

HEPARIN-INDUCED CARDIAC TAMPONADE AND LIFE-THREATENING HYPERKALEMIA IN A PATIENT WITH CHRONIC HEMODIALYSIS

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Heparin, a commonly used anticoagulant agent, is frequently used in patients undergoing hemodialysis. As with most medications, heparin has a significant side effect profile. Two of its most important side effects, major bleeding and hyperkalemia, may be devastating without immediate diagnosis and treatment. Major bleeding such as gastrointestinal, genitourinary or intracranial bleeding is occasionally encountered and rarely neglected. However, heparin-induced cardiac tamponade is rarely encountered and may be easily overlooked. Another side effect, heparin-induced hyperkalemia, an unusual but well-described side effect, is frequently forgotten until life-threatening arrhythmia has occurred. We report a case involving a 40-year-old male patient with uremia, who had received heparin for 10 days for deep vein thrombosis in the left lower extremity. Hemopericardium with cardiac tamponade and life-threatening hyperkalemia were both noted in this patient.

Key Words: heparin, cardiac tamponade, hyperkalemia
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As with most medications, heparin has a variety of side effects, including bleeding, thrombocytopenia [1,2], cumulative dose-dependent osteoporosis, skin necrosis, alopecia, hypersensitivity reactions, hypoaldosteronism [3] and hyperkalemia [4–9]. The major complication of heparin is bleeding. Factors that predispose a patient to bleeding include advanced age, serious concurrent illness, heavy consumption of alcohol, concomitant use of aspirin, and renal failure [3]. Another side effect, heparin-induced hyperkalemia, is an unusual but well-described side effect [4–9]. Patients at risk for heparin-induced hyperkalemia include those with diabetes mellitus (DM), renal insuff-

iciency, metabolic acidosis, the elderly, and those receiving concomitant drugs that can produce hyperkalemia [7,10, 11]. We report a patient with uremia, who had received heparin for 10 days for deep vein thrombosis (DVT) in the left lower extremity. As a result, hemopericardium with cardiac tamponade and life-threatening hyperkalemia developed in this patient.

CASE PRESENTATION

A 40-year-old male patient suffering from left thigh swelling and redness for 2 weeks was admitted to the cardiovascular ward at Kaohsiung Medical University. Tracing his medical history, we found him to have end-stage renal disease with regular hemodialysis (HD), DM with regular insulin control, and hypertension with regular drug control. Due to the symptoms in his left thigh, he was initially admitted to St. Joseph's Hospital in Kaohsiung, where a retrograde

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venography was performed and the patient was found to have DVT in his left lower extremity. He was prescribed heparin. As his symptoms did not subside after heparin use for 2 days, he was transferred to our hospital for further care. At our hospital, heparin treatment was continued, keeping partial thromboplastin time (PTT) within 1.5 to 2 times normal. At admission, 12-lead electrocardiography (ECG) showed normal tracing (Figure 1A), chest X-ray (CXR) showed mild cardiomegaly (cardiothoracic ratio 57%) (Figure 2A), and echocardiography showed only moderate mitral regurgitation without pericardial effusion (Figure 3A). The patient's laboratory data at admission are summarized in the Table. On the seventh hospital day, Tc-99m-labeled red blood cell subcutaneous radionuclide venography was performed and revealed resolution of the left thigh DVT. Heparin was discontinued on the eighth hospital day. Dyspnea was noted on the ninth hospital day. At that time, the patient's breathing sounds indicated bilateral lower lung inspiratory crackle, and CXR revealed cardiomegaly with pulmonary congestion (Figure 2B). As he was first suspected of having dyspnea caused by fluid overload, emergency additional HD was performed. However, after emergency HD, dyspnea only partially improved. On the 10th hospital day, dyspnea was aggravated again and all-purpose O₂ (60%, 10 L) was used. Arterial blood gas showed: pH, 7.378; PCO₂, 29.6 mmHg; PO₂, 101.8 mmHg; HCO₃, 17.1 mmol/L; SaO₂, 97.5%. The patient suddenly lost consciousness and went into cardiac arrest, for which cardiopulmonary resuscitation (CPR) was initiated. After 3 minutes of CPR and treatment with empirical intravenous epinephrine and calcium gluconate, the ECG monitor showed ventricular fibrillation waves, and the patient was administered direct-current (DC) shock 200 J. After DC shock, the ECG monitor showed wide-QRS rhythm without P waves (Figure 1B). Hyperkalemia-induced arrhythmia was suspected, so another dose of calcium gluconate and standard potassium-lowering agents were administered. The patient's pulse gradually recovered, but shock (blood pressure, 70/40 mmHg) was noted and the inotropic agent, dopamine, was administered. His laboratory data after this episode are listed in the Table. Twelve-lead ECG showed first-degree atrioventricular node block and higher T waves in leads V2–V6 (Figure 1C). We thoroughly reviewed his CXR films and found that the CXR of the ninth hospital day indicated a larger heart size (cardiothoracic ratio, 66%) than previous films (Figure 2B). Immediate bedside echocardiography was performed and the patient was found to be experiencing severe pericardial effusion with right ventricular (RV) early diastolic collapse (Figure

