C1 esterase inhibitor in pediatric cardiac surgery with cardiopulmonary bypass plays a vital role in activation of the complement system

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Abstract
Our prospective study was therefore designed to determine which part of the systemic inflammatory response after cardiac operations resulted from Cardiopulmonary bypass (CPB) in neonates and infants. After approval by the human ethical committee of the Gunma Children’s Medical Center (GCMC) and informed consent of the parents, 40 consecutive term congenital heart disease patients aged until 1 year who underwent long CPB time (> 3 h) at surgery were included in the prospective study between January 2012 and December 2014. C1 esterase inhibitor (C1-inh) drug (@Berinert) was generously provided by CSL Behring (King of Prussia, PA). The C1-inh (20 IU/kg) was given intravenously 60 min after CPB. Blood samples for complement factors were obtained before and 48 h after administration of C1-inh. Six patients did not survive and their data were not included. Of 34 patients included, median age was 6.5 months, median body weight was 6050 g, and 16 (47%) were female. According to the Mann–Whitney U test, there were no differences between the two groups concerning demographic and intraoperative data, postoperative chemical data. C1q concentration was only significant lower in patients with C1-inh non-treated group than in patients with C1-inh treated group. But, the consumption of C1q, C3, C4, CH50, and C1-inh in patients with C1-inhibitor non-treated group was observed early postoperatively. There is a significant difference in the values before and after C1-inh treatment between the two groups. The lower value in the C1-inh-treated group is explained by the activation of the classical pathway through the replenishment of complements by C1-inh treatment. This study proposes the administration of C1-inh is an effective therapy to reduce the activation and improve the clinical capillary leak syndrome.

Keywords C1 esterase inhibitor · Complements · Pediatric cardiac surgery

Abbreviations

| Abbreviation | Definition |
|--------------|------------|
| ACC          | Aortic cross clamp |
| AS           | Aortic stenosis |
| ASO          | Arterial switch operation |
| BDG          | Bidirectional Glenn |
| BT           | Body temperature |
| BTs          | Blalock–Taussig shunt |
| BW           | Body weight |
| CAVVR        | Common atroventricular valve regurgitation |
| cAVSD        | Complete atroventricular septal defect |
| CLS          | Capillary leak syndrome |
| CoA          | Coarctation of the aorta |
| CPB          | Cardiopulmonary bypass |
| C1-inh       | C1 esterase inhibitor |
| DKS          | Damus–Kaye–Stanse procedure |
| DORV         | Double outlet right ventricle |
| GCMC         | Gunma Children’s Medical Center |
| HAE          | Hereditary angioedema |
| HLHS         | Hypoplastic left heart syndrome |
| IAA          | Interruption of the aorta |
| LVOTO        | Left ventricular outlet tract obstruction |
| MAC          | Membrane attack complex |
| PA           | Pulmonary artery |
| PTFE         | Polytetrafluoroethylene |
| SA           | Single atrium |
| SV           | Single ventricle |
| TAPVC        | Total anomalous pulmonary vein connection |

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Introduction

The use of cardiopulmonary bypass (CPB) is necessary for the correction of many complex cardiac defects in neonates and infants. Surgical results for most defects have improved over the last several years, but there persists significant morbidity related to the inflammatory insult of CPB. CPB in combination with anaesthesia, medication, vascular injury and surgical stress affects the extent of inflammatory response. Complement system protein may be activated through the classical, alternative and lectin pathways, leading to generation of biologically active products, such as C5a and the terminal membrane attack complex (MAC), and ultimately contributes to endothelial cell disruption during CPB. Significant differences in the complement factor levels indicate a higher grade of complement activation and simultaneous contact activation in patients during and after CPB. Thus, the main cause of systemic inflammatory reaction after CPB is the contact of the blood to non-biologic surfaces of the CPB circuit and not surgical procedures or anaesthesia. To lessen the activation of the complement and contact systems during CPB, it is necessary to use inert materials in the CPB circuit. Because inhibiting drugs may lessen complement and contact system activation, they represent a further possibility for minimizing the damaging effects of CPB [1].

