monocytes ($\rho = 0.64$, $p = 0.003$) but was not correlated with the Syk ratio in neutrophils ($\rho = 0.28$, $p = 0.19$) (Supplementary Fig. 1). The ROC curve of the T1/T0 fluorescence Syk ratio in monocytes as a predictor of NOR requirement on POD 1 was generated (Fig. 6). The area under the curve was 0.85 [0.60–1.00]. The T1/T0 fluorescence Syk ratio threshold yielding the optimal sensitivity/specificity trade-off was 0.47, associated with a sensitivity of 100% (95% CI 40–100) and a specificity of 74% (95% CI 49–91); the positive and negative predictive values were 44% and 100%. With only four patients receiving NOR on POD 1, these estimates are very imprecise. When the population was dichotomised at this threshold, no patient with a ratio below 0.47 required NOR on POD 1 (0/14 versus 4/9, $p = 0.014$). To assess the discriminative ability of this threshold, patients were separated into two groups based on the value of the T1/T0 Syk fluorescence ratio in monocytes (Table 2). Patients with a ratio greater than 0.47 had longer aortic cross-clamping and CPB durations and a longer ICU stay than those with a ratio below 0.47 (57 [43–79] vs. 39 [32–46] min, $p = 0.01$; 75 [53–105] vs. 47 [39–52] min, $p = 0.02$; and 4.0 [3.0–10.0] vs. 2.5 [2.0–3.0] days, $p = 0.05$, respectively). This was also associated with greater biological alterations on POD 1. Patients with a Syk ratio > 0.47 had higher creatinine, blood lactate, and aspartate aminotransferase (AST) levels than patients with a Syk ratio < 0.47 . Interestingly, these patients with a high Syk ratio had a similar proportion of catecholamine requirement at the end of CPB compared to those with a low ratio (67% vs. 57%, $p = 1$), whereas no patient received NOR on POD 1 in the low Syk ratio group.

Table 2
Patient characteristics according to the value of the T1/T0 Syk ratio in monocytes

Variables	All patients (n = 23, 100%)	T1/T0 Syk Mo < 0.47 (n = 14, 60%)	T1/T0 Syk Mo > 0.47 (n = 9, 40%)	p
Clinical characteristics				
Age (years)	68 [56–74]	67 [57–72]	68 [54–76]	0.98
Male gender	17 (74)	9 (64)	8 (89)	0.34
Body mass index	27 [23–29]	28 [25–30]	24 [22–27]	0.16
Hypertension	15 (65)	10 (71)	5 (56)	0.66
Dyslipidaemia	11 (48)	9 (64)	2 (22)	0.09
Diabetes	7 (30)	5 (36)	2 (22)	0.66
LEAOD	2 (9)	2 (14)	0	0.50
LVEF < 50%	4 (17)	2 (14)	2 (22)	1.00
ACE inhibitor	12 (52)	9 (64)	3 (33)	0.21
Statin	14 (61)	10 (71)	4 (44)	0.38
Beta blocker	19 (83)	13 (93)	6 (67)	0.26
EuroSCORE II	1.4 [1.1–3.6]	1.2 [1.0–2.0]	3.6 [1.5–6.8]	0.07
Surgery				
Prior cardiac surgery	2 (9)	0	2 (22)	0.14
CABG	16 (70)	12 (86)	4 (44)	0.07
Valvular surgery	7 (30)	2 (14)	5 (56)	0.07
Aortic valve replacement	5 (22)	2 (14)	3 (33)	0.34
Mitral valve replacement	2 (9)	0	2 (22)	0.14
Aortic surgery	1 (4)	0	1 (11)	0.39
Continuous variables are expressed as the median and interquartile range [IQR] and were compared using the Mann–Whitney U test. Categorical variables are expressed as n (%) and were compared with Fisher's exact test.				
NOR: norepinephrine; POD: postoperative day; LEAOD: lower extremity arterial occlusive disease; LVEF: left ventricular ejection fraction; CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; AKI: acute kidney injury; AST: aspartate-aminotransferase; ICU: intensive care unit				

Variables	All patients (n = 23, 100%)	T1/T0 Syk Mo < 0.47 (n = 14, 60%)	T1/T0 Syk Mo > 0.47 (n = 9, 40%)	p
Clinical characteristics				
Aortic cross-clamping duration (minutes)	43 [33–57]	39 [32–47]	57 [43–79]	0.01
CPB duration (minutes)	50 [39–75]	47 [39–52]	75 [53–105]	0.02
Transfusion	6 (26)	3 (21)	3 (33)	0.64
Postoperative data				
Catecholamines at the end of CPB	14 (61)	8 (57)	6 (67)	1.00
Norepinephrine alone	9 (39)	7 (50)	2 (22)	0.23
Dobutamine alone	1 (4)	0	1 (11)	0.39
Norepinephrine and dobutamine	4 (17)	1 (7)	3 (33)	0.26
Norepinephrine on POD 1	4 (17)	0	4 (44)	0.014
Surgical site bleeding (mL)	805 [570–1150]	895 [560–1150]	775 [645–995]	0.82
Mechanical ventilation on POD 1	1 (4)	0	1 (11)	0.39
Postoperative atrial fibrillation	4 (17)	2 (14)	2 (22)	1.00
Postoperative AKI	3 (13)	1 (7)	2 (22)	0.54
ICU length of stay (days)	3.0 [2.0–5.0]	2.5 [2.0–3.0]	4.0 [3.0–10.0]	0.05
Blood parameters on POD 1				
Leukocyte count (G/L)	11.1 [9.6–13.2]	11.1 [9.2–12.6]	11.9 [9.9–13.2]	0.73
Platelet count (G/L)	173 [158–225]	182 [164–243]	160 [157–186]	0.13
Continuous variables are expressed as the median and interquartile range [IQR] and were compared using the Mann–Whitney U test. Categorical variables are expressed as n (%) and were compared with Fisher's exact test.				
NOR: norepinephrine; POD: postoperative day; LEAOD: lower extremity arterial occlusive disease; LVEF: left ventricular ejection fraction; CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; AKI: acute kidney injury; AST: aspartate-aminotransferase; ICU: intensive care unit				