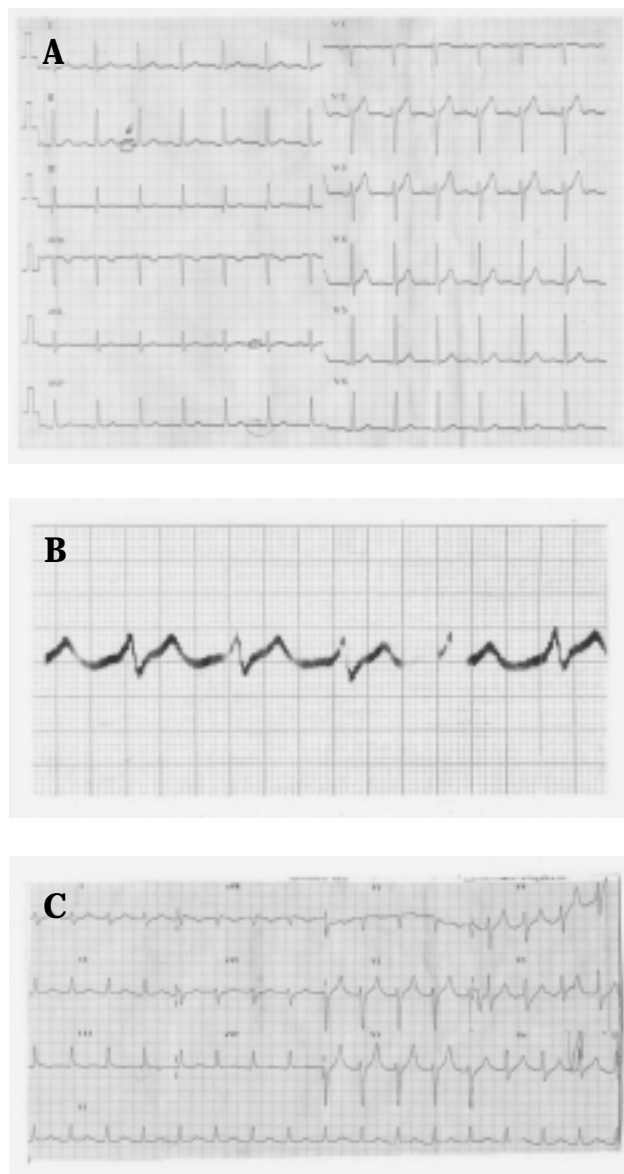


Figure 1. Electrocardiograms. (A) At admission, 12-lead electrocardiography (ECG) showed normal tracing. (B) After cardiopulmonary resuscitation and direct-current shock, ECG showed wide-QRS rhythm without P waves. (C) After resuscitation and treatment with potassium-lowering agents, 12-lead ECG showed first-degree atrioventricular block and higher T waves in leads V2–V6.

