Recurrent Cardiac Arrest during a Nontransplant Operation Due to Variant Angina in a Liver Transplantation Patient

Jaeyoung Yang, M.D., Dae Yoon Kim, M.D., Suk Koo Lee, M.D. and Gaabsoo Kim, M.D.

Department of Anesthesiology and Pain Medicine, Samsung Medical Center,
Sungkyunkwan University School of Medicine, Seoul, Korea

We report a case of recurrent cardiac arrest during a nontransplant operation in a liver transplant recipient with prior cardiac arrest during liver transplantation. A 45-year-old man who experienced cardiac arrest for 17 minutes during the preanhepatic phase of liver transplantation—which was performed 34 months ago—did not survive the recurrent cardiac arrest during portal venoplasty. Variant angina was not suspected for the first cardiac arrest; however, myocardial infarction by coronary vasospasm was revealed to be the cause of the second cardiac arrest.

Key Words: Liver transplantation, Heart arrest, Variant angina
중심 단어: 간이식, 심정지, 변이성 협심증

INTRODUCTION

Liver transplantation (LT) is a high-risk procedure with possible perioperative and long-term morbidities and mortalities. Unfavorable preoperative conditions together with acute hemodynamic changes can result in acute cardiovascular events perioperatively. Even though various preoperative cardiac evaluations are performed, it is not easy to diagnose variant angina in LT recipients who do not have any history of heart disease. We report a case of unexpected recurrent cardiac arrest during a nontransplantation operation in a LT recipient who experienced cardiac arrest during LT but was not diagnosed with variant angina after the first cardiac arrest.

CASE REPORT

A 45-year-old man (body weight 83.2 kg, height 173 cm) with liver cirrhosis from a complication of hepatitis B virus infection was admitted for living-donor LT. His preoperative cardiac evaluation including electrocardiogram (ECG) and echocardiography were within the normal range (ejection fraction of 72%). His Model for End-Stage Liver Disease (MELD) score and Child class were 17 and C. After proper anesthetic and surgical preparations including pulmonary artery catheterization, the operation began without any event. The initial arterial blood gas analysis (ABGA) results were as follows: pH, 7.427; $PaCO_2$, 35.3 mmHg; PaO_2, 211.4 mmHg; FiO_2, 0.48; HCO_3^-, 22.7 mEq/L; base excess (BE), −1.2 mEq/L; hematocrit (Hct), 33%; Na^+, 137 mmol/L; K^+, 4.5 mmol/L; and Ca^{2+}, 1.00 mmol/L. About one and a half hours into the surgery, the inferior vena cava (IVC) was partially clamped. An operator discovered an IVC injury and repaired it quickly without massive bleeding. Blood pressure and heart rate were maintained at around 100/50 mmHg and 70 beats per minute; however, ST segment of lead II decreased from −0.8 to −2.4 mm in ECG. Nitroglycerin infusion was

started at the rate of 1 μg/kg/min. On the ABGA measured 10 minutes prior to the cardiac arrest, pH, $PaCO_2$, HCO_3^-, and BE had changed to 7.24 mmHg, 35.3 mmHg, 14.7 mEq/L, and −11.6 mmol/L, respectively, although the rest of the values had not significantly changed. Thirty minutes after the ST depression event, the patient's blood pressure dropped to 60/40 mmHg. Within 30 seconds, sudden cardiac arrest accompanied by ventricular fibrillation and asystole occurred during dissection of the IVC for liver isolation. Chest compression was initiated immediately. His cardiac rhythm converted to a sinus rhythm after administration of 1 mg epinephrine five times, 0.5 mg atropine five times, 300 mg calcium chloride, and several 360 J defibrillations over 17 minutes of cardiopulmonary resuscitation (CPR). The patient's blood pressure increased to 110/65 mmHg, and his heart rate was 70 beats per minute. The operation was completed without any other issues. On postoperative day 2, both ECG and echocardiography taken in the intensive care unit (ICU) were within the normal range and no regional wall motion abnormality (ejection fraction 64%) was reported. Troponin I and creatinine kinase (CK)-MB levels were also within the normal range. He was discharged on postoperative day 33 without any other complications.

