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Case Report

Tetralogy of Fallot with Sepsis Induced Coagulopathy in Case of Spontaneous Intracerebral Haemorrhage & Subarachnoid Haemorrhage

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Abstract

Congenital heart disease is the most common cause of stroke in some children. A child aged 5 years 9 months came with complaints of decreased consciousness and shortness of breath, weight 23 kg and height 140 cm, blood pressure 140/95 mmHg, pulse 52x/minute, axillary temperature 36.7°C, respiratory rate 44x/minute and obtained SpO_2 62%–78% using a nasal cannula. The patient was diagnosed with Tetralogy of Fallot through echocardiography but it was not corrected, Intracerebral Haemorrhage & Subarachnoid Haemorrhage were discovered on a CT scan, and sepsis induced coagulopathy through other supporting examinations. Children with congenital heart disease (CHD) are more susceptible to infection, this occurs because there is an increased risk for children with congenital heart disease to experience severe complications due to common infections such as sepsis. Sepsis itself will cause a coagulopathy disorder called sepsis induced coagulopathy (SIC) whose mechanism is also based on sepsis. Each of tetralogy of Fallot and Sepsis induced coagulopathy have mutually supporting roles in the mechanism of intracerebral haemorrhage. Most ICHs are caused by hypertension, arteriovenous malformation (AVM), and aneurysm. The patient experiences left ventricular dilatation, this can cause a long-term condition of hypertension. Through the SIC mechanism it can cause systemic inflammation and vascular injury caused by mass production of inflammatory cytokines and their release into the circulation causing excessive activation of the clotting process, impaired fibrinolysis, and suppression of anticoagulant mechanisms which can cause endothelial dysfunction and thrombus formation.

Keywords: TOF, Sepsis induced coagulopathy, spontaneous ICH, subarachnoid hemorrhage

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I. Introduction

Tetralogy of Fallot is one of the most common forms of cyanotic congenital heart disease, accounting for 10% of all congenital heart cases. Tetralogy of Fallot is a condition that includes overriding aorta, ventricular septal defect, right ventricular outflow tract obstruction (RVOT), and right ventricular hypertrophy. Stroke is a neurological complication that makes heart disease one of the most frequently encountered risk factors for stroke in children.[1-3] Children with congenital heart disease show a reduced cellular immune response to infections and an increased level of pro-inflammatory cytokines. This immune activity profile is clinically relevant because it has an increased morbidity rate when they are exposed to common pathogens, especially in premature infants with congenital heart disease who have an increased risk of sepsis.[4] Sepsis is defined by "The Third International Consensus Definitions for Sepsis

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and Septic Shock" as a life-threatening organ dysfunction caused by a dysregulated body response to infection. An increase of at least 2 points in the Sequential Organ Failure Assessment (SOFA) score indicates sepsis.[5] Major organ dysfunctions, such as in the brain, heart, liver, and kidneys, often occur in the context of sepsis. Among the most consistent symptom groups accompanying the sepsis syndrome are coagulation failure/coagulopathy, namely Sepsis-Induced Coagulopathy (SIC) and Disseminated Intravascular Coagulation (DIC). In the condition of SIC, the hemostatic balance undergoes significant changes during sepsis, resulting in underlying mechanisms of complications such as bleeding/hemorrhagic events.[6,7]

II. Case

History

A 5 years 9 months old patient presented with a referral from the community health center, complaining of decreased consciousness and shortness of breath. History of complex febrile seizures and trauma are denied by the patient. Symptoms include dizziness, headache, and vomiting three times with yellowish content preceded by nausea at 12:00 PM. The patient then experienced weakness and decreased consciousness. The patient has a history of Tetralogy of Fallot and has been taking fero sulfate syrup

Physical Examination

On physical examination, the patient appeared moderately ill with a Glasgow Coma Scale (GCS) score of E3V3M4. Vital signs showed a blood pressure of 140/95 mmHg, irregular pulse at 52 beats per minute, axillary temperature of 36.7°C, respiratory rate of 44 breaths per minute, and SpO_2 ranging from 62% to 78% with the use of a nasal cannula. Anthropometric measurements indicated a weight of 23 kg and a height of 140 cm. On examination of the head and neck, congested conjunctiva, cyanosis, and jugular vein distention were observed, with no meningeal signs or lymph node enlargement. The thoracic examination revealed symmetrical movement of both hemithoraces, no retractions or pigeon chest deformity, vesicular breath sounds in both hemithoraces, and no rhonchi or wheezing on either side. Cardiac examination noted a single S1 sound, single S2 sound accompanied by a systolic ejection murmur in the pulmonary area. Abdominal examination showed a flat appearance on inspection, supple on palpation, tympanic on percussion, and normal bowel sounds on auscultation. Examination of the extremities revealed clubbing of the fingers and cyanosis.

