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MINIREVIEWS

Anastomotic techniques for rat lung transplantation

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Abstract

The first lung transplantation in the rat was achieved by Asimacopoulos *et al* using sutured anastomoses in 1971. Subsequent development of a cuffed technique to construct the anastomoses by Mizuta and colleagues in 1989 represented a breakthrough that resulted in simplification of the procedure and shorter warm ischemic times. Since then, a number of further variations on the technique of rat lung transplantation have been described. In spite of this, the procedure remains technically demanding and involves a long learning curve. This minireview describes the following new technical safeguards to further evolve the technique for cuffed anastomoses in rat lung transplantation: the use of anatomical landmarks to avoid twisting of the everted donor pulmonary vein and bronchus in the cuff, the use of the cuff tie as a landmark to avoid twisting of the anastomotic cuffs relative to the recipient vessels, distal ties on the recipient vessels to achieve a bloodless field and triangulation of the venotomy to avoid pulmonary vein tearing.

Key words: Lung transplantation; Rat; Surgery; Animal experiments; Technique

Core tip: This minireview describes the following new technical safeguards to further evolve the technique for cuffed anastomoses in rat lung transplantation: the use of anatomical landmarks to avoid twisting of the everted donor pulmonary vein and bronchus in the cuff, the use of the cuff tie as a landmark to avoid twisting of the anastomotic cuffs relative to the recipient vessels, distal ties on the recipient vessels to achieve a bloodless field and triangulation of the venotomy to avoid pulmonary vein tearing.

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INTRODUCTION

The first lung transplantation in the rat was achieved by Asimacopoulos *et al*[1] using sutured anastomoses in 1971. However, high complication rates and technical difficulties with the sutured anastomoses meant that this technique was not widely adopted. Subsequent development of a cuffed technique to construct the anastomoses by Mizuta *et al*[2] in 1989 represented a breakthrough that resulted in simplification of the procedure and shorter warm ischemic times. This technical breakthrough led to a surge in publications involving rat lung transplantation[3].

Since then, a number of further variations on the technique of rat lung transplantation have been described. In spite of this, the procedure remains technically demanding and involves a long learning curve[4]. Therefore many laboratories rely on dedicated microsurgeons who invest great deal of commitment and time in order to become facile with this model. However, the frequent turn-over of researchers in many laboratories calls for further technical improvements that shorten the learning curve and provide more reproducible outcomes by providing safeguards against complications. Here we describe in detail technical improvements and safeguards to further evolve the cuffed technique for rat lung transplantation.

ANASTOMOTIC CUFFS

Anastomotic cuffs should be made from PTFE, since this material was found to cause little foreign body reaction[5]. PTFE is also the most commonly used graft material for small caliber arteriovenous bypass grafting in human patients[6]. The anastomotic cuffs are made from PTFE angiocatheters that are clinically used for peripheral venous access (Exel Safelet Catheter, Exel International, Los Angeles, CA, United States). The angiocatheters are cut into sections of approximately 2 mm length, of which 1 mm forms the body of the cuff and a 1 mm elongation forms a wing (Figure 1)[7]. The wing is used to hold the cuff while the donor vessel is everted over the cuff. Additionally, we impress two grooves on the cuff with the back of a razor blade against the stylet of the angiocatheter to facilitate positioning of the circumferential ties[8]. Additionally, the surfaces of the cuff can be roughened with sandpaper to make the donor vessels less prone to slip while they are everted over the cuff[9,10].

Eighteen gauge and 16 gauge angiocatheters for the pulmonary artery (PA) and the pulmonary vein (PV) respectively for donor rats weighing approximately 300 g are used. Other investigators have used cuff sizes ranging from 24 gauge to 16 gauge for both PA and PV anastomoses[4,9-11]. We advocate against using small venous cuffs since a sufficiently large venous anastomosis is important to minimize complications from PV thrombosis. Smaller arterial cuffs are more acceptable since the pressure gradient across the arterial anastomosis is much higher than the pressure gradient across the venous anastomosis. For the bronchial anastomosis we also use 16 gauge cuffs. Others have used 14 gauge cuffs for the bronchus[9]. A large bronchial cuff size to optimize aeration of the donor lung is not unreasonable since the tough cartilaginous rings of the bronchus make this structure most resistant to tearing.

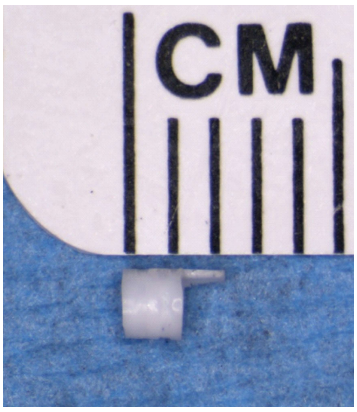

Figure 1 The anastomotic cuff.