Variables	All patients (n = 23, 100%)	T1/T0 Syk Mo < 0.47 (n = 14, 60%)	T1/T0 Syk Mo > 0.47 (n = 9, 40%)	p
Clinical characteristics				
Haemoglobin (g/dL)	11.6 [10.6–12.3]	11.6 [11.1–12.2]	11.9 [9.5–12.3]	0.85
Blood lactate level (mmol/L)	1.3 [1.1–1.8]	1.2 [1.0–1.5]	1.8 [1.4–2.7]	0.005
Creatinine level (μmol/L)	77 [60–115]	68 [56–77]	113 [97–125]	0.007
Potassium (mmol/L)	4.5 [3.9–4.9]	4.4 [3.9–4.7]	4.6 [4.3–5.0]	0.35
Troponin (μg/L)	3 [2–6]	3 [2–4]	5 [4–20]	0.08
AST (UI/L)	36 [29–61]	31 [27–37]	62 [35–96]	0.017
Continuous variables are expressed as the median and interquartile range [IQR] and were compared using the Mann–Whitney U test. Categorical variables are expressed as n (%) and were compared with Fisher's exact test.				
NOR: norepinephrine; POD: postoperative day; LEAOD: lower extremity arterial occlusive disease; LVEF: left ventricular ejection fraction; CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; AKI: acute kidney injury; AST: aspartate-aminotransferase; ICU: intensive care unit				

Sensitivity analyses were performed to assess whether the monocyte Syk ratio simply reflected baseline severity or the magnitude of the surgical insult. The ratio was not correlated with EuroSCORE II ($\rho = 0.24$, $p = 0.27$) or with CPB duration ($\rho = 0.37$, $p = 0.08$), but was lower after isolated CABG than after other procedures (median 0.21 versus 0.65, $p = 0.049$). The rank correlation between the monocyte Syk ratio and NOR requirement on POD 1 was $\rho = 0.47$ ($p = 0.025$) and remained of similar magnitude, although no longer significant, after adjustment for EuroSCORE II (partial $\rho = 0.42$, $p = 0.054$), for CPB duration ($\rho = 0.32$, $p = 0.15$), for procedure type ($\rho = 0.34$, $p = 0.12$) and for the three variables jointly ($\rho = 0.33$, $p = 0.16$). Stratified Wilcoxon-Mann-Whitney tests gave concordant results ($p = 0.12$ when stratified on procedure type and $p = 0.08$ on tertiles of CPB duration). In Firth penalised logistic regression, the ratio was associated with NOR requirement in the univariable model (odds ratio 11.6, 95% CI 1.3 to 8.8×10^3 , $p = 0.02$), whereas bivariable models did not converge, the profile penalised likelihood confidence limits failing to reach convergence, as expected with four events.

4. Discussion

4.1. Summary of the main results

This prospective study showed that the phosphorylated forms of SHP-1, Syk, and PLC- γ in monocytes and neutrophils exhibited different patterns over time after cardiac surgery with CPB. Surprisingly, the

immediate post-CPB measurements showed low monocyte activation, with reduced activator phosphorylation of Syk and PLC- γ and reduced inhibitor phosphorylation of SHP-1. However, no absolute fluorescence value after CPB was associated with NOR requirement on POD 1. This was related to significant interindividual heterogeneity in the basal state. We therefore focused on the T1/T0 Syk ratio in monocytes, which emerged as a prognostic marker of NOR requirement on POD 1. When the population was stratified according to this monocyte Syk ratio, the group with a high ratio had a greater NOR requirement on POD 1, higher creatinine, blood lactate, and AST levels, and a longer ICU stay.

4.2. Added value of the study

The threshold value of 0.47 yielded a sensitivity of 100% in this cohort. This figure must be interpreted with great caution: it rests on four events only, its confidence interval is correspondingly wide, and the threshold was both derived from and applied to the same dataset, which necessarily inflates apparent performance. The group of patients with a Syk ratio above this cut-off value appears to exhibit a more severe clinical condition, with greater biological alterations. Interestingly, this marker was not associated with NOR use at the end of CPB. A possible, but at this stage entirely hypothetical, application would be to help identify, among patients already receiving NOR at the end of CPB, those likely to require only a short vasopressor infusion. Whether such information could inform decisions on early mobilisation, central venous catheter removal or ICU discharge cannot be established from the present data: this would require validation in an independent cohort and, thereafter, prospective evaluation of a biomarker-guided strategy against usual care.