Complement factor C1 esterase inhibitor (C1-inh) levels decrease with CPB in infants. Stillier and colleagues [2] examined C1-inh levels in such patients. They found that after CPB, generalized edema, pulmonary edema, and weight gain were greater in infants with lower C1-inh levels. At 30 min post-CPB, the infants demonstrating these effects had C1-inh activity levels that were 51% of controls compared with 80% of controls in those who did not demonstrate capillary leak syndrome (CLS). This decrease was greater in infants who suffered post-CPB CLS. CLS show evidence of complement activation, decreased complement levels. We thus consecutively investigated several complement compounds before and after pediatric cardiac surgery with CPB. Based on this hypothesis, we tested whether C1-inh supplementation after CPB would ameliorate C1-inh decrease in pulmonary and cardiac dysfunction after CPB. Our prospective study was therefore designed to determine which part of the systemic inflammatory response after cardiac operations resulted from CPB in neonates and infants.

Patients and methods

After approval by the human ethical committee of the Gunma Children's Medical Center (GCMC) and informed consent of the parents, 40 consecutive term congenital heart disease patients aged until 1 year who underwent long CPB time (> 3 h) at surgery were included in the prospective study between January 2012 and December 2014. Though there was no evidence, it was thought that congenital heart disease patients who underwent short CPB time did not present pulmonary edema and capillary leak syndrome. Conventional general anesthesia was conducted with diazepam, fentanyl sulfate, and vecuronium. After induction of anesthesia, nasotracheal intubation was performed in the patients not receiving ventilatory support, and central venous catheters and peripheral arterial catheter were inserted. Perioperative antibiotic prophylaxis consisted of ampicillin. The CPB circuit included a roller pump, a disposable membrane oxygenator, and an arterial filter. Cooling and rewarming were carried out with a heat exchanger. The priming solution consisted of a crystalloid solution, mannitol (3 ml/kg), and leukocyte-depleted packed red blood cells to obtain a hematocrit value of the circulating volume of about 25%. For vasodilatation in the cooling and rewarming periods, all neonates received a continuous infusion of sodium nitroprusside 2 μg/kg/min and chlorpromazine 1 mg/kg. CPB was instituted with a perfusion index of 2.7 L/(min m²), which was maintained throughout the cooling phase. The pump was primed with 80–100 ml of packed cells and 50 ml of lactated Ringer’s solution, 1000 IU of heparin, 2.0 ml/kg of sodium bicarbonate 4.2%, and 3 ml/kg of mannitol 20% were added. CPB was instituted at a flow rate of 2.7 L/min/m² after systemic anticoagulation, and administration of dexamethasone, 1 mg/kg. During CPB the pH–stat method was used, with correction of PaO₂ to the patients’ hypothermic temperature to maintain a pH value of 7.40. After deep hypothermia was reached (minimal nasopharyngeal temperature averaging 25 °C), aortic cross-clamping was done and cardioplegia was induced with a single intra-aortic injection of a 4 °C cold St. Thomas solution (30 mL/kg), and cardiac arrest was instituted for a target period of not longer than 60 min. The surgical procedure was continued under high-flow perfusion (50% of the calculated initial perfusion rate). Rewarming was achieved under full-flow conditions. The lungs of the neonates were reventilated when core temperature reached 30 °C. Neutralization of heparin was achieved with protamine sulfate in a 1:1.5 ratio. Epinephrine, dopamine, olprinone and nitroglycerin were systematically administered for weaning the patients from CPB. After coronary reperfusion and at the end of the operation, the cardiac surgeon, as explained, assessed

| TAPS          | Total cavo-pulmonary shunt (Kawashima procedure) |
|---------------|--------------------------------------------------|
| TGA           | Transposition of the aorta                        |
| ToF           | Tetralogy of Fallot                                |
| VSD           | Ventricular septal defect                         |

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intraoperative myocardial function here. In cases of hemodynamic instability or myocardial dysfunction at the end of the operation, sternal closure was delayed until stabilization, and sternal wounds were closed with a polytetrafluoroethylene (PTFE) membrane.

