Changes in core temperature during graft warm ischemia and reperfusion phases during living donor liver transplant: Adult versus pediatric

Ibrahim Abdelkader Salama,[a] *MD;* ***Mohamed Hussein Abdullah,***[b] *MD;*
Wesam Saber Morad,[c] *MD*

a) Department of Hepatobilliary Surgery, Menophyia University, Shebin Elkom, Egypt.
b) Department of Anesthesia, Menophyia University, Shebin Elkom, Egypt.
c) Department of Public Health National Liver Institute, Menophyia University, Shebin Elkom, Egypt.

Abstract

Background: Maintaining normothermia is essential during liver transplant. Serious adverse outcomes from perioperative hypothermia are well documented.

Objective: To evaluate the core temperature changes during graft warm ischemia and reperfusion periods in adult and pediatric cases.

Method: 30 recipients,(adult n=15 and pediatric n=15) were enrolled in this study. Nasopharyngeal core temperature (NCT) was recorded at the following points: 5 and 30 minutes after induction of anesthesia (temp1&2), the lowest NCT during dissection phase (temp3), the lowest NCT during the anhepatic phase and before implantation of the graft (temp4), lowest NCT during warm ischemia (putting the graft at its bed till reperfusion) (temp5), also at 5 (temp6) and 30 minutes (temp7) after reperfusion, then before the end of surgery (temp8).

Results: Significant decrease in core temperature during the anhepatic phase (temp4), warm ischemia time (temp5), 5 minutes after reperfusion (temp6) and 30 minutes after reperfusion (temp7) with mean values of 36.4 ± 0.47ºC, 35.4±0.45ºC, 35.2±0.50ºC and 35.2±0.52ºC respectively in the pediatric group, while in adult group the mean values36.3±0.33ºC, 36.1±0.38ºC, 36.1±0.61ºC and 35.9±0.34ºC respectively.

Conclusion: Significant drop in NCT was observed at the beginning of the warm ischemia period that persisted through the reperfusion phase in both adult and pediatric recipients. Children with a body weight <14 kg had their core temperatures affected more than adult patients because of receiving relatively large grafts with a greater GRWR.

Key words: Hypothermia, ischemia reperfusion, living liver transplant.

Introduction:

Hypothermia is an important and frequent problem during liver transplant.[1] Prospective; randomized trials have shown that even mild hypothermia causes numerous adverse outcomes in a variety of patient populations. Hypothermia-induced complications include morbid myocardial outcomes[2] secondary to sympathetic nervous system activation,[3] surgical wound infection,[4] coagulopathy[5] increased allergenic transfusions,[6] negative nitrogen balance,[7] delayed wound healing,[8] delayed post anesthetic recovery period,[9] prolonged hospitalization,[8] shivering,[10] and patient discomfort.[11] The core thermal compartment is composed of highly perfused tissues whose temperature is uniform and higher when compared with the rest of the body. Temperature in this compartment can be traced either in the pulmonary artery, distal esophagus, tympanic membrane or nasopharynx.[12,13]

Liver transplant (LT) is considered to be an ultra major surgery, hypothermia during LT is multi factorial and results from massive fluid administration, convective and evaporative

losses from prolonged exposure of viscera, diminished hepatic energy production, and implantation of a cold graft of large thermal mass.[14] The liver graft volume to recipient body weight ratio (GRWR) of at least 1.0 is required to prevent liver dysfunction after liver transplantation.[15] Therefore, left lateral segmentectomy or lobectomy and right hepatectomy are performed for LDLT in pediatric and adult recipients respectively.

Aim of the work:

To study core temperature changes during graft warm ischemia and reperfusion phases in adult and pediatric recipients.

Patients and methods:

This study was carried out after approval from the local ethical transplant committee in the National Liver Institute - Menophyia University and informed consents from the patients (from parents in pediatric cases). Our living liver transplant program was initiated on April 2003. Thirty recipients were enrolled in this study from December 2008 to December 2010 and were divided equally into two groups (adult and pediatric). All donors were related to their recipients and were carefully assessed and approved by transplantation ethical committees.