Thirty-four months later, the patient was admitted due to elevated levels of total bilirubin. Stenosis of the portal vein was observed in abdominal computed tomography and ultrasonography, so we decided to perform portal venoplasty. His preoperative laboratory data, chest X-ray, and ECG were within the normal range. The operation began without any issues and his vital signs were stable. The initial ABGA results were as follows: pH, 7.459; $PaCO_2$, 32.9 mmHg; PaO_2, 176.5 mmHg; FiO_2, 0.53; HCO_3^-, 22.8 mEq/L; BE, −0.3 mEq/L; Hct, 39%; Na^+, 139 mmol/L; K^+, 5.3 mmol/L; and Ca^{2+}, 0.99 mmol/L. Blood pressure, heart rate, and ST segment level of lead II were approximately 100/60 mmHg, 70 beats/minute, and 0.3 mm, respectively. On the ABGA measured 30 minutes prior to the cardiac arrest, pH, $PaCO_2$, HCO_3^-, and BE had changed to 7.3 mmHg, 45.7 mmHg, 22.0 mEq/L, and −4.5 mmol/L, respectively, but the rest of the values had not significantly changed. Four hours after the surgery began when balloon dilatation of the portal vein was performed, the patient's blood pressure and heart rate dropped to 60/30 mmHg and 45 beats per minute. ST segment of lead II was depressed to −1.3 mm at the same time. Incremental ephedrine injections were not effective. Within 1 minute, ventricular fibrillation followed by asystole was observed and chest compression was started. A 100 mg lidocaine, 300 mg calcium chloride, 0.5 mg atropine, and 1 mg epinephrine were injected every 1 or 2 minutes. A 360 J defibrillation was applied regularly. Despite every effort for recovery, his cardiac rhythm did not recover. Extra-corporeal membrane oxygenation was applied after 60 minutes of CPR and the patient was transferred to the ICU. In the ICU, his blood pressure and heart rate were 140/90 mmHg and 140 beats per minute. Acute myocardial infarction was suspected based on postoperative laboratory
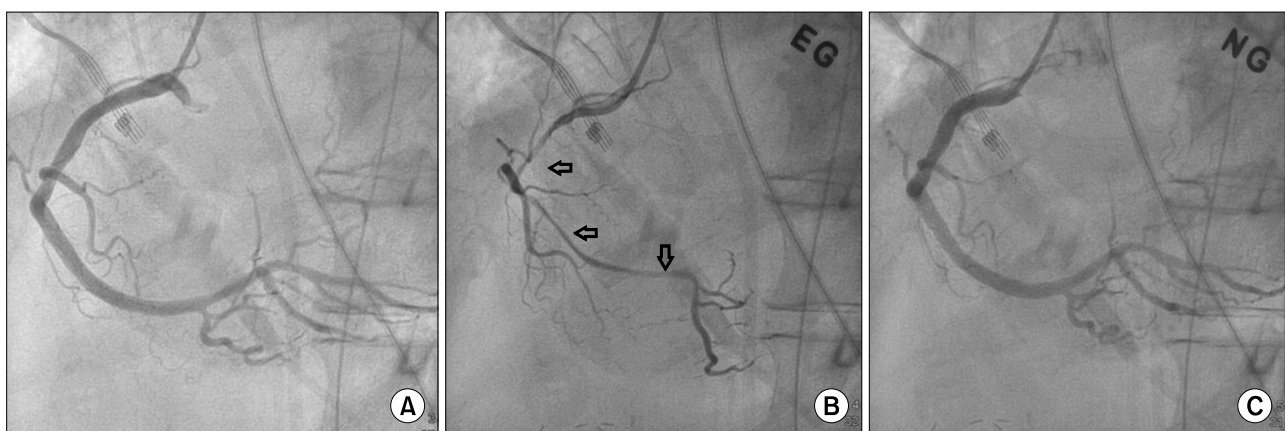

Fig. 1. Postoperative right coronary angiography in the left anterior oblique view. (A) Baseline right coronary angiography. (B) Right coronary angiography after intracoronary ergonovine injection. The arrows indicate diffuse coronary spasm of the right coronary artery induced by ergonovine. (C) Coronary spasm of the right coronary artery was reversed by intracoronary nitroglycerine injection.

data since troponin I (71.198 ng/mL; normal, <0.01 ng/mL), CK-MB (567.20 ng/mL; normal, 0~4.9 ng/mL), and lactate dehydrogenase (14,300 U/L; normal, 140 to 280 U/L) levels were all elevated. Acute coronary vasospasm in the left anterior descending artery and right coronary artery reversed by intracoronary nitroglycerin injection were observed in the coronary angiography taken in the ICU. He was diagnosed with acute myocardial infarction from acute intraoperative vasospasm (Fig. 1). Unfortunately, the patient expired on postoperative day 6.

