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A Comparison of the Effects of Sevoflurane and Desflurane on Corrected QT Interval Prolongation in Patients Undergoing Living Donor Liver Transplantation: A Prospective Observational Study

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ABSTRACT

Background. QT interval prolongation has frequently been observed in patients with advanced liver disease. We investigated the influence of inhalation anesthetics on the corrected QT (QTc) interval prolongation during surgery in patients undergoing living-donor liver transplantation.

Methods. Our study included 43 patients who were assigned to 2 groups: sevoflurane (n = 22) or desflurane anesthesia (n = 21). QTc intervals were measured at perioperative determined time points and calculated using Fridericia's formula.

Results. Intraoperative QTc intervals increased during the peri-intubation period versus baseline (*P* = .003) and were prolonged during the peri-reperfusion period (*P* < .001). However, there was no significant difference in intraoperative QTc interval changes between patients given sevoflurane or desflurane (*P* = .59).

Conclusions. In this prospective observational study, there was no significant difference in QTc intervals between sevoflurane and desflurane. QTc intervals increased during intubation and reperfusion relative to preoperative values in patients given either sevoflurane or desflurane.

CORRECTED QT (QTc) interval prolongation, which increases the risk of life-threatening arrhythmias, such as torsade de pointes, has been reported to be associated with liver diseases, such as liver cirrhosis [1]. The mechanism of QTc interval prolongation in patients with liver disease is unknown, but autonomic dysfunction, induced by altered concentrations of circulating neurotransmitters, has been suggested as a major cause because QTc interval prolongation typically improves after liver transplantation [1,2]. Specifically, QTc interval prolongation is observed in half of patients who have end-stage liver disease and are scheduled for living-donor liver transplantation [3]. Furthermore, in these vulnerable patients, QTc interval prolongation is aggravated during surgery, resulting in adverse cardiovascular events because surgical stimulation and tracheal intubation cause further disturbances, such as electrolyte imbalance, drugs, and sympathetic activation [4–7]. Thus, methods of minimizing QTc interval

prolongation in patients undergoing liver transplantation should be identified.

Inhalational anesthetics such as sevoflurane and desflurane have been reported to prolong the QTc interval during anesthesia [8–11]. Although desflurane is thought to increase the QTc interval more than sevoflurane by inducing sympathetic hyperactivity [12], this remains controversial [13,14]. Moreover, these previous studies targeted patients who did not have risk factors for QTc interval prolongation, so the effect of inhalational agents on the QTc interval in patients who have cardiac risk factors may be different. To our knowledge, no study has compared the effects of inhalational

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agents on the QTc interval prolongation in patients undergoing liver transplantation. Thus, we hypothesized that desflurane would increase the QTc interval more than sevoflurane in patients undergoing liver transplantation.

METHODS

This prospective observational study was a substudy. The parent study was a randomized controlled clinical trial comparing the incidence of postreperfusion syndrome between sevoflurane and desflurane anesthesia in patients undergoing living-donor liver transplantation, which was approved by the Institutional Review Board of Seoul National University Hospital (reference: H-1209-048-425) and registered at the ClinicalTrials.gov website (reference: NCT01886664, August 20, 2012). This substudy was also approved by the Institutional Review Board of Seoul National University Hospital (reference: H-1209-048-425) and registered at the ClinicalTrials.gov website (reference: NCT01899248, July 10, 2013). Written informed consent was obtained from all patients.

The participants were adults aged 18–65 who were scheduled for elective living-donor liver transplantation. Patients with body mass index >30 $kg \cdot m^{-2}$, cardiac arrhythmias, severe pulmonary hypertension, intraoperative use of inotropics before reperfusion, intraoperative cardiac arrest, or a history of liver transplantation were excluded. In the parent study, patients were randomized using a 1:1 ratio to either sevoflurane or desflurane groups. Random sequence of size 2 blocks that included A or B were generated and each concealed envelope had one letter within. Enrolled patients were allocated to their groups depending on the letter (A or B) inside the concealed envelopes that were opened up by an anesthesia nurse who was unaware of the study.