4.3. Comparison with other studies and physiopathological hypotheses

4.3.1. Phosphoprotein and vasoplegic shock

Our hypothesis was that proteins of the FcR signalling pathway, the predominant immunoreceptors on monocytes and neutrophils, could be involved in postoperative vasoplegic shock. This complication occurs in 10–50% of CPB procedures and is associated with poor outcomes and longer hospital stay [12–15]. Many factors contribute to the occurrence of vasoplegic shock after CPB, but its immunological pathophysiology remains poorly understood [16]. The tendency for studied protein expression to decrease immediately after CPB, at the same time that NOR requirement emerged, suggests that their phosphorylation level plays a limited role in the genesis of vasoplegic shock. Furthermore, no association was observed between absolute phosphorylation levels after CPB and NOR requirement on POD 1. Syk fluorescence values in monocytes after CPB were closer to basal values in patients requiring NOR, reflecting greater residual Syk activity in these cells. Syk is a tyrosine kinase that mediates FcR signalling. It activates multiple signalling pathways resulting in phagocytosis, cell-mediated cytotoxicity, and the production of reactive oxygen species and cytokines [17]. The greater activation of Syk in monocytes at the end of CPB may contribute to the relative pro-inflammatory state observed in these patients.

4.3.2. Immunodepression following CPB

The decrease in activator phosphorylation could suggest a state of immunodepression immediately after surgery, and may explain the increased risk of nosocomial infection following cardiac surgery [18–20]. This finding is consistent with the study by Justus et al. [21], who reported that cytokine production by monocytes in response to LPS stimulation was reduced after CPB. Indeed, Syk phosphorylation promotes cytokine production [22, 23]. Therefore, circulating pro-inflammatory cytokine levels may not accurately reflect the activation state of monocytes. This underlines the difficulty of separating pro- and anti-inflammatory phases after a physiological insult such as CPB, and suggests that the classical temporal model of inflammation – an initial pro-inflammatory phase followed by an anti-inflammatory phase – may be an oversimplification [24]. A new paradigm acknowledging the concurrent presence of pro- and anti-inflammatory signals may be more appropriate [25]. This distinction between the activation state of the effector cells and the load of circulating mediators deserves emphasis, because the two are often treated as interchangeable. Plasma cytokine concentrations quantify mediators already released into the circulation and integrate production, consumption, dilution by the priming volume and hepatic or renal clearance; the phosphorylation status of a signalling kinase describes the state in which the cells themselves have been left at the end of bypass. Puchinger et al. measured IL-6, its soluble receptor and soluble gp130 at nineteen timepoints in 93 elective cardiac surgical patients and found wide interindividual variability in circulating IL-6, with the resulting signalling predominantly anti-inflammatory once the balance between the soluble receptor and gp130 was taken into account [26]. A given plasma concentration therefore does not indicate the direction of the response it produces.

4.4. Limits and strengths

Our study has several limitations. First, the limited number of patients included, as well as the small number of patients with NOR on POD 1 ($n = 4$), limits the statistical power of the analysis and precludes definitive conclusions. Six protein ratios were tested against the primary endpoint and the association observed for the monocyte Syk ratio did not withstand Bonferroni correction (adjusted $p = 0.19$); it should therefore be regarded as a signal to be tested in a confirmatory study rather than as an established association. Second, the two groups exhibited differences in baseline characteristics: for example, patients requiring NOR on POD 1 had higher EuroSCORE II values. This may represent a confounding bias when interpreting the comparison of protein expression between groups. This bias is only partially mitigated by the use of a patient-specific T1/T0 ratio, which accounts for interindividual variability. The number of events did not permit conventional multivariable adjustment, so an independent association between the monocyte Syk ratio and NOR requirement cannot be claimed. Rank-based and penalised sensitivity analyses were nonetheless reassuring: the ratio was correlated neither with EuroSCORE II nor with CPB duration (Fig. 5), the two main variables distinguishing the groups, and its association with NOR requirement was attenuated but not abolished after adjustment for these variables and for procedure type. Third, the inclusion procedure was constrained by the logistics of sample processing: only patients operated on Tuesday mornings, with a maximum of two per week, could be included. This convenience sampling is a source of selection bias. In our institution, however, the operating schedule is

not organised by procedure type across the week: each operating day comprises a comparable case mix, and the whole spectrum of on-pump cardiac surgery was represented in the cohort, including isolated coronary artery bypass grafting, isolated aortic and mitral valve surgery, aortic surgery and redo procedures (Table 1). Restricting inclusions to a single operating day is therefore unlikely to have distorted the case mix, although the small number of patients included each week limits the extent to which our population can be considered representative of the overall cardiac surgical population. Fourth, the diagnostic threshold was derived from and evaluated in the same 23 patients without an independent validation set, so the reported sensitivity and specificity are optimistic and no conclusion regarding external validity can be drawn. Fifth, inclusions were restricted to a four-month summer period; seasonal variation in immune function has been described and may have influenced the absolute phosphorylation levels observed, although the use of a within-patient T1/T0 ratio should limit this effect. Sixth, our biomarker is not routinely measured and requires multiple processing steps by a trained technician. However, its measurement does not present technical difficulties for an immunology technician and does not require any specific equipment beyond a flow cytometer, which is available in all haematology laboratories. The measurements are derived from blood samples routinely collected before and after CPB. Moreover, results can be obtained rapidly at low cost. Finally, we used NOR requirement on POD 1 as a surrogate definition of vasoplegic shock. Although this is an objective and easily measurable criterion, NOR prescription depended on the clinical judgement of the anaesthetist and intensivist in charge. Nevertheless, NOR prescription followed a standardised protocol consistent with current expert recommendations for the management of vasoplegic shock [27].