DISCUSSION

The number of LT recipients who receive another non-transplant operation is expected to increase due to the growing number of LT cases and the improved survival rate of LT recipients.

Patients who receive LT frequently have characteristic hyperdynamic hemodynamic patterns[1,2]. Decreased systemic vascular resistance can increase cardiac output in these patients. As a result, their cardiac adaptation ability against physiologic stress is lower than normal. Although preoperative cardiovascular examinations are within the normal range, the possibility of cardiovascular events related to LT remains. If a patient experiences cardiac arrest during LT, it is certain that he or she will be allocated into the high-risk group for cardiovascular complications.

Variant angina was first described by Prinzmetal et al.[3] in 1959. He reported an atypical ischemic coronary syndrome that was not related with exercise, but rather associated with ST segment elevation on ECG. Even though the incidence of variant angina is 1% to 2.5% among patients with chest pain who receive a coronary angiogram, it is related with acute myocardial infarction, cardiac arrhythmias such as ventricular fibrillation, and ventricular tachycardia[4,5].

The typical clinical feature of variant angina is rest angina that responds well to nitrates. The chest pain can have a circadian pattern and is not exacerbated by physical exercise[6]. Based on the criteria established by the Coronary Vasomotion Disorders International Study Group (COVADIS), variant angina can be diagnosed by three criteria: (1) nitrate-responsive angina; (2) ECG changes during a transient ischemic event; and (3) demonstration of coronary vasospasm (>90% constriction) spontaneously or in response to provocative stimulation (acetylcholine or ergonovine)[6].

The exact underlying mechanism of coronary vasospasm is still unknown; however, the imbalance between sympathetic-parasympathetic systems was suggested as a possible mechanism. Stimulation of the parasympathetic nervous system or acetylcholine could induce coronary vasospasm[7].

It has been shown that abnormalities in nitric oxide in the endothelium are related with coronary vasospasm[8]. Enhanced phospholipase C enzyme activity has also been detected in smooth muscle in variant angina patients[9].

Smoking is a known predisposing factor for coronary vasospasm[10]. Anesthesia can also trigger coronary vasospasm although this is rare[11-14]. The cause of perioperative coronary vasospasm is still not known; however, several possible mechanisms have been suggested: an imbalance in vasoconstriction and vasodilation forces[15], increased catecholamine level due to anesthesia and surgery[15], increased alpha adrenergic receptor activity[16], stimulation of the parasympathetic nervous system[17], and release of vasoconstrictive substances from platelets[18]. An additional study found that ephedrine and inotropic drugs could lead to intraoperative coronary vasospasm during regional anesthesia[19].

There are many case reports suggesting that intraoperative manipulation of major vessels such as the carotid, coronary, iliac artery, and aorta can trigger coronary vasospasm by the previously mentioned mechanisms[20-24]. Because it requires handling the major vessels, LT surgery can be stressful enough to trigger a sympathetic and parasympathetic imbalance.

There have been several case reports on coronary vasospasm related with renal and heart transplantation[25-27]. Endothelial dysfunction has been suggested as a mechanism of coronary vasospasm in transplant recipients since immunosuppressive agents such as cyclosporine and tacrolimus are closely related with endothelial dysfunction[28,29], which is a strong triggering factor for coronary vasospasm[30]. Liver transplant recipients also have a risk of coronary vasospasm associated with immunosuppressant therapy.

In this case, a cardiac evaluation for variant angina was not performed after the first cardiac arrest because variant

angina was not suspected. Even though ST depression was observed prior to cardiac arrest, it was difficult to diagnose variant angina because the cardiac arrest was accompanied with an IVC injury.

Umphrey et al.(31) reported that perioperative short-term cardiovascular complications could be expected in patients based on preoperative dobutamine stress echocardiography results and MELD scores. However current American Heart Association guidelines for perioperative cardiac evaluation do not recommend a routine coronary angiogram, the gold standard method to diagnose variant angina, for patients who do not have cardiac disease even in high risk non-cardiac surgery(32). Ripoll et al.(33) suggested that pre-operative echocardiography was not statistically significant in its ability to predict perioperative cardiovascular events.

Matsusaki et al.(34) reported that the incidence of intra-operative cardiac arrest (ICA) during LT was 5.5%, and 90% of ICA occurred during the neohepatic phase. Most of the short-term cardiovascular events occur during anhepatic or reperfusion phases which are periods with significant hemodynamic changes(34).