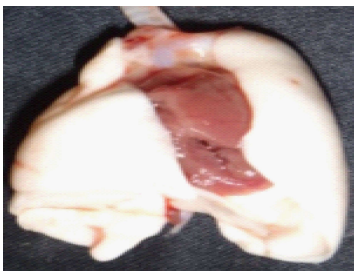

Figure 2 Donor pneumonectomy specimen.

MAGNIFICATION

Surgical magnification is necessary to perform rat lung transplantation. A 10 x dissection microscope (AmScope, Irvine, CA, United States) is ideal for hilar dissection and anastomoses. Others have described using 6-20 x magnification[4]. Ideally, frequent changing of the magnification strength should be avoided, since this negatively affects hand-eye coordination.

DONOR PROCEDURE

To prepare the donor lungs for anastomosis, it is necessary to isolate the donor PA, bronchus (B) and PV. This dissection starts with the heart-lung block in its anatomic position (Figure 2).

First, the PA is exposed by excising the thymus fat. The PA bifurcation is freed from the aortic arch by dividing the ligamentum arteriosum. The left PA is then divided at the bifurcation. Subsequently the left PA is circumferentially dissected free and traced towards the hilum of the lung.

Second, the bifurcation of the trachea is exposed by excising the surrounding mediastinal fat and lymphatic tissue. The left trachea is divided at its bifurcation and also circumferentially dissected free and traced towards

Figure 3 Eversion of the donor vein over the anastomotic cuff.

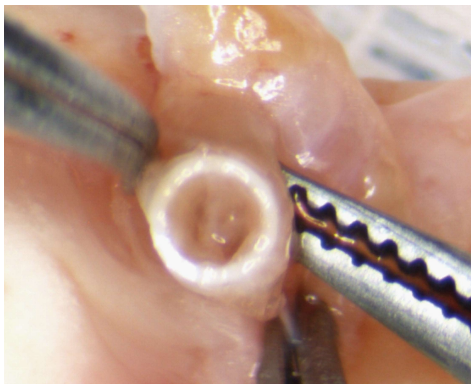

Figure 4 The pulmonary vein forms from the confluence of superior and inferior segmental veins. The ostia of these veins can be used as landmarks to avoid twisting the everted vein inside the anastomotic cuff.

the hilum of the lung.

Third, exposure of the PV, which lies dorsally, is improved by flipping the heart-lung block into prone position. The PV is freed from its attachments starting at its origin at the left atrium. Careful dissection of the vein is particularly important since the PV tears easily. Moreover, the pleura should be completely stripped from the vein in order to achieve the maximum PV length. Sufficient PV length is important to facilitate eversion of the PV over the cuff, since the elastic veins tend to retract. To free the proximal end of the vein, the left atrium is cut, leaving a rim of atrium on the ostium of the PV. The atrial rim greatly facilitates eversion of the PV over the venous cuff and does not interfere with perfusion of the anastomosis since it does not form part of the anastomotic lumen. The PV is then traced towards the hilum of the lung.

Fourth, the donor graft is freed from the remaining attachments to the heart. Each vessel is now carefully traced further towards the hilum by dissecting off the remaining parietal pleura in order to fully isolate the PA, B and PV. Isolation of the vessels serves to maximize the length of each vessel for eversion over the cuffs and prevents kinks after implantation of the graft.

ATTACHMENT OF THE ANASTOMOTIC CUFFS

Attachment of the cuffs should be performed on a tray covered with ice to control the temperature of the graft. The PV anastomosis is attached first, since the PV usually retracts to become the shortest vessel. This allows adjustment of the longer vessels to the same length as the cuffed PV. The cuff is held in place at the wing and the PV is pulled through the cuff. Next, the vein is everted over the cuff (Figure 3).

It is very important to avoid twisting the vein inside the cuff. In order to confirm that the vein is not twisted, the ostia of the superior and inferior lobar veins should be visualized inside the everted vein. If these ostia are found to be mal-aligned then the vessel should be rotated inside the cuff to orient them superiorly and inferiorly respectively (Figure 4).

When adequate orientation of the vein is confirmed, the everted vein is secured to the cuff with a circumferential tie. We use a 7-0 silk, but others have used 8-0 monofilaments[2]. The first loop secures the everted vessel to the middle of the cuff using a single knot. This loop need not enclose the entire circumference of the everted vessel as long as it holds the vessel in place. The ends of the tie are then looped around the everted vessel another time, this time close to the edge of the cuff. This loop is intended to form a circumferential seal around the everted vessel and is secured with two throws. The knots should be tied facing anterior relative to the donor lung. This allows the knot to serve as an anterior landmark to orient the cuff inside in the recipient vessel without twisting.