3B). Emergency pericardiocentesis was performed and 800 mL dark-red pericardial effusion was drained. After pericardiocentesis, RV early diastolic collapse disappeared (Figure 3C) and blood pressure returned to 110/70 mmHg. Because potassium was still high (8.7 mmol/L) after treatment, a second emergency additional HD was given after pericardiocentesis. The patient gradually regained consciousness and was weaned from the endotracheal tube

Table. Laboratory data

Component	Upon admission	After cardiopulmonary resuscitation
WBC ($\times 10^9/L$)	13.72	10.27
Hemoglobin (g/L)	62	67
Platelets ($\times 10^9/L$)	350	566
GOT/GPT (U/L)	19/21	1,124/751
Na/K/Cl (mmol/L)	128/4.8/89	136/9.2/94
PT (s) (patient/control)	12.9/11.4	–
PTT (s) (patient/control)	48.6/32.2	–
Bilirubin (T/D) ($\mu\text{mol/L}$)	12.0/5.1	20.5/6.0
CK/CK-MB (U/L)	–	316/3.7
Troponin-I ($\mu\text{g/L}$)	–	0.42

WBC = white blood cell; GOT = glutamate-oxaloacetate transaminase; GPT = glutamate-pyruvate transaminase; PT = prothrombin time; PTT = partial thromboplastin time; T = total; D = direct; CK = creatine kinase; MB = isoenzymes from myocardial tissue.

after being intubated for 24 hours. Thereafter, serum potassium level gradually decreased and pericardial effusion did not accumulate again. He was discharged without event 19 days after admission.

DISCUSSION

Heparin, the most commonly used anticoagulant agent, is frequently used in patients with acute coronary syndrome, stroke, pulmonary embolism, DVT, and patients receiving diagnostic or therapeutic procedures which may induce thrombosis, such as coronary angiography, percutaneous coronary intervention, and HD. Heparin has been reported to have a variety of side effects, including bleeding, thrombocytopenia, osteoporosis, skin necrosis, alopecia, hypersensitivity reactions, hypoaldosteronism and hyperkalemia [1–9]. Among the side effects, major bleeding and hyperkalemia may be the most devastating if not immediately diagnosed and treated. Major bleeding, such as gastrointestinal bleeding, genitourinary or intracranial bleeding, is occasionally encountered and rarely overlooked. However, heparin-induced massive pericardial effusion is rarely encountered and can easily be overlooked without a detailed examination, and diagnosis is not usually established until cardiac tamponade develops. Another side effect, heparin-induced hyperkalemia, is also unusual but well-described in previous reports [4–9]. This side effect is frequently



Figure 2. Chest X-ray (CXR) films. (A) At admission, CXR showed mild cardiomegaly (cardiothoracic ratio, 57%). (B) On the ninth hospital day, CXR revealed a larger heart size (cardiothoracic ratio, 66%) than previous films.