Anesthetic Management and Surgical Procedure

On arrival in the operating room, patients were monitored using electrocardiography (ECG), pulse oximetry, and noninvasive blood pressure measurements. General anesthesia was induced by 40 mg lidocaine with 2 $mg \cdot kg^{-1}$ propofol and tracheal intubation was facilitated with 0.6 $mg \cdot kg^{-1}$ rocuronium. After tracheal intubation, mechanical ventilation was initiated at a tidal volume of 8 mL/kg and respiratory rate of 10/min using oxygen/air (fractional inspired oxygen 0.5). Anesthesia was maintained with sevoflurane or desflurane, according to the group assignment. The inhalation anesthetic was maintained at 1 minimum alveolar concentration (2% for sevoflurane or 7% for desflurane) during the operation. Before the anesthesiologist unaware of the group to which the patient has been randomized, who was designated to manage the patient during reperfusion entered the operating room, the vaporizers on the anesthesia machine were covered and the monitor setting was altered to hide the concentration of the inhalation anesthetic to comply with the double-blind protocol. Cisatracurium at 0.2 $mg \cdot kg^{-1} \cdot h^{-1}$ was infused for neuromuscular relaxation during the surgery.

The right radial and femoral arteries were cannulated for invasive blood pressure monitoring. Under ultrasound guidance, a 7-Fr double-lumen central venous catheter (ARROW, Arrow International Inc., Reading, Pa, United States) and a 9-Fr large-bore catheter (Advanced Venous Access Device, HF, Edwards Lifesciences, Irvine, Calif, United States) were placed in the right internal jugular vein. A pulmonary artery catheter (Swan-Ganz CCOmbo V, Edwards Lifesciences) was inserted into the pulmonary artery through the central venous catheter. The donor liver graft was preserved with histidine-tryptophan-ketoglutarate solution (Custodiol, Köhler Chemie GmbH, Alsbach-Hähnlein, Germany). The surgeon who performed the liver transplantation was blinded to group assignments. Anastomosis of the liver graft was performed using the piggyback technique. Just before anastomosis between the hepatic vein of the graft and the inferior vena cava of the recipient, the graft was perfused with 5% albumin though the portal vein. After anastomosis of the portal vein, the graft was reperfused by release of hepatic vein and portal vein clamps.

The anesthesiologist, who was blinded to group assignments (vaporizers on the anesthesia machine were covered with a
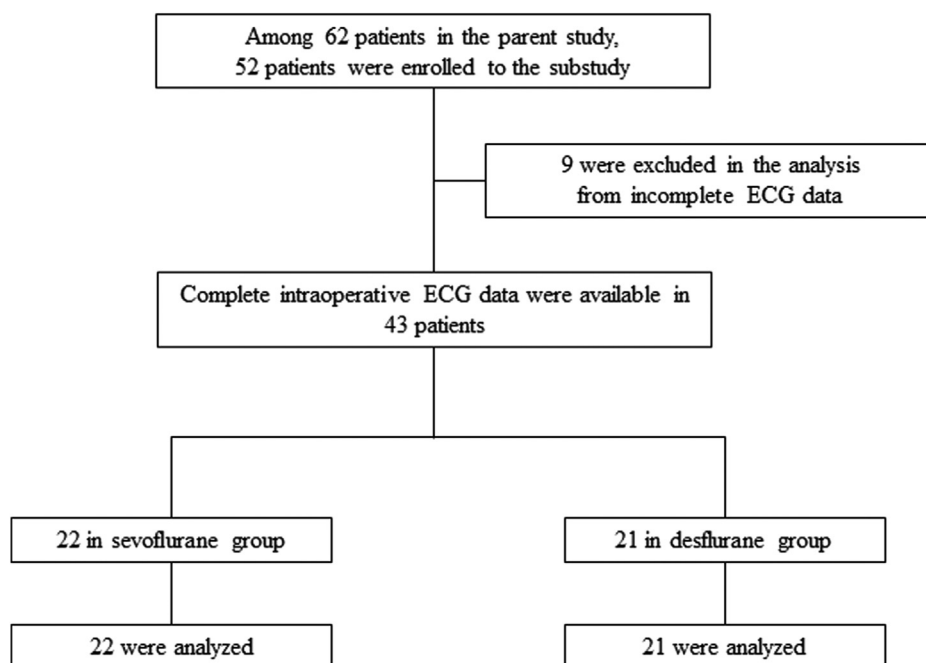

Fig 1. Flow diagram for the study.