Laboratory Examination

Based on laboratory examination results from August 14, 15, and 18 2023, as shown in Table 1, several significant findings related to the subject's hematology, liver function, electrolytes, and renal function were noted. On a complete hematology examination dated August 14, 2023, the subject's hemoglobin level was found to be 19.9 g/dl, exceeding the expected normal range (13.5–17.5 g/dl), and the leukocyte count was also elevated at 16.5 x 10^3 / L (normal: 4.5–10 x 10^3 / L). The neutrophil to lymphocyte ratio (N/L) reached 6.1. Additionally, the subject's hematocrit was high at 65% (normal: 41.0–53.0%), while the platelet count was within the normal range at 150 x 10^3 / L. Liver function tests showed that the subject's blood albumin level on August 14, 2023, was normal at 4.2 g/dl (normal: 3.4–4.8 g/dl), indicating good liver function. However, electrolyte tests revealed a low potassium level of 2.75 mmol/L (normal: 3.5–5.0 mmol/L) and a slightly elevated serum creatinine level of 0.8 mg/dl (normal: 0.5–1.2 mg/dl). Laboratory tests on August 15, 2023, showed an increase in hemoglobin to 20.3 g/dl and leukocytes to 17.3 x 10^3 / L. Electrolyte tests indicated a decrease in platelet count to 100 x 10^3 / L, below the normal range (normal: 150–450 x 10^3 / L), which may indicate a risk of bleeding or coagulation disorders. The last laboratory test on August 18, 2023, showed a decrease in the subject's sodium level to 131.6 mmol/L (normal: 135–155 mmol/L) and an increase in potassium level to 3.46 mmol/L (normal: 3.5–5.0 mmol/L).

Blood gas examination over six days is shown in Table 1, indicating fluctuations in the subject's respiratory condition. The patient experienced

Table 1. Laboratory Examination Result

Examination	14/08/23	15/08/23	16/08/23	17/08/23	18/08/23	19/08/23
Hemoglobine	19.9	20.3	-	-	-	-
Leukocyte	16.5	17.3	-	-	-	-
N/L Ratio	6.1H	-	-	-	-	-
Hematocryte	65	64,8	-	-	-	-
Thrombocyte	150	100	-	-	-	-
Albumin	4.2	3.7	-	-	-	-
Natrium	140,6	140,6	-	-	131.6-	
Kalium	2.75	2.75	-	-	3.46	-
Chloride	104,8	104,8	-	-	98.4	-
SK/BUN	0.8/6	-	-	-	-	-
Phosphor	-	1.88	-	-	0.77	-
Magnesium	-	0.72	-	-	0.42	-
Calcium	-	2.34	-	-	2.20	-
Patient's PPT	-	-	-	-	19.7	-
PPT Control	-	-	-	-	10.3	-
Patient's APPT	-	-	-	-	35.1	-
APPT Control	-	-	-	-	28.1	-
GDA	102	110	81	50	48	39
SpO_2	35-51%	60%	95-98	52	2-30	47-58
PO_2	38	35	40	38.9	39.8	30.4
PCO_2	51.2	60	58	61.2	66.2	70.2
PH	7.46	7.4	7.65	7.52	7.48	7.68
$AADO_2$	605	640	630	650	708	720

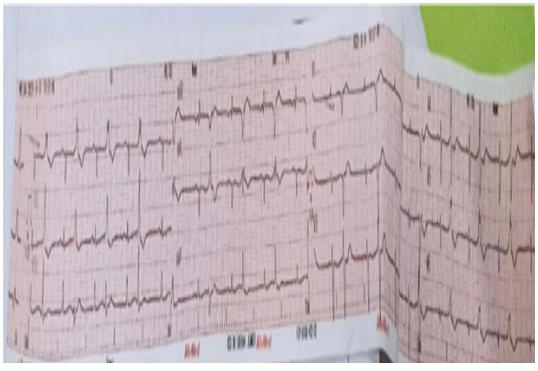

Figure 1. ECG Examination Results show PVC Bigeminy

respiratory failure for six consecutive days, marked by PO_2 below 60% and PCO_2 above 6.7 Kp, accompanied by fluctuating and low SpO_2 levels up to the sixth day and very high $AADO_2$ from the first to the sixth day.