Adequate preoxygenation was done before the administration of any pharmacological agents. In the adult group (n=15), induction was done by fentanyl 2µg/kg, propofol 2-3 mg/kg. I.V, while muscle relaxation was made by I.V rocuronium. In the pediatric group (n=15), intravenous access had been established previously in 12 cases either for the pretransplant medications or for preoperative ICU management. So, intravenous induction was preceded in them while the remaining (3 children) were accomplished by sevoflurane inhalational induction. Atropine was given 10-30µg/kg. Fentanyl 2µg/kg, sodium thiopental, 4-6 µg/kg. I.V, in cases of intravenous induction, while muscle relaxation was made by I.V rocuronium. Maintenance of anesthesia in both groups was achieved using isoflurane, and a mixture of air and oxygen (FiO_2 0.4) in a low flow of one L/min.

Core temperature was monitored by nasopharyngeal probe using (Cicero EM-Drager Medical AG&Co-Germany). Operating room temperature was set at 24°C the night before surgery. The heat conservation strategies and the warming devices included water mattress (hyper-hypothermic bad, seabrook, medical system Inc, Cincinnati, Ohio, USA) and forced air worming device (Bair Hugger, Arizant Health care Inc, USA) and both were set at 38°C from before induction tell the end of surgery, and low flow anesthesia of 1L/minute. Moreover, the four extremities were wrapped with cotton bandages, and then covered by stockinet. A filter humidifier (Altec, Rusch Mirandola, Italy) was used to maintain the humidity of anesthetic gases. Fluids and blood products were warmed and transfused by using (Bair Hugger, Ranger, blood and fluid warming system, Arizant Health care Inc, USA), and fast flow fluid warmer (level 1 ,H-1200, smith medical ASD Inc, Rockland, USA). Head and extremity wraps, to prevent intraoperative hypothermia. The goals of fluid management in all our recipients were to maintain normovolemia, adequate oxygen-carrying capacity and homeostasis. Fluid given consisted of crystalloids (Ringer's acetate), albumin 5% and blood products. The size of the obtained hepatic grafts were determined according to recipient size and preoperative radiological evaluation.[16,17] In the adult group, right or extended right hepatectomy was obtained, while left lateral hepatectomy was enough for the pediatric cases.

The weight of the graft is obtained before implantation. Prior to engraftment, the donor graft was removed and prepared for implantation in a back table procedure. The graft was flushed and preserved in HTK solution (Custodiol, Bretschnieder HTK solution, Bensheim, Germany) and, if any vascular reconstruction was necessary, it was performed **Figure(1)**.

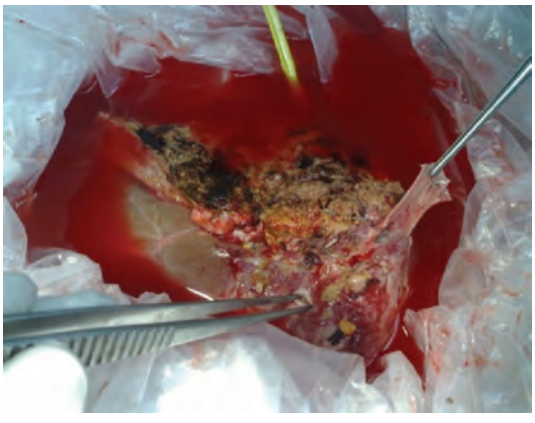

Figure (1): Graft flushing and vascular reconstruction in back table prior to implant.

Recipient operations:

Left lateral segment / Left lobe (in pediatric group):

After hepatectomy with caval preservation, the graft was implanted in a piggyback fashion, either to extended orifices of the right, middle, and left hepatic veins in children or to the orifices of the middle and left hepatic veins in adults.[18,19] A surgical loupe was used for arterial anastomoses in most pediatric cases and biliary reconstructions were performed with a Roux-en-Y limb. Doppler ultrasound was performed before and after closure of the abdomen.