**C1-inhibitor drug (@Berinert) dosing and postoperative care**

C1-inh drug (@Berinert) was generously provided by CSL Behring (King of Prussia, PA). The C1-inh (20 IU/kg) was given intravenously after CPB. If necessary, fentanyl and midazolam were administered for analgesia and sedation. All patients were weaned from the ventilator as soon as possible. Dopamine and epinephrine were infused continuously as necessary to optimize mean arterial pressure, central venous pressure, pulse amplitude, capillary refill time, and diuresis. Furosemide, ethacrynic acid, and spironolactone were administered to promote diuresis.

**Collection of samples**

Blood samples for complement factors were obtained before and 48 h after administration of C1-inh. Arterial blood gas analysis was performed, and hemodynamic parameters were evaluated at the second day points.

**Statistical analysis**

Differences in the measured parameters in the two groups were assessed by the Mann–Whitney U test. We investigated the influence of age, weight, and sex on the determined concentrations and activities in a multiple regression analysis. Statistical significance was assumed when the p value was less than 0.05.

**Results**

Six patients (two that received Berinert and four that non-received Berinert) did not survive and their data were not included. These patients need the extracorporeal membrane oxygenation until 48 h after an open-heart operation in operating room and in the intensive care unit. Accordingly, obtaining the blood samples of complement factors until 48 h after administration of C1-inh was not possible. Of 34 patients included, median age was 6.5 months, median body weight was 6050 g, and 16 (47%) were female. Table 1 shows the mean age, body weight, diagnosis, duration of operation, duration of anesthesia, duration of CPB time, duration of aortic cross-cramp time, and nadir body temperature with C1-inhibitor non-treated group (non-INH, 26 cases) and Table 2 with C1-inhibitor treated group (INH, 8 cases). According to the Mann–Whitney U test, there were no differences between the two groups concerning demographic and intraoperative data. There were no differences between the two groups concerning demographic and intraoperative data (Tables 1, 2). Postoperative chemical data and 48 h after CPB, AST, ALT, lactate, CK-MB, WBC, CRP, duration of inotropic support, duration of mechanical ventilation and duration of ICU stay did not differ between the two groups (Table 3). The results of the pre and postoperatively activated complement and contact system are summarized in Table 4. Preoperatively, there were no differences in complement between two groups. Postoperatively, C1q concentration was only significant lower in patients with C1-inhibitor non-treated group than in patients with C1-inhibitor treated group. But, the consumption of C1q, C3, C4, CH50 and C1-inh in patients with C1-inhibitor non-treated group was observed early postoperatively. C1-inhibitor activity differed in the two groups.

**Discussions**

There are three kinds of course inclusive of classical pathway, alternative pathway and lecition pathway, which activated by many factor that much protein in a complement system in sequence. To the best of our knowledge, cardiopulmonary bypass can result in a post-CPB syndrome that is characterized by increased vascular permeability, generalized edema, pulmonary dysfunction, and cardiac dysfunction [3–5]. This syndrome seems to be more intense in neonates and can result in prolonged ventilation, coagulopathy, postcardiotomy cardiac failure, and increased mortality. This is a systemic inflammatory response that appears to be fueled by activation of the complement, contact, coagulation, and fibrinolytic pathways [6]. More recently, Tassani et al. have shown that prophylactic administration of C1INH before CPB is an effective therapeutic approach to reduce the inflammatory response and improve clinical parameters after cardiac surgery requiring CPB in neonates [7].