Table 1. Characteristics of Patients' Measured QTc Intervals During Living-Donor Liver Transplantation

	Sevoflurane (n = 22)	Desflurane (n = 21)	P
Age; y	52 (7)	52 (10)	.92
Male	15 (68)	17 (81)	.36
Height; cm	165.7 (9.4)	165.9 (9.9)	.94
Weight; kg	60.9 (8.6)	62.2 (13.0)	.7
Body mass index; kg·cm^{-2}	22 (2)	22 (4)	.72
Underlying disease			
Hypertension	1 (5%)	5 (24%)	.1
Diabetes	4 (18%)	7 (33%)	.31
Chronic obstructive pulmonary disease	1 (5%)	0 (0)	>.99
History of coronary disease	1 (5%)	0 (0)	>.99
Chronic kidney disease	0 (0)	1 (5%)	.49
Pulmonary hypertension	0 (0)	2 (10%)	.23
Etiology of liver disease			
Alcoholic	4 (18%)	1 (5%)	.35
Nonalcoholic	18 (82%)	21 (95%)	.11
MELD score	12 (5%)	12 (5%)	.75
Preoperative medication			
Beta blocker	2 (9%)	1 (5%)	.72
Calcium channel blocker	1 (5%)	3 (15%)	.34
Antiarrhythmics	0 (0)	0 (0)	>.99
Antibiotics	22 (100%)	21 (100%)	>.99
Serum electrolyte levels			
Potassium; mmol·L^{-1}	4.04 (0.56)	3.99 (0.54)	>.99
Calcium; mmol·L^{-1}	8.7 (0.41)	8.6 (0.69)	.44
Magnesium; mg·dL^{-1}	1.73 (0.26)	1.88 (0.17)	.2
Preoperative hemoglobin; g·dL^{-1}	11.6 (2.2)	11.3 (2.1)	.37
Preoperative QTc interval; ms	453.3 (46.6)	451.3 (38.3)	.88

Note: Values are presented as the mean (SD) or number of patients (%).
Abbreviation: MELD, model for end-stage liver disease.

blanket), managed the patient according to a standardized protocol during reperfusion. Postreperfusion syndrome was defined as a >30% decrease in mean arterial pressure relative to that at initiation of reperfusion lasting more than 1 minute and occurring within 5 minutes of reperfusion. Postreperfusion syndrome was treated with 5 mg of ephedrine administered intravenously. If the mean arterial pressure decreased to <40 mm Hg, 10 μg of epinephrine was administered intravenously. If postreperfusion syndrome continued, repeated doses of ephedrine or epinephrine were administered intravenously every minute for 5 minutes. Titrated infusion of dopamine was administered intravenously if postreperfusion syndrome continued despite 5 doses of ephedrine or epinephrine. The occurrence of postreperfusion syndrome was recorded.

Anastomosis of the hepatic artery and bile duct were performed consecutively. All patients were transferred to the intensive care unit after surgery. The anesthesiologists who managed patients in the intensive care unit were also blinded to group assignments. The length of intensive care unit stay was recorded.

QTc Interval

Preoperative QTc intervals were recorded in the ward using a 12-lead ECG machine. Intraoperative QTc intervals were recorded at the following time points: before anesthetic induction, before, immediately after, and at 3, 5, and 10 minutes after tracheal intubation, at 5 minutes before and 1, 2, 3, and 20 minutes after reperfusion, and at skin closure. These time points were expressed as baseline, pre-intubation, I0, I3, I5, I10, reperfusion-5, R1, R2, R3, R20, and skin closure, respectively.

Intraoperative QTc intervals were obtained and calculated according to the methods in our previous study [15]. In the operating room, ECG signals were recorded using a continuous monitoring ECG system (Solar 8000M, GE Medical System, Milwaukee, Wis, United States). ECG data in lead II were collected with an analog-to-digital converter (DI-149, DATAQ Instruments Inc., Akron, Ohio, United States), which was connected to the analog output of the patient monitor and stored on a personal computer. ECG data were analyzed using LabChart software (version 6; AD Instruments, Colorado Springs, Colo, United States). QTc interval was measured automatically by LabChart software using the ECG curves of 4 consecutive beats to acquire a more accurate representation of the ECG waveform. If the automatic method did not correctly detect the onset of the QRS complex or the end of T wave, the QT interval was measured manually. QT interval measurements were performed by an anesthesiologist who was unaware of group assignment. The QTc interval was calculated using Fridericia's formula to preclude interference by heart rate (QTc = QT/RR1/3) [15]. The mean arterial pressure and heart rate were recorded at the same time points as the QTc interval (before anesthetic induction, before, immediately after, and at 5 and 10 minutes after tracheal intubation, at 5 minutes before and 1, 2, 3, and 20 minutes after reperfusion, and at skin closure).