Right lobe (in adult group):

After hepatectomy with caval preservation, the graft was implanted also in a piggyback fashion. The opening of the left and middle hepatic veins was oversewn. To ensure optimal graft outflow, the right hepatic vein orifice was enlarged by making a caudal extension onto the inferior vena cava. Donor portal vein was anastomosed to the recipient's right or main portal vein. Arterial anastomoses were done using surgical loupe. Biliary reconstruction was individualized. Duct- to-duct anastomosis with stent when technically favorable was done. Most often, Roux-en-Y hepatico-jejunostomy was used. Multiple ducts near each other were reconstructed as a single duct anastomosis by suturing the opposing duct sidewalls together. In the event of multiple ducts with significant size discrepancy with the recipient common bile duct, a Roux-en-Y limb was constructed for biliary enteric drainage **Figure(2)**.

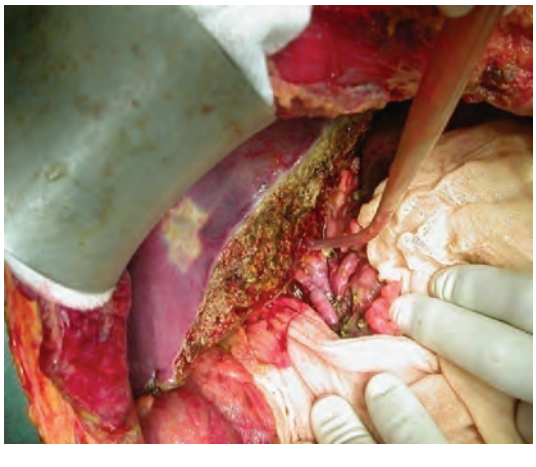

Figure (2): Implantation of a right lobe in adult recipient.

Measurements:

Nasopharyngeal core temperature (NCT) was recorded at the following points: 5, 30 minutes after induction of anesthesia (temp1&2), the lowest NCT during dissection phase (temp3),the lowest NCT during the anhepatic phase and before implantation of the graft (temp4), lowest NCT during warm ischemia (putting the graft at its bed till reperfusion) (temp5), also at 5 (temp6), and 30 minutes (temp7) after reperfusion, then before the end of surgery (temp8).

Statistical analysis:

Student t-test was done for normally distributed quantitative variables to measure mean and standard deviation (SD).

P-value < 0.05 was considered significant. Mann-Whitney test was done for quantitative variables which were not normally distributed and p-value < 0.05 was considered significant. In each group, Paired t- test was done to compare NCT changes all through the surgical procedure. Spearman's correlation test was done to study correlation between one qualitative variable and one quantitative variable or two quantitative variables of not normally distributed data and p- value less than 0.05 was considered significant.

Results:

Thirty recipients were enrolled in this study. The indications of the transplantation in pediatrics were mainly for biliary atresia in 8 children, congenital hepatic fibrosis in 2, Byler's disease in 2, Budd-chiari syndrome in one child, hepatoblastoma in one child and Haemangioma in one child. In the adults the indications were mainly post HCV cirrhosis in 9 patients, cryptogenic cirrhosis in 2 patients, HCC in 2 patients and 2 patients with primary scleroses cholangitis (PSC) **Table(1)**.

Table (1): Indication of transplantation in pediatrics and adult patients.

Pediatrics indications	Number	Adult indication	Number
Biliary atersia	8	Post HCV Cirrhoses	9
Congenital hepatic fibrosis	2	Cryptogenic cirrhoses	2
Byler's disease	2	HCC	2
Haemangima	1	PSC	2
Budd-Chiari syndrome	1		
Hepatoblatoma	1		

HCC: Hepatocelluler carcinoma, ESLD: End stage liver disease, HCV: Hepatitis C virus, PSC: Primary scelerosing cholangitis

The left lateral segment (segment 2, 3) was used in 15 pediatric recipients, while right lobe without middle hepatic vein (segment 4-8) was used in 14 adult recipients and left lobe (segment 1-4) was used in one adult recipient. Age, height, recipient weight, liver graft weight, cold ischemia time and anhepatic phase time were significantly greater in adult group. However graft recipient weight ratio was significantly greater in pediatric group **Table(2)**. The remaining liver volume in all donors was ≥ 35% of the calculated whole liver volume, and macro vesicular steatosis in all grafts was ≤ 10% (estimated by routine percutaneous liver biopsy in all donors). There were no complications related to any of the warming devices in any patient.