Thus, although the complement system is originally a defense system for protection against foreign microorganisms, its strong activation induces excessive complement consumption and persistent inflammatory reactions. After surgery, it impairs vascular endothelial cells in the lungs and kidneys, causes swelling of parenchymal cells, and triggers an organ failure. Therefore, multiple defense systems are established by several proteins, called complement regulators, to prevent excessive and persistent complement activation and invasion of autologous cells [8, 9]. C1-inhibitor, called C1 inactivator, covalently binds to and inhibits the active sites (serine) of activated C1r and C1s in the C1 step of the classical pathway to suppress
**Table 1** Clinical data and duration of cardiac operation with C1-inhibitor non-treated group

| No | Sex | Age (m) | BW (g) | Diagnosis | Procedure | Duration of operation | Duration of CPB time | Duration of ACC time | Nadir BT during CPB |
|----|-----|---------|--------|-----------|-----------|-----------------------|---------------------|---------------------|---------------------|
| 1  | F   | 0.2     | 3500   | TGA       | ASO       | 613                   | 219                 | 112                 | 30.1                |
| 2  | M   | 0.33    | 2937   | TGA       | ASO       | 331                   | 210                 | 119                 | 27.8                |
| 3  | M   | 0.4     | 2800   | TGA       | ASO       | 377                   | 245                 | 118                 | 29.2                |
| 4  | F   | 0.47    | 2670   | TGA       | ASO       | 440                   | 278                 | 141                 | 27.8                |
| 5  | F   | 2       | 3390   | AS, IAA, VSD | Norwood | 619                   | 461                 | 98                  | 29.6                |
| 6  | M   | 3       | 3500   | CoA, VSD  | CoA repair | 410                   | 212                 | 96                  | 28.8                |
| 7  | M   | 3       | 4324   | AS, CoA DORV | Norwood | 445                   | 282                 | 102                 | 25.4                |
| 8  | F   | 3       | 3170   | TAPVC (II) | TAPVC repair | 445                   | 273                 | 136                 | 28.8                |
| 9  | M   | 4       | 4500   | AS, IAA VSD | Norwood | 457                   | 287                 | 87                  | 25.8                |
| 10 | M   | 4       | 6000   | SV, CoA   | Arch repair, BDG | 560                   | 365                 | 123                 | 31.2                |
| 11 | M   | 4       | 4054   | SV, CAVVR | CAVV repair, BDG | 439                   | 304                 | 77                  | 28                  |
| 12 | F   | 4       | 4900   | AS, IAA VSD | Norwood | 569                   | 376                 | 107                 | 29.7                |
| 13 | F   | 4       | 5000   | DORV, LVOTO | ASO       | 451                   | 308                 | 184                 | 29.1                |
| 14 | F   | 5       | 6100   | cAVSD     | cAVSD repair | 390                   | 237                 | 75                  | 32.9                |
| 15 | F   | 7       | 4760   | CoA, SV, s/pBTS | CoA repair, BDG | 426                   | 257                 | 42                  | 28.1                |
| 16 | M   | 7       | 7300   | TOF       | ToF repair | 381                   | 255                 | 134                 | 34.4                |
| 17 | M   | 8       | 8400   | SV        | DKS, BDG  | 381                   | 216                 | 105                 | 30.3                |
| 18 | F   | 8       | 7200   | DORV, PA  | Rastelli ope | 401                   | 234                 | 128                 | 31.2                |
| 19 | F   | 8       | 6800   | TOF, PA   | Rastelli ope | 451                   | 284                 | 141                 | 31.9                |
| 20 | M   | 9       | 7700   | SV        | DKS, TCPS | 375                   | 218                 | 53                  | 32.1                |
| 21 | M   | 9       | 4500   | VSD,s/p CoA repair | VSD closure, PA plasty | 355                   | 190                 | 88                  | 34                  |
| 22 | F   | 10      | 7600   | TOF       | ToF repair | 332                   | 228                 | 124                 | 34.3                |
| 23 | M   | 11      | 8400   | DORV     | DORV repair | 434                   | 267                 | 143                 | 34                  |
| 24 | M   | 11      | 8900   | cAVSD    | cAVSD repair | 564                   | 401                 | 230                 | 29.7                |
| 25 | M   | 11      | 7400   | VSD      | VSD closure | 484                   | 289                 | 162                 | 33.7                |
| 26 | M   | 11      | 6500   | cAVSD    | cAVSD repair | 347                   | 188                 | 114                 | 34.4                |
| Median | 4.5 | 4950 | | | | 436.5 | 262 | 116 | 29.9 |