Statistical Analysis

The primary outcome was the maximum QTc interval during 3 minutes after reperfusion. Power analysis indicated that a minimum of 21 patients would be required for a type 1 error of 0.05 and a power of 0.8 to detect a difference of 30 ms in QTc interval between the sevoflurane and desflurane groups, assuming that the standard deviation (SD) of the QTc intervals was 34 ms, based on a previous study [7]. Data on age, weight, height, body mass index, end-stage liver disease score, serum electrolyte levels, preoperative hemoglobin, preoperative QTc interval, and length of intensive care unit stay were compared between groups using Student t test or the Mann-Whitney U test. Data on gender, underlying disease, preoperative medication, etiology of liver disease, and incidence of postreperfusion syndrome were compared using a χ^2 test or Fisher exact test. QTc intervals during anesthesia were compared using generalized estimating equations. The QTc intervals of reperfusion and intubation, respectively, were the highest values among those measured at least 1 minute after each step. The number of patients whose QTc interval was more than 500 ms was compared using Fisher exact test. Values are presented as means (SD) or number of patients (%). SPSS software (version 18.0 for Windows; SPSS Inc., Chicago, Ill, United States) was used for all statistical analyses. P values <.05 were considered to indicate statistical significance.

RESULTS

The parent study of this substudy was a randomized controlled clinical trial comparing the incidence of postreperfusion syndrome between sevoflurane and desflurane anesthesia in patients undergoing living-donor liver transplantation conducted from December 2012 to November 2013. This substudy was a prospective observational study conducted from January to November 2013. Because of the

discrepancy in the study start dates between the parent study and this substudy, among 62 patients in the parent study, 52 patients were enrolled in this study. Of those 52, complete intraoperative ECG data were available only in 43 patients, and these 43 patients (22 patients in the sevoflurane group and 21 patients in the desflurane group) were finally analyzed (Fig 1).

Serum Electrolyte and Hemodynamic Variable

Patient characteristics did not significantly differ between groups (Table 1). There was also no significant difference in preoperative QTc intervals on ECG, serum electrolyte levels including calcium, potassium, and magnesium, or the etiology or severity of the liver disease (Table 1). Intraoperatively, mean arterial pressure and heart rate at each study time point were not significantly different between the 2 groups ($P > .05$; Fig 2).

Intraoperative QTc Interval, Intensive Care Unit, and Hospital Stay

Intraoperative QTc interval changes are shown in Fig 3. There was no significant difference in intraoperative QTc interval between the 2 groups ($P = .59$). The maximum QTc interval during 3 minutes after reperfusion was not significantly different between the sevoflurane and desflurane groups (452 ± 55 ms and 473 ± 30 ms, respectively; $P = .125$). QTc intervals increased significantly during intubation and reperfusion relative to baseline ($P = .003$ and $<.001$, respectively). At skin closure, the QTc interval also increased significantly from the baseline ($P = .001$). The numbers of patients with QTc intervals >500 ms were not significantly different between the 2 groups during intubation, reperfusion, and skin closure (Table 2). Among the 43 patients, postreperfusion syndrome occurred in 24 (55.7%) patients (8 in the sevoflurane group, 16 in the desflurane group). Consistent with the parent study, postreperfusion syndrome occurred less frequently in the sevoflurane group than the desflurane group (38.7% vs 77.4%; $P = .014$).

However, there were no significant differences in the length of intensive care unit stay (5.4 ± 1.3 vs 6.1 ± 2.6 days; $P = .269$) or hospital stay (15.5 ± 5.3 vs 18.5 ± 8.4 days; $P = .164$).