Table (2): Differences between studied groups regarding recipient criteria, grafts and intraoperative events.

	Groups	Mean ± SD	t- test	p- value
age(yr)	Pediatric group Adult group	2.78±1.47 44.20±4.75	4.67*	< 0.01
weight(kg)	Pediatric group Adult group	9.66±2.6 82.86±7.41	35.98	< 0.01
PELD score	Pediatric group	17.8±5.33		
MELD score	Adult group	16.8±2.08		
Duration of surgery (hrs)	Pediatric group Adult group	9.59±1.92 13.93±1.44	7	< 0.01
Graft Weight (gm)	Pediatric group Adult group	264±46 956±79	29.08	< 0.01
GRWR	Pediatric group Adult group	2.84±0.48 1.16±0.15	12.83	< 0.01
CIT (min)	Pediatric group Adult group	29±6 48±13	4.86	< 0.01
WIT (min)	Pediatric group Adult group	44±7 41±9	0.95	> 0.05
Anhepatic phase time (min)	Pediatric group Adult group	88±14 104±18	2.76	< 0.05

*PELD score; pediatric end stage liver disease, MELD; model of end stage liver disease, , GRWR; graft recipient body weight ratio, CIT; cold ischemia time, WIT; warm ischemia time and Anhepatic phase time.*Mann Whitney test*

Changes in NCT during the surgical procedure in both groups:

Thirty minutes after induction of anesthesia, mild but not significant hypothermia was present in both groups, and NCT dropped from (temp1) 37±0.28°C to reach (temp2) 36.8±0.27°C in the pediatric group, while in the adult group it dropped from (temp1) 36.9±0.43°C to reach (temp2) 36.8±42°C. During the dissection phase (temp3) the mean NCT in pediatric and adult group were 36.4±0.30°C and 36.7±0.44°C respectively. However, both groups experienced a significant decrease in core temperature during the anhepatic phase (temp4), warm ischemia time (temp5), 5 minutes after reperfusion (temp6) and 30 minutes after reperfusion (temp7) with mean values of 36.4 ± 0.47°C, 35.4±0.45°C, 35.2±0.50°C and 35.2±0.52°C respectively in the pediatric group, while in adult group the mean values 36.3±0.33°C, 36.1±0.38°C, 36.1±0.61°C and 35.9±0.34°C respectively **Figures(3,4)**.

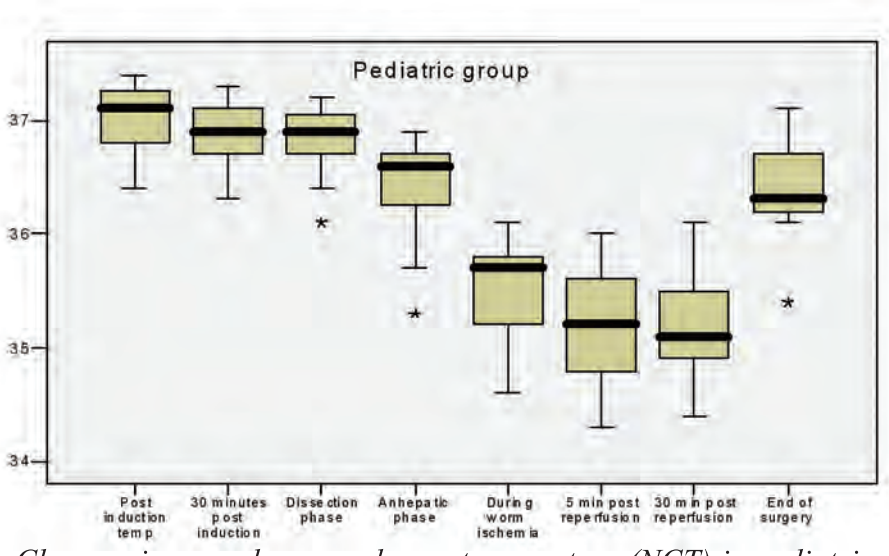

Figure (3): Changes in nasopharyngeal core temperature (NCT) in pediatric groups during phases of liver transplantation procedure.