**Table 2** Clinical data and duration of cardiac operation with C1-inhibitor treated group

| No | Sex | Age (m) | BW (g) | Diagnosis | Procedure | Duration of operation | Duration of CPB time | Duration of ACC time | Nadir BT during CPB |
|----|-----|---------|--------|-----------|-----------|-----------------------|---------------------|---------------------|---------------------|
| 1  | M   | 0.07    | 3240   | TAPVC, CoA | TAPVC repair, Arch repair | 539                   | 236                 | 83                  | 25.9                |
| 2  | M   | 6       | 3446   | HLHS      | Norwood   | 900                   | 397                 | 57                  | 25.1                |
| 3  | F   | 6       | 6200   | cAVSD    | cAVSD repair | 572                   | 202                 | 127                 | 32.9                |
| 4  | F   | 8       | 6600   | TOF, PA  | Rastelli ope | 490                   | 260                 | 114                 | 31.9                |
| 5  | F   | 11      | 5000   | VSD, PS  | VSD closure, PA plasty | 410                   | 185                 | 108                 | 34.8                |
| 6  | M   | 11      | 7290   | IAA, VSD, s/p Norwood | Rastelli | 625                   | 255                 | 143                 | 33.7                |
| 7  | F   | 11      | 8700   | cAVSD    | cAVSD repair | 515                   | 260                 | 185                 | 29.1                |
| 8  | F   | 11      | 6600   | cAVSD    | cAVSD repair | 578                   | 265                 | 197                 | 32.1                |
| Median | 9.5 | 6600 | | | | 417 | 258 | 121 | 32.0 |
complement activity. In addition, it inhibits, the enzymatic activities of the coagulation, kallikrein, and plasmin systems, besides the complement system. In fact, in cases deficient in congenital complement control (e.g., Hereditary Angioedema; HAE), bradykinin, as well as C3a and C5a strongly induced by the classical pathway initiated by C1 activation, is deeply involved [10].

In the present study, after the prolonged use of CPB, complement components significantly reduced by about 20–40%, as reported by the authors. In the C1-INH-treated group, it reduced by about 15%, suggesting suppressed complement reduction. Of note, there is a significant difference in the values before and after C1-INH treatment between the two groups. The lower value in the C1-INH-treated group is explained by the activation of the classical pathway through the replenishment of complements by C1-INH treatment. In the future, bradykinin and cytokine levels will be examined.

In summary, C1 INH is an important regulator of plasma protein cascade systems such as the classical pathway of complement, the intrinsic pathway of coagulation and inflammatory reactions. Thus, severe diminished C1 INH in pediatric cardiac surgery with cardiopulmonary bypass plays a vital role in activation of these systems. This study proposes the administration of C1 INH is an effective therapy to reduce the activation and improve the clinical capillary leak syndrome.