Echocardiography

The 2D echocardiography examination indicates situs solitus, meaning the position of the organs in the chest is normal. The atrioventricular (AV) and ventriculoarterial (VA) connections are normal (concordant). Pulmonary venous return is detected as normal. The heart chambers show dilation of the right atrium (RA) and right ventricle (RV). Valve examination reveals trivial mitral regurgitation (trivial MR) and trivial tricuspid regurgitation (trivial TR). There is an overriding aorta of less than 40%, as well as severe pulmonary valvular stenosis with a pressure gradient (PG) of 69 mmHg. No patent ductus arteriosus (PDA) is detected. The atrial septum appears intact, but there is a malalignment of the ventricular septum (VSD). The aorta arch is normally located on the left side. The ejection fraction, measured by the M-MODE method, is 60.6%, indicating that the

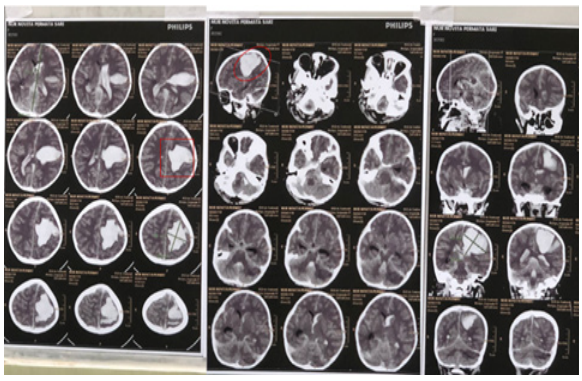

Figure 2. CT Scan Result

heart's pumping function is still within normal limits. The conclusion of this examination indicates the presence of Tetralogy of Fallot.

CT scan

In Figure 2, the CT Scan examination shows an intracerebral hemorrhage in the left and right frontoparietal lobes, compressing the left lateral ventricle and causing a 3 mm midline shift to the left. There is also intraventricular hemorrhage, subarachnoid hemorrhage, and mild non-communicating hydrocephalus.

Anesthesia Management

Administration of anesthesia was performed using general anesthesia with brain protection techniques, accompanied by endotracheal intubation with rocuronium 20mg. The

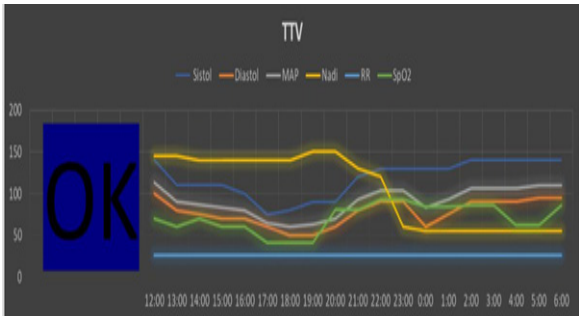

Figure 3. Operating Room Patient Observation Results

patient received induction drugs: intravenous midazolam 2mg, fentanyl 25mcg, ketamine 25 mg, and propofol 25+25 mg intravenously. After completion of the induction and intubation process, respiratory control was managed using a ventilator with rocuronium 20mg/hour, and

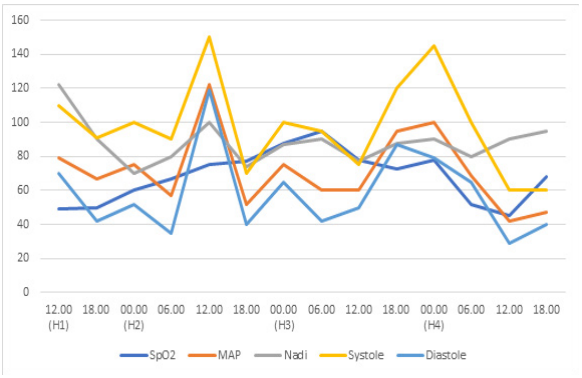

Figure 4. The Postoperative Day 1-4 Patient Observation Results

vital signs were monitored every 5 minutes. Maintenance was carried out with 1 vol% sevoflurane inhalation. The operation lasted for 1 hour and 30 minutes.