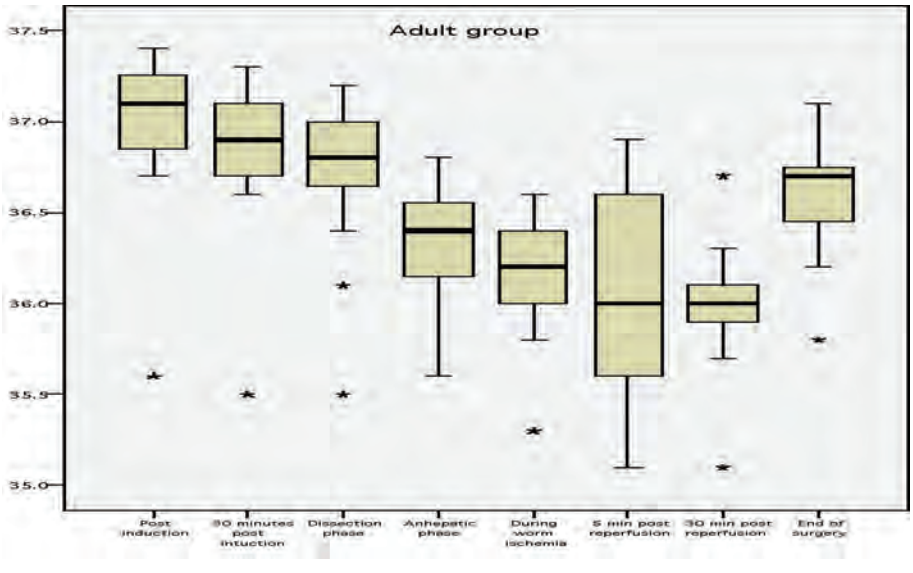

Figure (4): Changes in nasopharyngeal core temperature (NCT) in adult groups during phases of liver transplantation procedure.

The decrease in NCT at the time of implantation which is the warm ischemia time (temp5) and 5 minutes after reperfusion phase (temp6) was found to be correlated with GRWR only not the graft weight in the pediatric group **Table(3)**.

Table (3): The correlation of GRWR and graft weight at different phases of surgery.

		Temp 5	Temp 6	Temp 7
Pediatric group				
GRWR	P-value	.048*	.044*	.667
Graft weight (gm)	P-value	.175	.402	.954
Adult group				
GRWR	P-value	.905	.539	.964
Graft weight (gm)	P-value	.687	.549	1.00

*Temp 5: during warm ischemia, Temp 6: 5min post reperfusion, Temp 7: 30min post reperfusion, GRWR: graft recipient body weight ratio, * positive correlation with $p < 0.05$.*

Discussion:

Core temperature is usually measured as an approximation to hypothalamic temperature. As hypothalamic temperature cannot be measured directly, various sites have been used to give an approximation.[20,21] Tympanic membrane temperature is usually thought to give a good estimate, but nasopharyngeal, esophageal and bladder are acceptable alternatives. The lower third of the esophagus may be unreliable in LT as the cold donor graft is placed in close proximity.

Generally, following induction of anesthesia there is an internal core to-peripheral redistribution of body heat that usually reduces core temperature by 0.5 to 1.5ºC in the first 30 minutes.[22] However, this post induction decrease in core temperature did occur in recipients of the present study and this might be attributed to the adequate heat conservation methods used that minimized the surface temperature of the recipients so decreasing the effect of redistribution. During the dissection phase, core temperatures decreased slightly in both groups, but decreased significantly during the warm ischemia and reperfusion phases.

It is known that in non–liver transplantation surgical procedures, normothermia usually can be maintained with an operating room temperature of 24ºC to 26ºC regardless of type and length of anesthesia or surgery.[23,24] Since room temperature is stabilized at 24ºC, therefore, the sudden decrease in NCT in the anhepatic phase and especially the reperfusion phase must be inherent to the liver transplantation procedure.