5. Conclusion

This proof-of-concept translational study suggests that the phosphorylation status of Syk in monocytes may represent a candidate biomarker for the occurrence of vasoplegic shock following cardiac surgery with CPB, warranting prospective validation in larger cohorts. If confirmed, this marker may allow enhanced recovery selection for patients at low risk of postoperative complications. The results also confirm the complexity of the inflammatory response following CPB, with evidence of an early immunodepression phase concurrent with the initial pro-inflammatory response. A larger prospective study will be necessary to validate the performance of this candidate biomarker and its utility in guiding enhanced recovery decisions.

Abbreviations

ACE: angiotensin-converting enzyme

ACT: activated clotting time

CABG: coronary artery bypass grafting

CPB: cardiopulmonary bypass

FcR: Fc receptor

ICU: intensive care unit

ITAM: immunoreceptor tyrosine-based activation motif

FSC/SCC: forward scatter/side scatter

LEOAD: lower extremity arterial occlusive disease

LPS: lipopolysaccharide

LVEF: left ventricular ejection fraction

NOR: norepinephrine

PLC-G: phospholipase C gamma

POD: postoperative day

SHP-1: Src homology 2 domain-containing phosphatase 1

Syk: spleen tyrosine kinase

Declarations

Ethics approval and consent to participate

The study protocol was approved by the French institutional review board Comité de protection des personnes Est I (ID-RCB 2018-A00216-49) and the dataset was declared to the Commission Nationale de l'Informatique et des Libertés (declaration number 2191694v0). This non-interventional observational study did not require registration in a public clinical trial registry under the applicable national regulation at the time it was conducted. All patients received oral and written information the day before surgery and provided written informed consent. The study was performed in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The de-identified dataset generated and analysed during the current study is available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests. SP holds an elected position within ARCOTHOVA, the learned society that funded this work. ARCOTHOVA had no role in the design or conduct of the study, in the collection, analysis or interpretation of the data, or in the decision to submit the manuscript.

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Authors' contributions

All authors contributed to the study conception and design. KB, CdT, HF and MHN performed material preparation, data collection and analysis. KB wrote the first draft of the manuscript and all authors commented on previous versions. All authors read and approved the final manuscript.

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Not applicable.