Post surgical management

After the surgery, the patient was transferred to the intensive care unit for further care. Observations of the patient's hemodynamic condition were conducted from day 1 to day 4, as shown in figure 3 and figure 4.

III. Discussion

The patient was diagnosed with Tetralogy of Fallot 2 years ago, they were advised to undergo corrective surgery at RSUD Soetomo Surabaya, but they refused, resulting in uncorrected Tetralogy of Fallot. Physical examination revealed clubbing of the fingers, cyanosis, and low SpO_2. This event is caused by megakaryocytes bypassing the pulmonary vascular and entering the systemic circulation, or by clusters of platelets that form and/or enter the systemic circulation. These can release growth factors originating from platelets, causing clubbing. Right-to-left shunting in Tetralogy of Fallot leads to inadequate blood flow to the lungs for oxygenation, resulting in low SpO_2 and cyanotic condition due to reduced capillary oxygen saturation.[2,3]

Children with congenital heart disease are more susceptible to infections, this increased risk of complications due to decreased granulocyte

activity against bacterial infections, T and B lymphocyte levels, undifferentiated T cells, T-Cell Receptor Excision Circles (TREC) levels, IgA and IgG, complement system, and increased suppressor T-cell function activity. This immune activity profile is clinically relevant as it increases morbidity when exposed to common pathogens, therefore in infants with congenital heart disease have an increased risk of sepsis.[4] Decision-making in diagnose sepsis is based on the SOFA Score (Sequential Organ Failure Assessment), it requires a minimum of 2 points to indicate sepsis in an individual.[5] SOFA Score assessment includes PaO_2, FiO_2, mechanical ventilation, platelet count, Glasgow Coma Scale, bilirubin, mean arterial pressure (MAP), and serum creatinine levels, The patient scored 7.5 The patient also experienced sepsis-induced coagulopathy (SIC), diagnosed by criteria set by the International Society on Thrombosis and Haemostasis Diagnosis of Disseminated Intravascular Coagulation (DIC) and SIC. It is confirmed based on platelet count, PTT, and SOFA Score. A score of 4 or above indicates SIC; the patient scored is 5.6.

Intracerebral hemorrhage (ICH) causes the patient to experience decreased consciousness. The occurrence of sepsis in spontaneous ICH in patients with congenital heart disease (CHD) correlates with each other. Intracerebral hemorrhage can result from coagulopathy caused by sepsis and various manifestations of congenital heart disease. Sepsis-induced coagulopathy (SIC) can lead to hemostasis imbalance, and sepsis can cause septic emboli originating from infections complicating the systemic vascular system. Large bacterial inocula form in vulnerable blood vessel areas, such as heart valve thrombus growth. These thrombi can break into smaller particles and distribute through the systemic bloodstream, potentially causing septic cerebral emboli and complications like hemorrhage.[7] The patient's congenital heart disease condition is also a risk factor for stroke. Right-to-left shunting allows emboli to enter the arterial circulation without passing through the lungs, termed paradoxical emboli and thrombosis.[8] The headache complained of by the patient is a symptom of subarachnoid hemorrhage (SAH). Head CT scan shows SAH due to the rupture of berry or saccular aneurysms at the branching of the intracranial blood vessels of the circle of Willis. Risk factors for SAH include hypertension, family history, and smoking. Pulmonary hypertension commonly occurs in patients with Tetralogy of Fallot (TOF), which can lead to systemic hypertension. There is a relationship between hypertension and intracranial aneurysm rupture; hypertension also influences aneurysm formation and rupture.9 On the ECG examination, the patient exhibits premature ventricular contractions (PVC) in a bigeminy pattern.