In the anhepatic phase, the native liver (large heat producer) is absent and those patients produce less heat. This is also, associated with increase heat losses.[14] On the other hand, the donor graft, which has been preserved in 4ºC HTK solution, is then placed in the abdominal cavity. During vascular reconstruction, the graft is flushed with 4ºC lactated Ringer's solution to wash the cold preservative solution from the new graft before reperfusion. The cold donor graft and cold lactated Ringer's flush solution caused a significant decrease in core temperature in both groups during the anhepatic phase but it was more significant in the pediatric age group than the adult age group. The additional decrease in core temperature after reperfusion was caused by the hypothermic blood coming from the hepatic veins to the circulation after passing through the cold donor graft.[25]

Although the decrease in NCT in the anhepatic and reperfusion phases must be related to the amount of the cold graft tissue (graft weight) and the recipient size. These 2 factors can be obtained by using the graft recipient weight ratio (GRWR). It is well known that in pediatric living donors liver transplantation, the smallest functional unit of a graft should include the hepatic artery, portal vein, hepatic vein, and bile duct. So, a left-lateral liver graft should consist of at least segments 2 and 3. Which although small, it may still be large for a pediatric recipient, which may affect core temperature significantly. Our results showed that the core temperature in pediatric patients with body weight less than 14 Kg with a mean value of 9.66 (2.66) kg, and receiving a liver graft with a greater GRWR 2.84 (0.48), decreased significantly more than in adult recipients with mean body weight 82.86 (7.41) kg and GRWR 1.16 (0.14).

Efforts to maintain normothermia or slight hyperthermia in the dissection phase are necessary to prevent severe hypothermia with subsequent complications in the anhepatic and reperfusion phases.[26,27] Steib A and associates,[28] evaluated the benefit of an esophageal rewarmer, used during liver transplantation surgery, and they concluded that the esophageal heat exchanger allowed better rewarming after revascularization of the graft, but was unable to prevent cardiac hypothermia at unclamping.

In conclusion, A sudden significant drop in NCT was observed at the beginning of the warm ischemia period that persists through the reperfusion phase in both adult and pediatric recipients. Children with a body weight less than 14 kg had their core temperatures affected more than adult patients because of receiving relatively large grafts with a greater GBWR. Several heat conservation and preservation strategies are of great importance to reduce such risk. Correlation with the other associated clinical conditions like post reperfusion

syndrome, graft survival and post operative ICU course are points of further future evaluation.

References:

1- Sessler DI: Intraoperative hypothermia is a frequent problem during orthotopic liver transplantation. *Anesthesiology* 1990; 73: 433-440.

2- Frank SM, Fleisher LA, Breslow MJ, Higgins MS, Olson KF, Kelly S, Beattie C: Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events: A randomized clinical trial. *JAMA* 1997; 277: 1127-1134.

3- Frank SM, Higgins MS, Fleisher LA, Sitzmann JV, Raff H, Breslow MJ: Adrenergic, respiratory, and cardiovascular effects of core cooling in humans. *Am J Physiol* 1997; 272: 557-562.

4- Melling AC, Ali B, Scott EM, Leaper DJ: Effects of preoperative warming on the incidence of wound infection after clean surgery: A randomized controlled trial. *Lancet* 2001; 358: 876-880.

5- Winkler M, Akça O, Birkenberg B, Hetz H, Scheck T, Arkilic CF, Kabon B, Marker E, Grubl A, Czepan R, Greher M, Goll V, Gottsauner-Wolf F, Kurz A, Sessler DI: Aggressive warming reduces blood loss during hip arthroplasty. *Anesth Analg* 2000; 91: 978-984.

6- Widman J, Hammarqvist F, Sellden E: Amino acid infusion induces thermogenesis and reduces blood loss during hip arthroplasty under spinal anesthesia. *Anesth Analg* 2002; 95: 1757-1762.

7- Carli F, Emery PW, Freemantle CA: Effect of peroperative normothermia on postoperative protein metabolism in elderly patients undergoing hip arthroplasty. *Br J Anaesth* 1989; 63: 276-282.

8- Kurz A, Sessler DI, Lenhardt RA: Study of wound infections and temperature group. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. *N Engl J Med* 1996; 334: 1209-1215.