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Figures

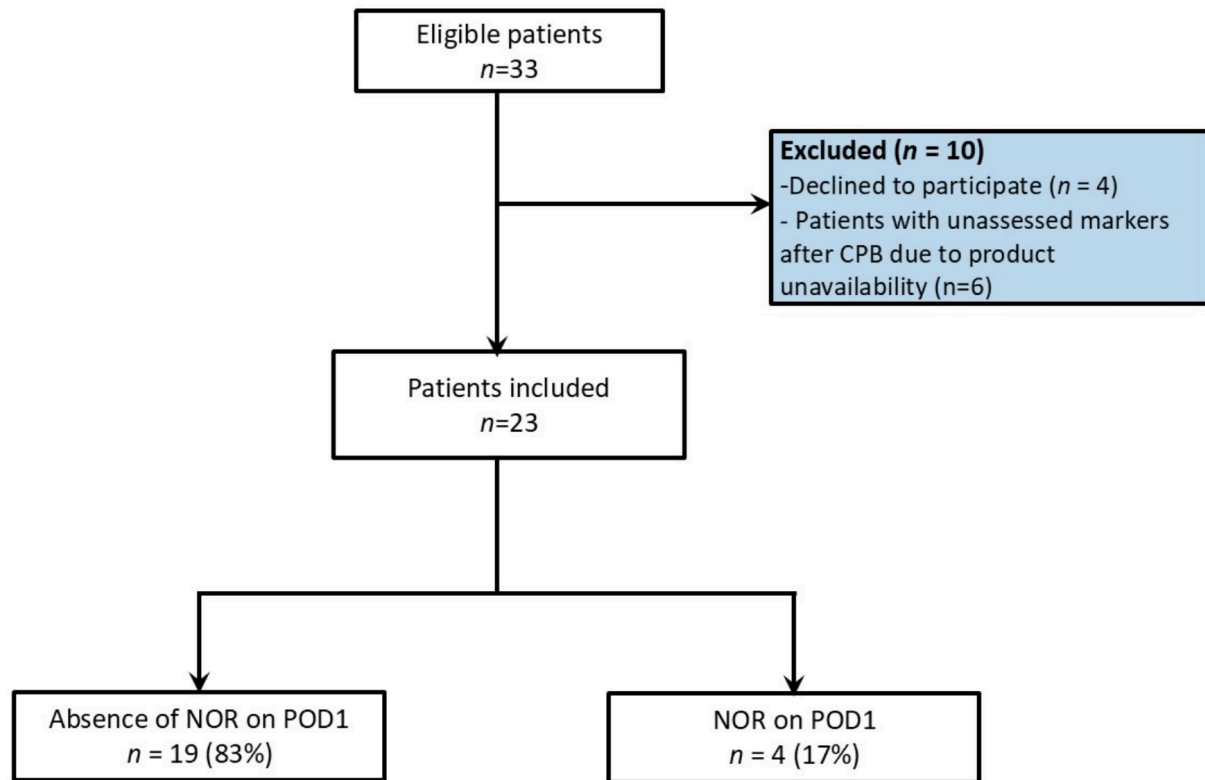


Figure 1

Flowchart

NOR: norepinephrine; POD: postoperative day

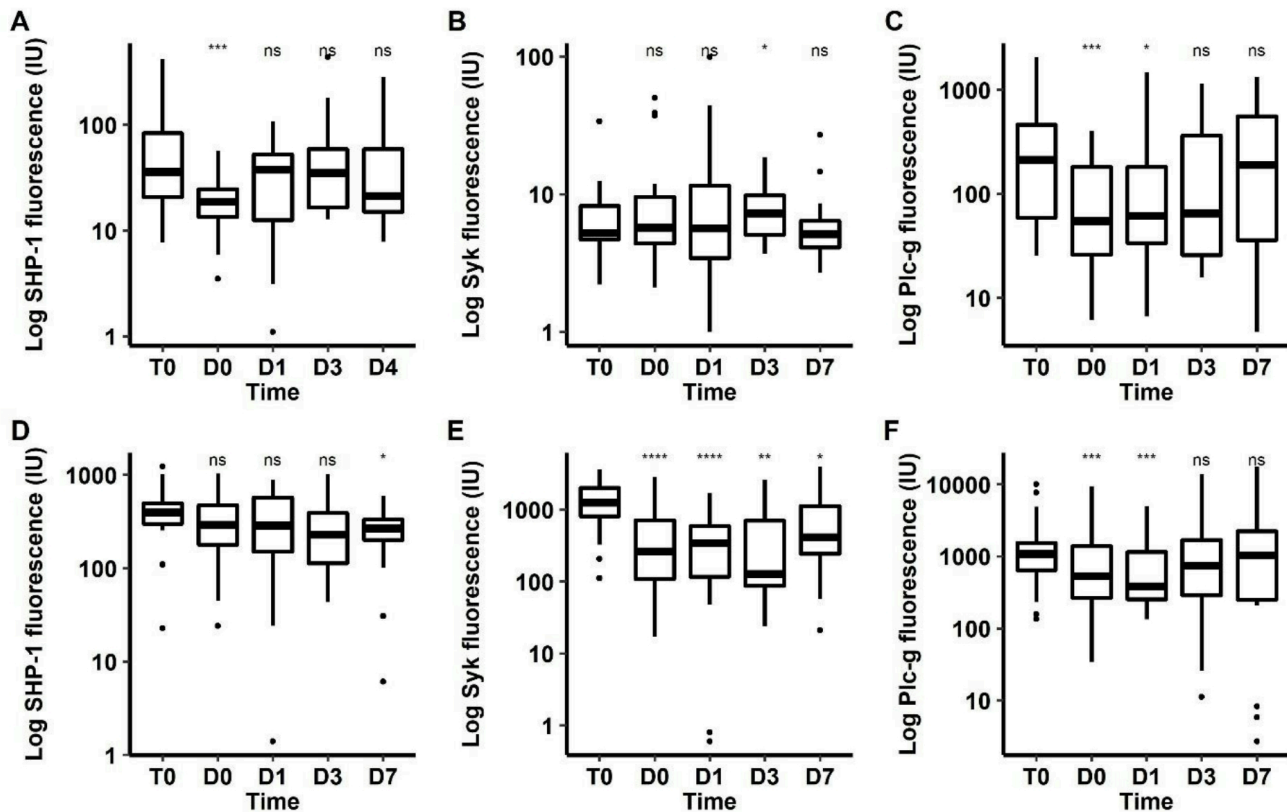


Figure 2

Box plots of flow cytometric fluorescence of proteins of interest over the first week

A, B, C: fluorescence in neutrophils. A: SHP-1, B: Syk, C: PLC-G

D, E, F: fluorescence in monocytes. D: SHP-1, E: Syk, F: PLC-G

T0, induction; T1, end of cardiopulmonary bypass; T2, POD 1; T3, POD 3; T4, POD 7

The p value refers to the paired comparison according to the Wilcoxon test for paired samples between T0 and T1/T2/T3/T4.

p value signification: *p < 0.05; **p < 0.01; ***p < 0.001; ****p < 0.0001

PLC-G: phospholipase C gamma; POD: postoperative day; SHP-1: Src homology 2 domain-containing phosphatase 1; Syk: spleen tyrosine kinase