This condition involves additional heartbeats where PVCs typically occur before a normal heartbeat, resulting in a pause before the regular heartbeat resumes. In this patient, PVCs occur continuously alternating with regular sinus rhythm, appearing with each second sinus beat. The patient's hypokalemia (2.75 mmol/L) forms the basis for the mechanism of PVC occurrence. Potassium (K+) is a primary intracellular cation critical for maintaining cell membrane excitability. Low serum potassium levels increase the transmembrane electrochemical gradient, leading to cell hyperpolarization and disrupting depolarization and contraction. This can cause disturbances in cardiac conduction pathways, potentially resulting in arrhythmias.[10] The patient's hypokalemia was corrected with a 6.9 cc KCL drip over 6 hours. Trepanation is performed based on indications outlined in the AHA Guidelines for the Management of Spontaneous Hemorrhage, where patients with cerebellar hemorrhage experiencing worsening neurological conditions or brainstem compression and/or hydrocephalus due to ventricular obstruction undergo immediate hemorrhage removal surgery.[11] The use of ketamine is chosen because ketamine can stimulate the cardiovascular system and mediate activation of the central sympathetic nervous system by increasing plasma levels of epinephrine and norepinephrine. This leads to maintaining blood pressure, heart rate, and respiration. Ketamine also does not significantly alter systemic vascular resistance

(SVR) in patients or children with atrial or ventricular septal defects, atrioventricular canal defects, or Tetralogy of Fallot, resulting in a more stable condition for the patient.[12] Following trepanation, the patient experienced respiratory failure, indicated by post-operative arterial blood gas analysis showing PaO_2 and $PaCO_2$ levels. Respiratory failure is a condition where there is inadequate gas exchange to meet metabolic needs, resulting in hypoxia with or without hypercarbia. Respiratory failure is diagnosed through arterial blood gas analysis, with $PaO_2 < 60$ mmHg, or $PaCO_2 > 45$ mmHg. Mechanistically, respiratory failure is classified into 3 types: type 1 respiratory failure is characterized by oxygen transfer impairment leading to hypoxia, type 2 respiratory failure involves inadequate ventilation causing CO_2 retention, and mixed type respiratory failure combines elements of type 1 and type 2. In this patient, mixed type respiratory failure (type 1 and type 2) occurred.[13]

The uncorrected Tetralogy of Fallot condition in the patient is the primary cause of mixed respiratory failure. Right-to-left shunting occurs when blood that should pass through the pulmonary veins bypasses the alveoli, leading to inadequate oxygenation and reducing the oxygen content in the blood that reaches systemic circulation, resulting in decreased PaO_2. Significant shunting causes hypoxemia and can occur with sepsis, liver failure, and pulmonary embolism. Blood shunted does not undergo gas exchange in the alveoli, hence the hypoxemia it causes cannot be fully corrected by increasing FiO_2.[14]

The A-a gradient has significant clinical utility as it can help determine the source of hypoxemia, aiding in narrowing down the etiology of hypoxemia to either extrapulmonary (outside the lungs) or intrapulmonary (within the lungs) origins. The A-a gradient, or alveolar-arterial gradient, measures the difference between the oxygen concentration in the alveoli and the arterial system. The A-a gradient is calculated using the formula: A-a Gradient = PAO_2 - PaO_2. PAO_2 represents alveolar oxygen tension and PaO_2 represents arterial oxygen tension. Arterial oxygen tension (PaO_2) can be directly assessed with an arterial blood gas (ABG) test or estimated using a venous blood gas (VBG) test. Alveolar oxygen tension (PAO_2) is estimated using the alveolar gas equation: $PAO_2 = (Patm - PH_2O) FiO_2 – PaCO_2/RQ$.[14]

On the first day, the patient's $AaDO_2$ value was 605 mmHg, which is already very high. This value increased on the second day to 640 mmHg, and slightly decreased on the third day to 630 mmHg. However, on the fourth day, the $AaDO_2$ value increased again to 650 mmHg. A significant increase was observed on the fifth day with a value of 708 mmHg, reaching its peak on the sixth day at 720 mmHg. For PO_2 values, on the first day, the patient's PO_2 was 38 mmHg, indicating low arterial oxygen levels, which could suggest impaired oxygenation. On the second day, the PO_2 value slightly decreased to 35 mmHg, showing a further decline in the blood's oxygenation capacity. However, on the third day, there was a significant increase in the PO_2 value to 40 mmHg, possibly indicating a temporary improvement in lung gas exchange. On the fourth day, the PO_2 value slightly decreased to 38.9 mmHg, almost the same as the first day. On the fifth day, the PO_2 value increased slightly again to 39.8 mmHg but remained at a level indicating hypoxemia. On the sixth day, the PO_2 value dropped drastically to 30.4 mmHg.