During the first cardiac arrest, ST depression was detected prior to the cardiac event and nitroglycerin infusion was initiated. This may have aided in the relief of coronary vas-ospasm leading to an early recovery from cardiac arrest. The patient did not experience any cardiovascular symptoms un-til the second operation.

The progression of the second cardiac arrest was too abrupt and nitroglycerin was not immediately administered. Without nitroglycerin or calcium channel blockers, vaso-pressors were continuously injected for the cardiac re-suscitation which may have exacerbated the coronary vaso-spasm during the second cardiac arrest.

In conclusion, the messages from this case are simple and clear. If a LT patient has a cardiac event at a relatively un-expected time such as during the preanhepatic phase, ICA such as variant angina should be suspected as the cause of the cardiac event even though it is rare. If ST segment change is detected, nitroglycerin infusion should be initiated early during LT surgery.

According to Ertel et al.(35) report, the reoperation rate within 90 days of LT is surprisingly high at 29.3%. Tho-rough preoperative cardiac evaluation and vigilant intra-operative monitoring are advised for liver transplant recipi-ents who had intraoperative cardiac events and plan to un-dergo another surgery.

REFERENCES

1) Baik SK, Fouad TR, Lee SS. Cirrhotic cardiomyopathy. Orphanet J Rare Dis 2007;2:15.
2) Moller S, Henriksen JH. Cirrhotic cardiomyopathy: a patho-physiological review of circulatory dysfunction in liver disease. Heart 2002;87:9-15.
3) Prinzmetal M, Kennamer R, Merliss R, Wada T, Bor N. Angina pectoris. I. A variant form of angina pectoris: pre-liminary report. Am J Med 1959;27:375-88.
4) Fontaine B, Bertrandias E, Chelly J, Kieffer JP, Tournay D, Peyrat D, et al. Prinzmetal's angina during myocardial revascularisation. Cardiovascular complications in 71 pa-tients (author's transl). Anesth Analg (Paris) 1979;36:545-50.
5) Bory M, Pierron F, Panagides D, Bonnet JL, Yvorra S, Desfossez L. Coronary artery spasm in patients with normal or near normal coronary arteries. Long-term follow-up of 277 patients. Eur Heart J 1996;17:1015-21.
6) Beltrame JF, Crea F, Kaski JC, Ogawa H, Ong P, Sechtem U, et al. International standardization of diagnostic criteria for vasospastic angina. Eur Heart J 2015 Aug 4 [Epub]. DOI: http://dx.doi.org/10.1093/eurheartj/ehv351.
7) Inazumi T, Shimizu H, Mine T, Iwasaki T. Changes in auto-nomic nervous activity prior to spontaneous coronary spasm in patients with variant angina. Jpn Circ J 2000;64:197-201.
8) Stern S, Bayes de Luna A. Coronary artery spasm: a 2009 update. Circulation 2009;119:2531-4.
9) Nakano T, Osanai T, Tomita H, Sekimata M, Homma Y, Okumura K. Enhanced activity of variant phospholipase C-delta1 protein (R257H) detected in patients with coro-nary artery spasm. Circulation 2002;105:2024-9.
10) Green MS, Gomes S. Intraoperative coronary artery vaso-spasm: a twist in the tale! Middle East J Anaesthesiol 2011;21:299-304.
11) Fujita Y, Sasaki Y, Endoh E, Kimura K, Fukui A, Ohsumi A, et al. Intraoperative coronary artery spasm during non-coronary artery surgery. J Cardiothorac Anesth 1990;4:740-3.
12) Zainea M, Duvernoy WF, Chauhan A, David S, Soto E, Small D. Acute myocardial infarction in angiographically normal coronary arteries following induction of general anesthesia. Arch Intern Med 1994;154:2495-8.
13) Kindgen-Milles D, Vester EG, Muller EE. Intra- and post-operative myocardial ischemia without significant coronary artery stenosis. Acta Anaesthesiol Scand 1998;42:478-80.

14) Sidi A, Dahleen L, Gaspardone A. Coronary vasospasm during anesthesia induction: awareness, recognition, possible mechanisms, anesthetic factors, and treatment. J Clin Anesth 2008;20:64-9.

15) Hayashida M, Matsushita F, Suzuki S, Misawa K. Coronary artery spasm immediately after the long-standing operation for cancer of the tongue. Masui 1992;41:1986-90.

16) Crea F, Chierchia S, Kaski JC, Davies GJ, Margonato A, Miran DO, et al. Provocation of coronary spasm by dopamine in patients with active variant angina pectoris. Circulation 1986;74:262-9.