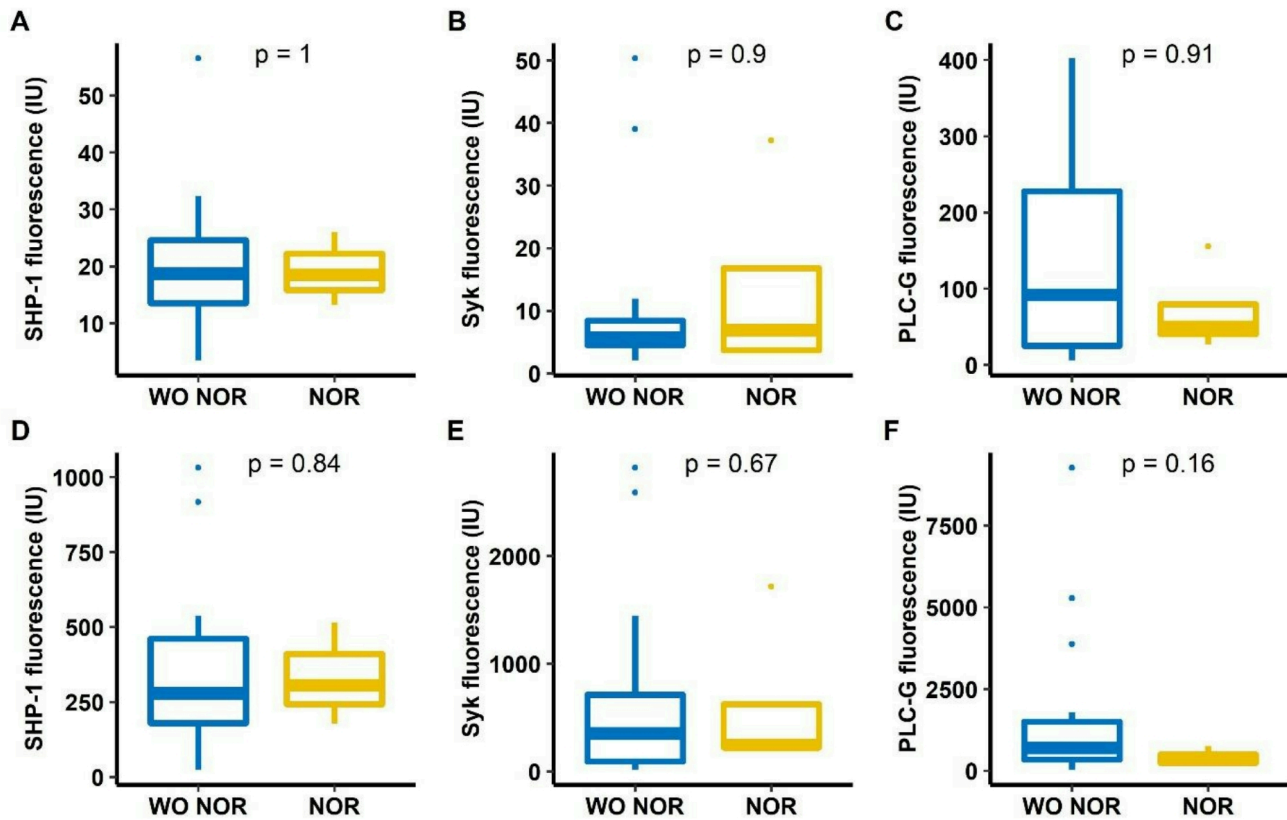


Figure 3

Protein fluorescence at the end of CPB according to norepinephrine use on POD 1

A, B, C: fluorescence in neutrophils. A: SHP-1, B: Syk, C: PLC-G

D, E, F: fluorescence in monocytes. D: SHP-1, E: Syk, F: PLC-G

NOR: norepinephrine; PLC-G: phospholipase C gamma; SHP-1: Src homology 2 domain-containing phosphatase 1; Syk: spleen tyrosine kinase; WO NOR: without norepinephrine