Table 3 Post-operative clinical outcome data

|                      | C1-inhibitor non-treated group (n = 26) | C1-inhibitor treated group (n = 8) | P value |
|----------------------|----------------------------------------|-----------------------------------|---------|
| AST (< 30 IL/l)      |                                        |                                   |         |
| Post 0 h             | 157.9 ± 74.2                           | 195.3 ± 87.9                      | 0.51    |
| Post 48 h            | 52.4 ± 26.3                            | 67.9 ± 27.7                       | 0.43    |
| ALT (< 30 IL/l)      |                                        |                                   |         |
| Post 0 h             | 18.9 ± 13.7                            | 25.4 ± 9.5                        | 0.15    |
| Post 48 h            | 20.4 ± 12.4                            | 26.8 ± 15.0                       | 0.28    |
| Lactate (0.5–1.6 mmol/l) |                                   |                                   |         |
| Post 0 h             | 1.7 ± 1.8                              | 1.8 ± 1.6                         | 0.63    |
| Post 48 h            | 1.0 ± 0.4                              | 1.1 ± 0.5                         | 0.39    |
| CK-MB (< 20 U/l)     |                                        |                                   |         |
| Post 0 h             | 130.9 ± 63.5                           | 155.6 ± 87.1                      | 0.69    |
| Post 48 h            | 44.0 ± 65.8                            | 22.3 ± 9.9                        | 0.55    |
| WBC (< 9000/μL)      |                                        |                                   |         |
| Post 0 h             | 10,796 ± 3173                          | 12,512 ± 2740                     | 0.13    |
| Post 48 h            | 10,939 ± 2996                          | 12,112 ± 2580                     | 0.16    |
| CRP (< 0.3 mg/dl)    |                                        |                                   |         |
| Post 0 h             | 0.3 ± 0.3                              | 0.1 ± 0.2                         | 0.30    |
| Post 48 h            | 8.3 ± 5.5                              | 8.6 ± 5.8                         | 0.66    |
| Duration of inotropic support (h) |                                 |                                   |         |
| Post 0 h             | 204.9 ± 101.8                           | 180.8 ± 109.3                     | 0.57    |
| Duration of mechanical ventilation (h) |                              |                                   |         |
| Post 0 h             | 179.3 ± 121.8                           | 164.4 ± 115.0                     | 0.78    |
| Duration of ICU stay (days) |                                |                                   |         |
| Post 0 h             | 12.8 ± 6.0                             | 12.8 ± 9.1                        | 0.85    |

Table 4 Pre and postoperative complement data

|                      | C1-inhibitor non-treated group (n = 26) | C1-inhibitor treated group (n = 8) | P value |
|----------------------|----------------------------------------|-----------------------------------|---------|
| C1q (8.8–15.3 mg/dl) |                                        |                                   |         |
| Pre                  | 6.14 ± 2.12                            | 6.46 ± 1.22                       | 0.508   |
| Post                 | 4.77 ± 0.92                            | 5.86 ± 1.13                       | **0.045** |
| P value              |                                        |                                   | 0.564   |
| C1 inh (70–130%)     |                                        |                                   |         |
| Pre                  | 93.2 ± 18.7                            | 90.9 ± 22.2                       | 0.964   |
| Post                 | 71.3 ± 13.7                            | 80.4 ± 18.0                       | 0.115   |
| P value              | **< 0.001**                            |                                   | 0.3706  |
| C3 (86–160 mg/dl)    |                                        |                                   |         |
| Pre                  | 80.0 ± 17.1                            | 79.0 ± 24.9                       | 0.873   |
| Post                 | 56.3 ± 11.5                            | 61.8 ± 11.6                       | 0.121   |
| P value              | **< 0.001**                            |                                   | 0.124   |
| C4 (17–45 mg/dl)     |                                        |                                   |         |
| Pre                  | 16.2 ± 6.6                             | 15.8 ± 3.2                        | 0.964   |
| Post                 | 10.9 ± 4.1                             | 12.3 ± 3.0                        | 0.628   |
| P value              | **0.002**                              |                                   | 0.072   |
| CH50 (25–50/ml)      |                                        |                                   |         |
| Pre                  | 43.0 ± 14.0                            | 37.6 ± 21.8                       | 0.873   |
| Post                 | 31.9 ± 13.3                            | 31.3 ± 21.2                       | 0.792   |
| P value              | **0.042**                              |                                   | 0.482   |