DISCUSSION

In this prospective observational study, QTc interval increased in patients given either sevoflurane or desflurane during intubation and reperfusion in living-donor liver
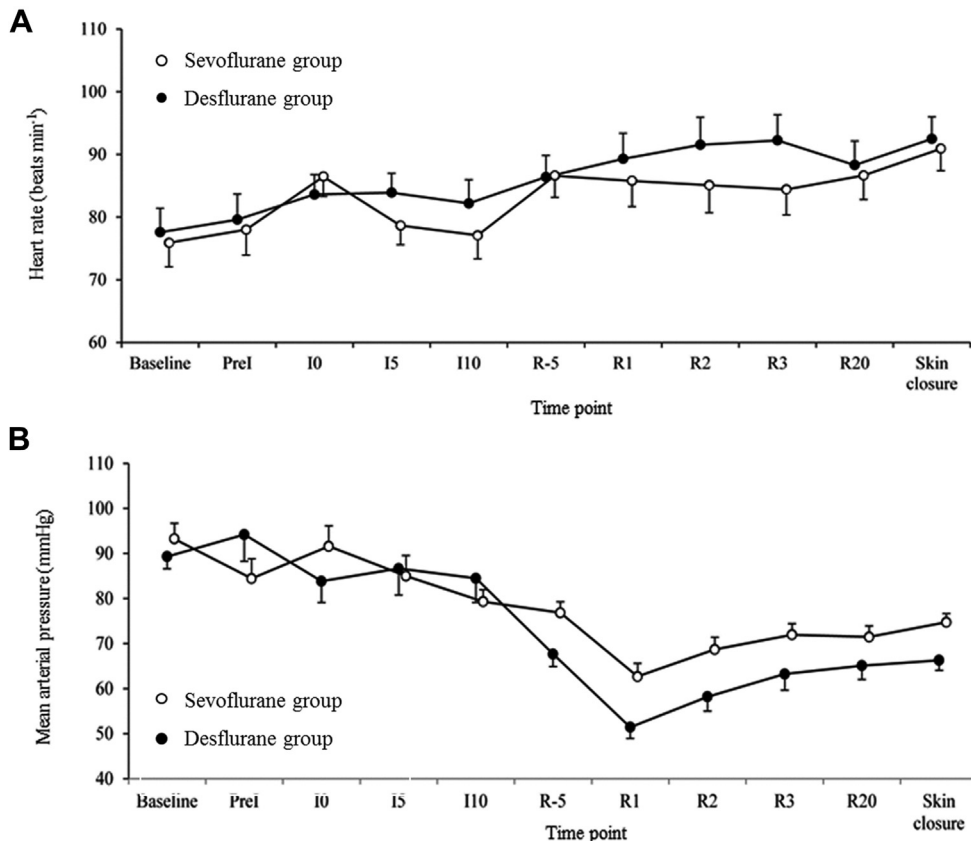

Fig 2. Intraoperative changes in heart rate (**A**) and mean arterial pressure (**B**) during operation. Abbreviations are for time points, where pre indicates before, numbers indicate minutes after each step, and I and R stand for intubation and reperfusion, respectively.

Fig 3. Intraoperative changes of corrected QT interval. Abbreviations are for time points, where pre indicates before, numbers indicate minutes after each step, and I and R stand for intubation and reperfusion, respectively.
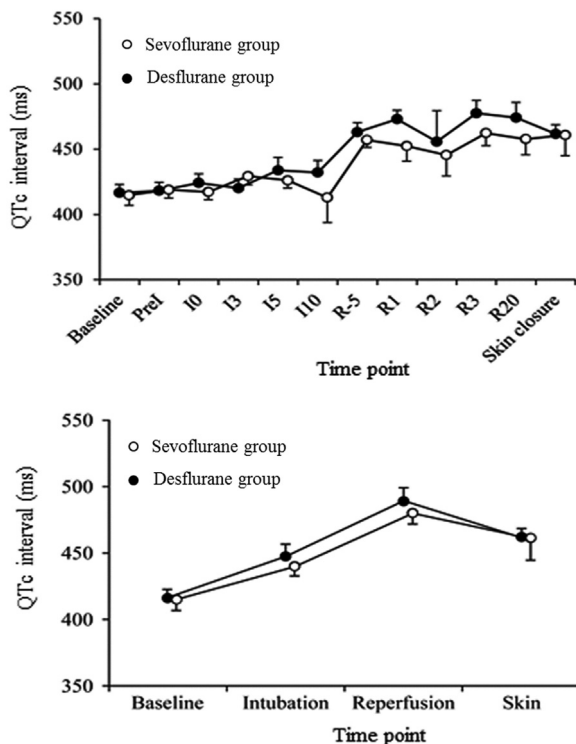
transplantations. However, there was no significant difference in intraoperative QTc interval prolongation between the 2 anesthetics at any time point analyzed, including the peri-intubation and peri-reperfusion periods.