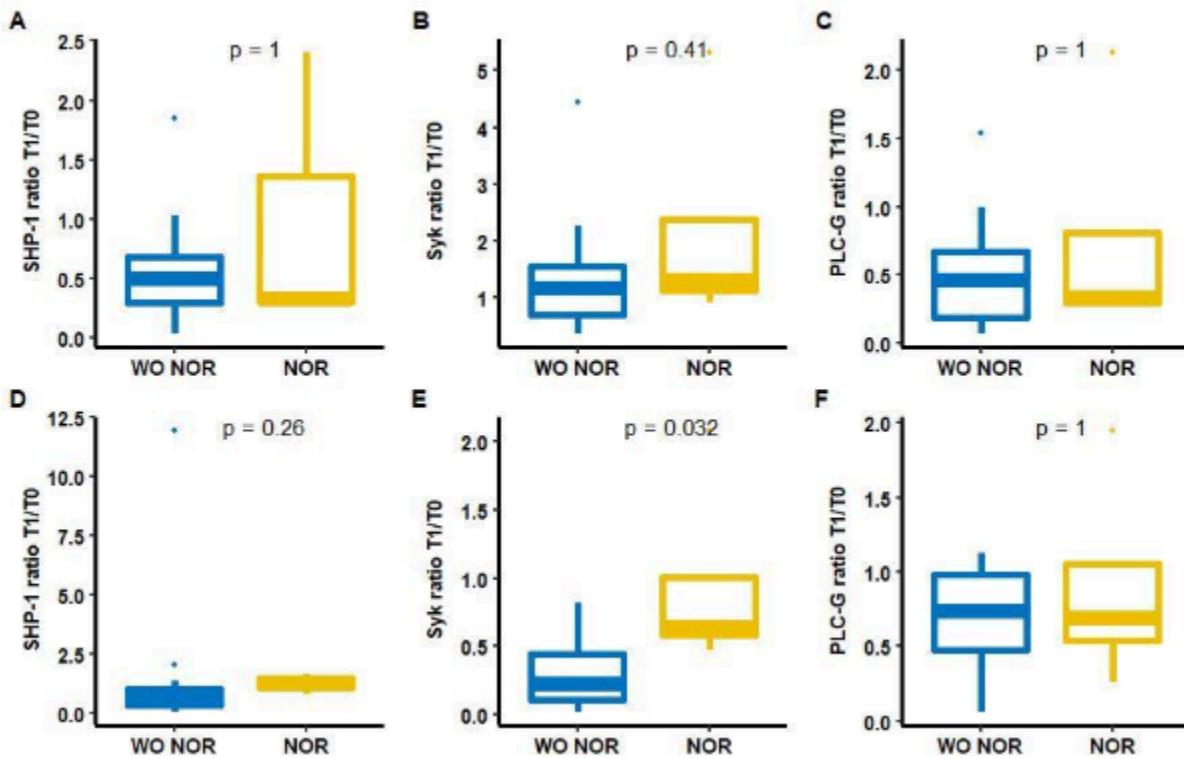


Figure 4

T1/T0 fluorescence ratios according to norepinephrine use on POD 1

A, B, C: fluorescence in neutrophils. A: SHP-1, B: Syk, C: PLC-G

D, E, F: fluorescence in monocytes. D: SHP-1, E: Syk, F: PLC-G

T0: Induction of anaesthesia, T1: end of CPB

NOR: norepinephrine; PLC-G: phospholipase C gamma; SHP-1: Src homology 2 domain-containing phosphatase 1; Syk: spleen tyrosine kinase; WO NOR: without norepinephrine

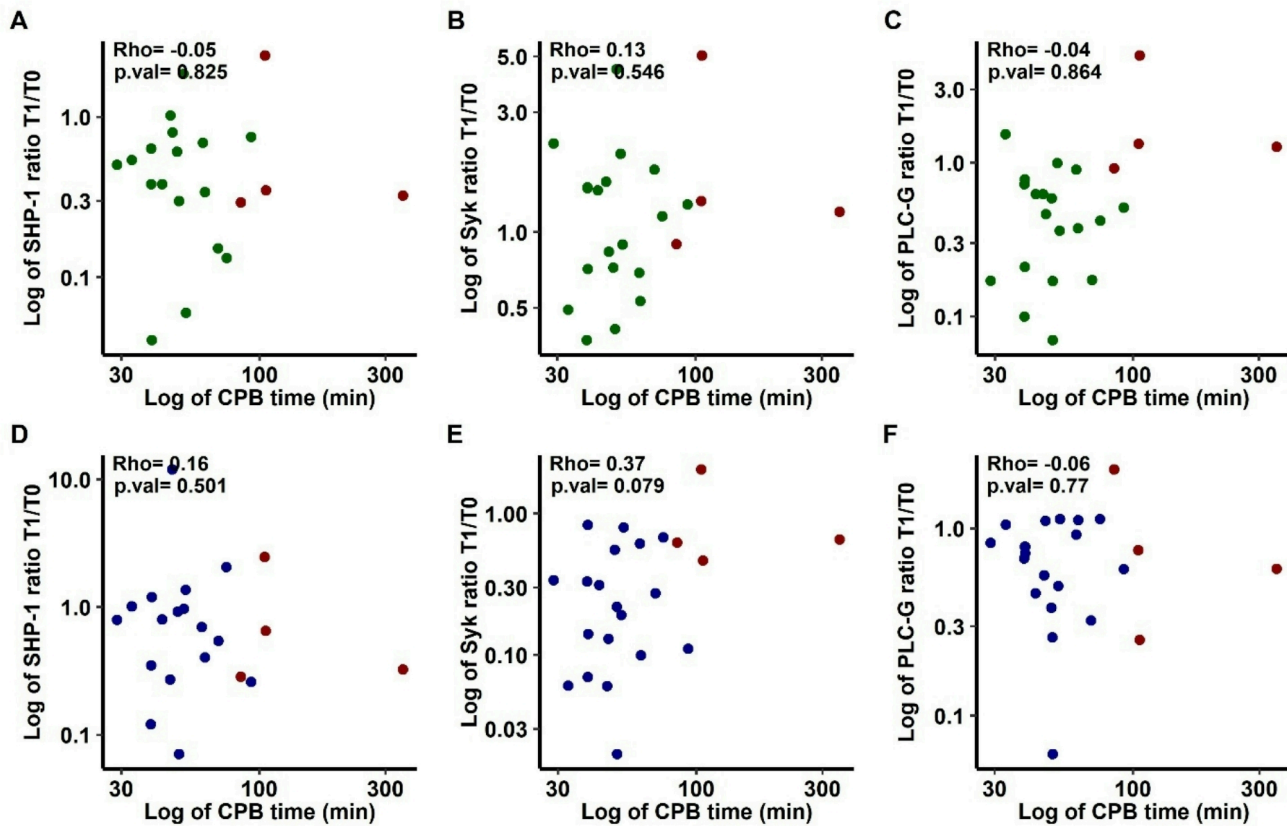


Figure 5

Correlation between the T1/T0 fluorescence ratios of the proteins of interest and CPB duration