Bold values indicate worse results than another group
Limitations

Despite the strengths of our methodology and the consistency of our findings, some limitations should be delineated. First, although powered to detect a difference in postoperative CLS between those who did and did not receive C1-inh, the dosage of C1-inh was relatively small and the incidence of CLS was lower in this study. It is therefore possible that the large dosage may observe the difference in those groups in large trials. Second, anesthetic management was left to the discretion of treating anesthesiologists. This may have affected the outcome given the potential differing effects of anesthetic medications on the development of postoperative CLS. Third, the limited sample size from a single center and restrictive inclusion may place some limitations on generalizability. As this was a single-center study, the results should be replicated in a large multi-center trial.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Informed consent Informed consent was obtained from the patient/participant (delete as appropriate) for publication of their individual details and accompanying images in this manuscript. The consent form is held by the authors’ institution.

References

1. Sonntag J, Dähnert I, Stiller B, Hetzer R, Lange PE (1998) Complement and contact activation during cardiovascular operations in infants. Ann Thorac Surg 65(2):525–531
2. Stiller B, Sonntag J, Dähnert I, Alexi-Meskishvili V, Hetzer R, Fischer T, Lange PE (2001) Capillary leak syndrome in children who undergo cardiopulmonary bypass: clinical outcome in comparison with complement activation and C1 inhibitor. Intensive Care Med 27(1):193–200
3. Kubicki R, Grohmann J, Siepe M, Benk C, Humburger F, Rensing-Ehl A, Stiller B (2013) Early prediction of capillary leak syndrome in infants after cardiopulmonary bypass. Eur J Cardiothorac Surg 44(2):275–281
4. Lu F, Fernandes SM, Davis AE III (2013) The effect of C1 inhibitor on myocardial ischemia and reperfusion injury. Cardiovasc Pathol 22(1):75–80
5. Baig K, Nassar R, Craig DM, Quick G Jr, Jiang HX, Frank MM, Lodge AJ, Anderson PA, Jaggers J (2007) Complement factor 1 inhibitor improves cardiopulmonary function in neonatal cardiopulmonary bypass. Ann Thorac Surg 83(4):1477–1483
6. Appachi E, Mossad E, Mee RB, Bokesch P (2007) Perioperative serum interleukins in neonates with hypoplastic left-heart syndrome and transposition of the great arteries. J Cardiothorac Vasc Anesth 21(2):184–190
7. Tassani P, Kunkel R, Richter JA, Oechsler H, Lorenz HP, Braun SL, Eising GP, Haas F, Paek SU, Bauernschmitt R, Jochum M, Lange R (2001) Effect of C1-esterase-inhibitor on capillary leak and inflammatory response syndrome during arterial switch operations in neonates. J Cardiothorac Vasc Anesth 15(4):469–473
8. Pabst S, Hamscho N, Roller F, Stracke H, Schranz D, Lämmler C, Alzen G, Krombach GA (2014) C1-esterase inhibitor deficiency in pediatric heart transplant recipients: incidence and findings on ultrasound. Pediatr Radiol 44(3):258–264
9. Hövels-Gürich HH, Vazquez-Jimenez JF, Silvestri A, Schumacher K, Minkenberg R, Duchateau J, Messmer BJ, von Bernuth G, Seghaye MC (2002) Production of proinflammatory cytokines and myocardial dysfunction after arterial switch operation in neonates with transposition of the great arteries. J Thorac Cardiovasc Surg 124(4):811–820
10. Zeerleder S, Caliezi C, van Mierlo G, Eerenberg-Belmer A, Sulzer I, Hack CE, Wuijlem WA (2003) Administration of C1 inhibitor reduces neutrophil activation in patients with sepsis. Clin Diagn Lab Immunol 10(4):529–535

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