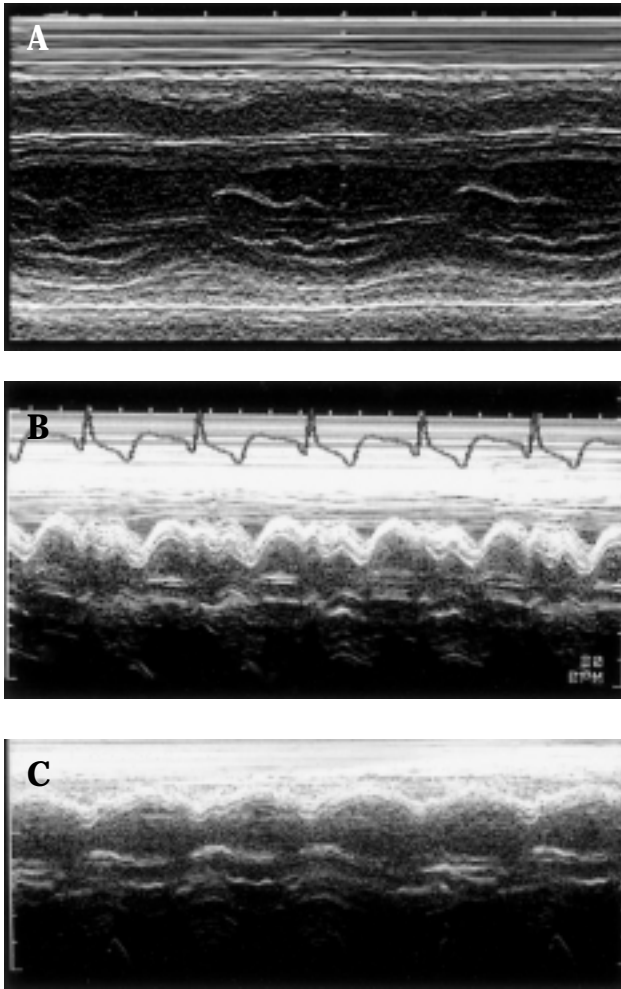


Figure 3. Echocardiograms. (A) At admission, M-mode echocardiography showed no pericardial effusion. (B) Before pericardiocentesis, M-mode echocardiography showed right ventricular (RV) early diastolic collapse. (C) Just after pericardiocentesis, repeated M-mode echocardiography showed disappearance of RV early diastolic collapse.

overlooked until life-threatening arrhythmia is noted [4]. In our case, heparin was used for 10 days to treat left lower extremity DVT. We discontinued it because repeated venography revealed that his DVT had resolved. Two days after discontinuation, however, the patient was found to have developed hemopericardium with cardiac tamponade and life-threatening hyperkalemia. Emergency pericardiocentesis and HD were successfully performed and he was discharged after 19 days of hospitalization.

Drug-induced hemopericardium with cardiac tamponade has been reported to occur in patients using thrombolytic agents or glycoprotein IIb-IIIa receptor antagonists [12–15]. Malouf et al, studying the role of anticoagulation in the development of pericardial effusion and late tamponade after

cardiac surgery, demonstrated that larger pericardial effusions and cardiac tamponade were more likely to occur among patients if they were excessively anticoagulated [16]. In our case, although heparin was used for 10 days, PTT remained within the therapeutic range and no excessive anticoagulation was noted. However, this patient was uremic, and renal failure has been proven to predispose patients using heparin to bleeding [3]. Although echocardiography at admission revealed no pericardial effusion, hemorrhagic pericardial effusion gradually developed in the patient after prolonged heparin use. This pericardial effusion eventually became large enough to cause cardiac tamponade, which was diagnosed by repeated echocardiography. Emergency pericardiocentesis was successfully performed and 800 mL of bloody pericardial effusion was drained. After pericardiocentesis, echocardiographic signs of cardiac tamponade (RV early diastolic collapse) disappeared and the patient experienced an immediate elevation of blood pressure.