A, B, C: neutrophils. A: SHP-1, B: Syk, C: PLC-G

D, E, F: monocytes. D: SHP-1, E: Syk, F: PLC-G

Red dots indicate patients who received NOR on POD 1. Rho: Spearman correlation coefficient.

CPB: cardiopulmonary bypass; NOR: norepinephrine; PLC-G: phospholipase C gamma; POD: postoperative day; SHP-1: Src homology 2 domain-containing phosphatase 1; Syk: spleen tyrosine kinase

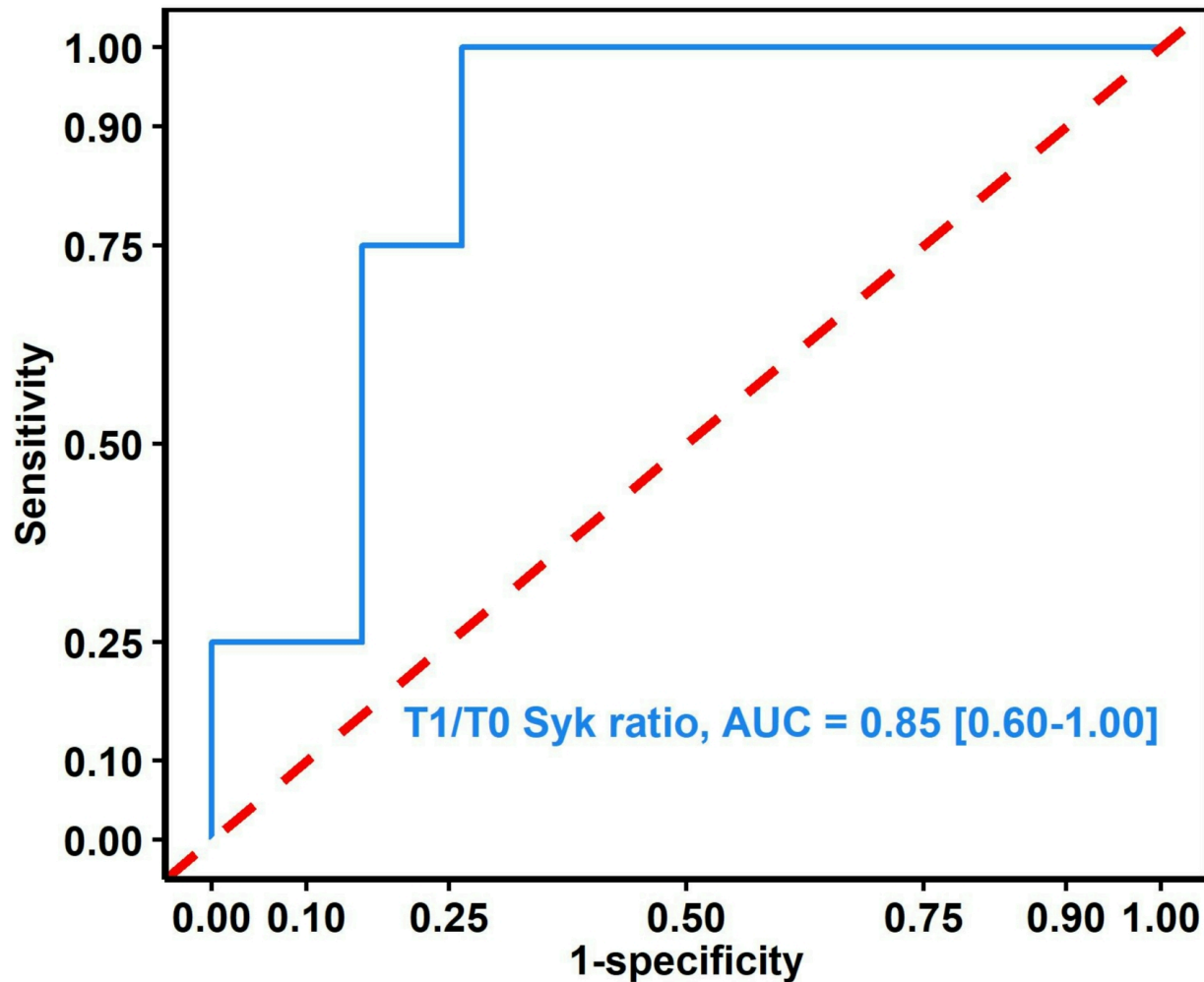


Figure 6

ROC curve of the monocyte T1/T0 Syk ratio for norepinephrine use on POD 1

ROC: receiver operating characteristic; NOR: norepinephrine; POD: postoperative day; AUC: area under the curve; CPB: cardiopulmonary bypass

Supplementary Files

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