9- Lenhardt R, Marker E, Goll V, Tschernich H, Kurz A, Sessler DI, Narzt E, Lackner F: Mild intraoperative hypothermia prolongs postanesthetic recovery. *Anesthesiology* 1997; 87: 1318-1323.

10-Just B, Delva E, Camus Y, Lienhart A: Oxygen uptake during recovery following naloxone. *Anesthesiology* 1992; 76: 60-64.

11-Sessler DI, Rubinstein EH, Moayeri A: Physiological responses to mild perianesthetic hypothermia in humans. *Anesthesiology* 1991; 75: 594-610.

12-Bissonnette B, Sessler DI, La Flamme P: Intraoperative temperature monitoring sites in infants and children and the effect of inspired gas warming on esophageal temperature. *Anesth Analg* 1989; 69: 192-196.

13-Cork RC, Vaughan RW, Humphrey LS: Precision and accuracy of intraoperative temperature monitoring. *Anesth Analg* 1983; 62: 211-214.

14-Russell SH, Freeman JW: Prevention of hypothermia during orthotopic liver transplantation: Comparison of three different introperative warming methods. *Br J Anaesth* 1995; 74: 415-418.

15-Higashiyama H, Yamaguchi T, Mori K, Nakano Y, Yokoyama T, Takeuchi T, et al: Graft size assessment by preoperative computed tomography in living related partial liver transplantation. *Br J Surg* 1993; 80: 489-492.

16-Cheng YF, Lee TY, Chen CL, Huang TL, Chen YS, Lui CC: Three-dimensional helical computed tomographic cholangiography: Application to living related hepatic transplantation. *Clin Transplant* 1997; 11: 209-213.

17-Cheng YF, Chen CL, Huang TL, Chen TY, Lee TY, Chen YS, et al: Single imaging modality evaluation of living donors in liver transplantation: Magnetic resonance imaging. *Transplantation* 2001; 72: 1527-1533.

18-Millis J M, Cronin DL, Brady LM, et al: Primary living-donor liver transplantation at the university of Chicago: Technical aspects of the first 104 recipients. *Ann Surg* 2000; 232: 104-111.

19-Takayama T, Makuuchi M, Kawasaki S, et al: Outflow Y-reconstruction for living related partial hepatic transplantation. *J Am Coll Surg* 1994; 179: 226-229.

20-Cork RC, Vaughan RW, Humphrey LS: Precision and accuracy of intraoperative temperature monitoring. *Anesthesia and Analgesia* 1983; 62: 211-214.
21-Earp JK, Finlayson DC: Relationship between urinary bladder and pulmonary artery temperatures: A preliminary study. *Heart and Lung* 1991; 20: 265-270.
22-Matsukawa T, Sessler DI, Sessler AM, Schroeder M, Ozaki M, Kurz A, Cheng C: Heat flow and distribution during induction of general anesthesia. *Anesthesiology* 1995; 82: 662-673.
23-El-Gamal N, El-Kassabany N, Frank SM, Amar R, Khabar HA, El-Rahmany HK, Okasha AS: Age-related thermoregulatory differences in a warm operating room environment (approximately 26 degrees C). *Anesth Analg* 2000; 90: 694-698.
24-Morris RH, Wilkey BR: The effects of ambient temperature on patient temperature during surgery not involving body cavities. *Anesthesiology* 1970; 32: 102-107.
25-Borland LM, Roule M, Cook DR: Anesthesia for pediatric orthotopic liver transplantation. *Anesth Analg* 1985; 64: 117-124.
26-Valeri CR, Feingold H, Cassidy G, Ragno G, Khuri S, Altschule MD: Hypothermia-induced reversible platelet dysfunction. *Ann Surg* 1987; 205: 175-181.
27-Winkler M, Akca O, Birkenberg B, Hetz H, Scheck T, Arkilic CF, et al: Aggressive warming reduces blood loss during hip arthroplasty. *Anesth Analg* 2000; 91: 978-984.
28-Steib A, Beller JP, von Bandel M, Beck F, Chabrol JL, Otteni JC: Oesophageal thermal tube for intraoperative hypothermia in liver transplantation. *Acta Anaesthesiol Scand* 1993; 37(2): 199-202.