Prolonged preoperative QTc interval has been observed in approximately half of patients with end-stage liver disease [5,7,16], and, even in patients whose QTc intervals are within the normal range, QTc interval is prolonged during liver transplantation [5]. This corresponds with the result of our study. In our study, preoperative QTc interval >440 ms was observed in 9 of patients and QTc interval prolongation was significantly aggravated at the end of surgery compared with the preoperative value [17,18]. This is because of the additive effects of risk factors for QTc prolongation, such as sympathetic stimulation, dynamic hemodynamic changes, and abrupt electrolyte imbalances during transplantation, which are associated with life-threatening arrhythmias [7,16].

Table 2. Incidence of Perioperative QTc Interval >500 ms

	Baseline	Intubation	Reperfusion	Skin Closure
Sevoflurane (n = 22)	0 (0)	0 (0)	5 (23%)	3 (14%)
Desflurane (n = 21)	0 (0)	2 (10%)	5 (24%)	2 (10%)
P		.489	>.99	>.99

Note: Values are presented as the number of patients (%).

Several previous studies observed perioperative QTc changes in patients with end-stage liver disease [3,19,20]; however, most assessed QTc changes before and after transplantation. Few studies have observed intraoperative QTc changes during the risky intraoperative periods. Therefore, we observed QTc changes within short time intervals, especially during the peri-intubation and the peri-reperfusion periods. In previous studies, tracheal intubation prolonged QTc interval regardless of anesthetic induction agent [10,21,22]. One possible mechanism of this QTc prolongation is increased sympatho-adrenal activity caused by laryngoscopy and stimulation of pharyngeal and laryngeal nerves during tracheal intubation. Moreover, the peri-reperfusion period is also a risky period for QTc prolongation because of hemodynamic changes and abrupt increases in potassium concentrations in the circulating blood [23]. Consistent with previous results, QTc intervals during the peri-intubation and the peri-reperfusion periods were also prolonged in the present study; however, there was no significant difference between the sevoflurane and desflurane groups.

Inhalation anesthetics have been reported to prolong the QTc interval [8–14], and several previous studies have compared various inhalation agents' effects on QTc interval [12–14]. Yildirim et al observed that sevoflurane, isoflurane, and desflurane all prolonged QTc, QT dispersion, and QTc dispersion at 3 and 10 minutes after reaching 1 MAC of end-tidal anesthetic concentration, but there were no significant intergroup differences in patients undergoing noncardiac surgery [13]. In another study comparing effects on QTc interval during the peri-induction period, QTc interval was more prolonged with desflurane than sevoflurane, which was thought to be related to the sympathetic activity of desflurane [14]. Kazanci et al reported no significant difference in QTc dispersion according to anesthetic, although QT dispersion was more prolonged with desflurane than sevoflurane anesthesia [12]. However, the study population in most of these studies included patients without severe comorbidities. To the best of our knowledge, this is the first report comparing the effects of sevoflurane and desflurane on intraoperative QTc prolongation in patients with end-stage liver disease. The concentration of inhalation anesthetic is known to be associated with the degree of QTc interval prolongation regardless of the kinds of anesthetics [11,24]. Therefore, in our study, we maintained 1 minimum alveolar concentration of the inhalation anesthetics during surgery in both groups. As a result, there was no significant difference between the 2 groups at any time point although the maximal QTc interval value was higher in the desflurane group than the sevoflurane group during each study period (Fig 3).

This study has several limitations. Because this was a substudy, the results may not be applicable to patients who met the exclusion criteria of the parent study (eg, age older than 65 years, body mass index >30, preoperative cardiac arrhythmias or severe pulmonary hypertension, intraoperative use of inotropics before reperfusion, and

intraoperative cardiac arrest), and randomization of the study population in the parent study would not be applicable to our study population. However, several factors known to affect cardiac outcome, including QTc interval, in patients with end-stage liver disease (eg, age, gender, MELD score, Child-Pugh score, liver disease etiology, preoperative medication, and preoperative serum electrolyte levels) were balanced between the groups [19,25,26]. In addition, the purpose of this study was to compare the 2 kinds of inhalation anesthetics on the QTc interval prolongation. Therefore, we maintained 1 minimum alveolar concentration of the inhalation anesthetics regardless of the kinds of the inhalation anesthetics.

In conclusion, with respect to intraoperative QTc interval prolongation, there was no significant difference between sevoflurane and desflurane anesthesia in patients undergoing elective living-donor liver transplantation. QTc interval increased relative to preoperative values during intubation and reperfusion in surgeries using either sevoflurane or desflurane.

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