The decrease in PaO_2 levels in this patient is most likely due to a right-to-left shunt, leading to hypoxemia and an increased A-a gradient. In a right-to-left shunt, some pulmonary blood flow is diverted away from the alveoli, resulting in ventilation without perfusion and a higher V/Q ratio. Although diffusion between capillaries and alveoli is unaffected, arterial PO_2 decreases due to the lack of ventilation in the shunted blood, resulting in an increased A-a gradient. Arterial PCO_2 also increases due to impaired gas exchange. Due to the plateau in the oxyhemoglobin dissociation curve, small changes in arterial blood oxygen content cause significant shifts in PO_2. Consequently, a right-to-left shunt causes more hypoxemia than hypercapnia. In

general, increasing FiO_2 through supplemental oxygen therapy does not improve hypoxemia in patients with a right-to-left shunt, the increased oxygen content in the inhaled air never reaches the shunted blood for gas exchange.[14,15]

Blood glucose monitoring was performed from the first postoperative day to the sixth postoperative day. On the first and second days, the patient's blood glucose levels were in the range of 102–115 mg/dL. A decrease in blood glucose began on the third day. On the third day, the patient's blood glucose level was 81 mg/dL while receiving a 25 cc bolus of D40. On the fourth, fifth, and sixth postoperative days, the patient's random blood glucose levels dropped drastically. On the fourth day, the patient's blood glucose was 50 mg/dL. On the fifth day at 06:35, while receiving the same treatment of a 25 cc bolus of D40, the patient's blood glucose was 48 mg/dL, and on the sixth day, the patient's blood glucose was 39 mg/dL. The underlying mechanism for low blood glucose in this patient is likely due to sepsis. Current sepsis therapy focuses on antimicrobial treatment and supporting organ function, while other aspects of the body's response to infection, such as metabolism, hemostasis, and thermoregulation, are not fully addressed. In sepsis, changes occur in the endocrine and autonomic nervous systems. Activation of these systems, known as the neuroendocrine response, is dynamic and has a significant impact on metabolism. This is caused by several triggers, primarily pro-inflammatory cytokines—IL-1, IL-6, and TNF-α. These cytokines play a key role in activating the neuroendocrine response, mediating metabolic changes, and can directly alter metabolism. The most important pro-inflammatory cytokines are interleukin 1 (IL-1), IL-6, and tumor necrosis factor α (TNF-α). They contribute, among other things, to the development of a procoagulant state, increased production of reactive oxygen species (ROS), and nitric oxide (NO).[16]

IV. Conclusion

Congenital heart disease (CHD) that remains uncorrected can render individuals vulnerable. When exposed to an infection, children with CHD experience decreased granulocyte activity, increasing susceptibility to bacterial infections. This diminished immunologic profile escalates the risk of sepsis, which in turn may complicate into Sepsis Induced Coagulopathy. The occurrence of Tetralogy of Fallot (TOF) in patients causes right-to-left shunting, allowing emboli to enter the arterial circulation without passing through the lungs. In conditions of sepsis and SIC, this can lead to septic emboli. Large bacterial inocula form in vulnerable blood vessels, such as heart valve thrombi, which break into smaller particles and distribute systemically, potentially causing septic cerebral emboli and complications like hemorrhagic stroke (ICH). Both TOF and SIC increase the risk of hemorrhagic stroke; in this case patient experiences intracerebral hemorrhage (ICH). After hematoma evacuation through trepanation, the patient was transferred to the ICU for hemodynamic monitoring. Post-operative monitoring revealed respiratory failure characterized by unstable $AADO_2$, PO_2, and PCO_2 levels, likely due to uncorrected TOF causing right-to-left shunting. This leads to blood bypassing the lungs without oxygenation, reducing oxygen content in the bloodstream (PaO_2). The patient also experienced hypoglycemia post-operatively, possibly due to disrupted metabolism from sepsis-induced dysregulation of pro-inflammatory cytokines, affecting the neuroendocrine balance critical for metabolism.

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