Hyperkalemia may result from a variety of factors, including an increase in potassium intake, a decrease in potassium excretion, or a shift of potassium from intracellular to extracellular fluid [17]. Many drugs, including potassium supplements, angiotension-converting enzyme inhibitors, non-steroidal anti-inflammatory drugs, and potassium-sparing diuretics, may also cause hyperkalemia. Numerous case reports have implicated heparin as a cause of hyperkalemia [4–9] and several mechanisms may be responsible for heparin-induced hyperkalemia [18]. Heparin appears to directly interfere with the production of aldosterone, reduce the number and affinity of angiotension II receptors, and induce a progressive atrophy of the zona glomerulosa. Inhibition of aldosterone occurs within 1 week after the initiation of heparin [11]. However, clinically significant hyperkalemia rarely occurs and is often transient because most patients are able to compensate through other mechanisms that decrease serum potassium [19]. Patients at risk for heparin-induced hyperkalemia are those unable to compensate for decreased aldosterone concentrations by regulating serum potassium through other pathways. These include patients with DM, renal insufficiency, metabolic acidosis, the elderly, and those receiving concomitant drugs that can produce hyperkalemia [7,10,11]. Prolonged heparin therapy has also been associated with a greater risk of hyperkalemia [7]. When hyperkalemia does occur, it usually becomes detectable between days 1 and 3 of heparin administration, peaks between days 3 and 5, continues for the duration of heparin therapy, and returns to normal within 1 week after discontinuation of the drug [18,19]. In our case, serum potassium level was 4.8 mmol/L at admission. During his stay at the hospital, he did not receive a potassium-rich

diet. The patient had uremia and was receiving regular HD. Before he was found to have hyperkalemia, he was not only receiving regular HD, but, as he was suspected of having dyspnea caused by fluid overload, he had also received additional emergency HD. Therefore, his diet and a decrease in potassium excretion were not the likely causes of his hyperkalemia. His hyperkalemia was caused by either overproduction or intercellular shift, or it was drug-induced. No apparent source of potassium overproduction was noted in our case, except massive bloody pericardial effusion. Although we found a report of hyperkalemia associated with massive cephalhematoma in a newborn infant [20], this cause was unlikely because we found no evidence of hemolysis (follow-up total/direct bilirubin level, 20.5/6.0 $\mu\text{mol/L}$). Metabolic acidosis was noted in our patient. This acid-base abnormality might result in a shift of potassium from intracellular to extracellular fluid and cause hyperkalemia. However, this metabolic acidosis might play a minor role in the development of hyperkalemia because the additional emergency HD could excrete potassium shifted from intracellular fluid. Our patient was a DM case with uremia, which, as mentioned earlier, predisposed him to heparin-induced hyperkalemia [7,10–11]. Consequently, prolonged use of heparin probably played a major role in the development of hyperkalemia in our case.

The major treatment for heparin-induced hyperkalemia is discontinuation of the drug. Potassium concentrations generally return to normal within 1 week after discontinuation of heparin [11,18]. If discontinuation of heparin is not feasible, fludrocortisone has been reported to be a reasonable therapy for these patients [21]. In our case, discontinuation of heparin, standard potassium-lowering agents and emergent additional HD were successfully performed to reverse the complication of hyperkalemia and hyperkalemia-induced life-threatening arrhythmia.

In conclusion, our case demonstrates that prolonged heparin use may simultaneously cause cardiac tamponade and life-threatening hyperkalemia. These side effects are frequently overlooked until patients develop serious complications. Therefore, a series of serum potassium concentration monitors and echocardiography follow-up are necessary to avoid these lethal complications in patients receiving heparin for prolonged periods.

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一位長期洗腎的病人因肝素的使用 而引起心包膜填塞和危及生命的高血鉀症

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肝素 (一種常使用的抗凝血劑) 經常用在須要洗腎的病人身上。正如大部份的藥品一樣，它也有一些重要的副作用。這些副作用當中，大出血和高血鉀症，若無立即的診斷和治療可能會造成嚴重的後果。而大出血像是胃腸道、泌尿道和腦出血是偶爾會遇到但較不會被忽略的；但是，肝素引起心包膜填塞的副作用反而很少遇到而較易被忽略。另外，肝素引起的高血鉀症 (一種不常見但已被証實的副作用) 常常在危及生命的心律不整出現時才被發現。這裡，我們報告一位 40 歲男性的洗腎病人，因左腳下肢靜脈栓塞而接受 10 天的肝素治療。很不幸地，心包膜出血而引起心包膜填塞和危及生命的高血鉀症都發生在這位病人身上。

關鍵詞：肝素，心包膜填塞，高血鉀症
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