17) Yasue H, Touyama M, Shimamoto M, Kato H, Tanaka S. Role of autonomic nervous system in the pathogenesis of Prinzmetal's variant form of angina. Circulation 1974;50:534-9.

18) Rubenstein MD, Wall RT, Baim DS, Harrison DC. Platelet activation in clinical coronary artery disease and spasm. Am Heart J 1981;102(3 Pt 1):363-7.

19) Hirabayashi Y, Saitoh K, Fukuda H, Mitsuhata H, Shimizu R. Coronary artery spasm after ephedrine in a patient with high spinal anesthesia. Anesthesiology 1996;84:221-4.

20) Fuse K, Makuuchi H, Konishi T, Nakanishi S, Nishiyama S, Nishimura S, et al. Coronary artery spasm during coronary artery bypass surgery: its diagnosis, treatment and prevention. Jpn J Surg 1988;18:626-35.

21) Truong AT, Truong DT, Brown DL. Recurrent intraoperative coronary artery spasm in a patient with coronary artery aneurysm. J Clin Anesth 2006;18:530-3.

22) Kwok OH, Chow WH, Chiu SW. Coronary artery spasm of a non-culprit vessel during off-pump bypass surgery. Asian Cardiovasc Thorac Ann 2004;12:91.

23) Choi SS, Lim YJ, Bahk JH, Do SH, Ham BM. Coronary artery spasm induced by carotid sinus stimulation during neck surgery. Br J Anaesth 2003;90:391-4.

24) Nagaoka H, In-nami R, Funakoshi N, Fujiwara A, Ito A, Iesaka Y, et al. Successfully treated intraoperative coronary artery spasm in a patient with type B dissecting aortic aneurysm: a case report. Kyobu Geka 1992;45:619-22.

25) Biyik I, Akturk IF, Yalcin AA, Celik O, Oner E. Immunosuppressive therapy induced coronary vasospasm and acute myocardial infarction in a patient undergoing new renal transplantation. Postepy Kardiol Interwencyjnej 2015;11: 141-5.

26) Santoro F, Lopizzo A, Centola A, Cuculo A, Ruggiero A, Di Biase M, et al. Very late coronary spasm inducing acute myocardial infarction in a heart transplant recipient. J Cardiovasc Med (Hagerstown) 2014 Jul 10 [Epub]. DOI: http://dx.doi.org/10.2459/JCM.0000000000000049.

27) Ferguson ME, Pearce FB, Hsu HH, Misra VK, Kirklin JK. Coronary artery spasm during angiography in a pediatric heart transplant recipient: subsequent prevention by intracoronary nitroglycerin administration. Tex Heart Inst J 2010;37:469-71.

28) Jeanmart H, Malo O, Carrier M, Nickner C, Desjardins N, Perrault LP. Comparative study of cyclosporine and tacrolimus vs newer immunosuppressants mycophenolate mofetil and rapamycin on coronary endothelial function. J Heart Lung Transplant 2002;21:990-8.

29) Textor SC, Wiesner R, Wilson DJ, Porayko M, Romero JC, Burnett JC Jr, et al. Systemic and renal hemodynamic differences between FK506 and cyclosporine in liver transplant recipients. Transplantation 1993;55:1332-9.

30) Lanza GA, Careri G, Crea F. Mechanisms of coronary artery spasm. Circulation 2011;124:1774-82.

31) Umphrey LG, Hurst RT, Eleid MF, Lee KS, Reuss CS, Hentz JG, et al. Preoperative dobutamine stress echocardiographic findings and subsequent short-term adverse cardiac events after orthotopic liver transplantation. Liver Transpl 2008;14:886-92.

32) Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol 2014;64:e77-137.

33) Ripoll C, Catalina MV, Yotti R, Olmedilla L, Perez-Pena J, Lo Iacono O, et al. Cardiac dysfunction during liver transplantation: incidence and preoperative predictors. Transplantation 2008;85:1766-72.

34) Matsusaki T, Hilmi IA, Planinsic RM, Humar A, Sakai T. Cardiac arrest during adult liver transplantation: a single institution's experience with 1238 deceased donor transplants. Liver Transpl 2013;19:1262-71.

35) Ertel AE, Wima K, Chang AL, Hoehn RS, Hohmann SF, Edwards MJ, et al. Risk of reoperation within 90 days of liver transplantation: a necessary evil? J Am Coll Surg 2016;222:419-28.