The bronchial cuff is attached second. Usually the bronchus is longer than the PV, so it needs to be cut to a length that is appropriate relative to the PV after it is pulled through the cuff. Twisting of the bronchus inside the cuff is avoided by orienting the membranous part of the bronchus posteriorly. The bronchus is everted over the cuff and secured to the cuff in the same fashion as the PV.

The PA cuff is attached last. The PA usually also needs to be cut to a length that is appropriate relative to the venous cuff. Analogous to the PV and bronchus, the PA is pulled through the cuff, everted and secured to the cuff in the same fashion as the PV. Special attention needs to be paid to avoid twisting the PA before everting it over the cuff, since there are no anatomical landmarks to help with its orientation. However, since the pressure inside the PA is higher than inside the PV or bronchus, perfusion of the arterial cuff is most resistant to twisting. Finally, the wings are cut off all three cuffs.

After all cuffs have been attached, the lung is re-wrapped in soaked gauze. It is important to make sure that fluid does not enter the bronchus through capillary action. This can be achieved by folding the gauze so that the hilum is left free.

RECIPIENT PROCEDURE

Exposure

First, the recipient left lung is brought into the wound by putting traction on the inferior pole of the lung with two cotton swabs. Once the inferior pole of the lung has been mobilized, the remainder of the inferior pulmonary ligament can be divided with scissors. Care must be taken not to damage the pulmonary vein, which is confluent with the inferior pulmonary ligament. The tidal volume is decreased before the recipient lung is clamped and retracted ventrally. This affords excellent exposure of the dorsal aspect of the pulmonary hilum. The pleura over the dorsal pulmonary hilum is divided. Bronchial arteries, which originate from the aorta and typically running over the membranous part of the bronchus, need to be cauterized or tied. This allows dissection of the PA, bronchus and PV. Care should be taken not to damage the vagus nerve, which is often brought over the root of the hilum by traction on the recipient lung. Once the posterior aspect of PA, bronchus and PV are dissected free, the ventral aspect of the hilum is exposed by retracting the recipient lung dorsally. The animal is also re-positioned on its back. This improves visualization of the hilum since the dissection microscope provides a top view only. Next, the pleura over the ventral aspect of the hilum is divided. Division of the hilar pleura invariably causes a pneumothorax of the accessory lobe, since the accessory lobe pleura is fused with the pleura covering the left PV. However, it is usually possible to avoid causing a right sided pneumothorax by starting the dissection of the PV hilar pleura distally and carefully preserving the pleura overlying the proximal PV, which is continuous with the right parietal pleura. Subsequent dissection completely isolates the PA, bronchus and PV. Particular care should be taken while dissecting the pulmonary vein, since it can tear easily. The goal of this dissection should be to provide maximum length of the recipient hilar vessels, since this makes it easier to create the anastomoses. In order to further increase the length of the donor vessels, the right accessory lobe vein can be divided[11] or interposition grafts can be fashioned from the donor descending aorta[7]. These additional steps are not necessary in rats weighing 300 g since sufficient length can be achieved by careful dissection.

CREATION OF THE ANASTOMOSES

The PV anastomosis is technically the most difficult because the recipient vein tears easily. We create the PV anastomosis first, since this affords the greatest degree of freedom to position the graft favorably so that the PV cuff can be pushed into the recipient vein without tension. It is important to avoid twisting the vein during creation of the anastomoses since the low blood pressure in the PV means that blood flow is compromised by relatively modest twisting or kinking. In order to minimize the potential for PV twisting or kinking, others have advocated constructing the bronchial anastomosis first to immobilize the graft before the PV anastomosis is constructed[9].

The PV typically forms from the confluence of an upper and a lower segmental vein. Rarely, the PV forms from the confluence of 3 or more veins. First, the upper segmental vein is divided between two ligatures. This increases the length of the vessel that is available to create the anastomosis. Moreover, leaving one strand of the proximal ligature long allows it to serve as a handle to triangulate the venotomy. Second, the distal PA is tied off with 7-0 silk to stop inflow of blood into the lung. It is important that this tie sits as distal as possible to maximize the length of PA available for anastomosis. Third, the remaining segmental PVs are tied off as distal as possible and the main PV is clamped as proximal as possible. This prevents antegrade or retrograde flow of blood into the part of the PV that will be used for the anastomosis. A bloodless represents an important safeguard for creating the anastomosis without tearing since it improves visualization. Fourth, the pulmonary vein is opened transversely with a microscissor. Again the venotomy should be as distal as possible to ensure sufficient length of the vessel is available to insert the cuff. The venotomy is then extended longitudinally along the vein to the ostium of the tied superior segmental vein. This maneuver opens a right-angled flap in the vein and allows triangulation of the venotomy between the long suture handle on the superior segmental vein, the intact back wall of the vein and a forceps holding the tip of the flap (Figure 5).

Triangulation is another important safeguard against tearing the fragile vein by opening a wide mouthed venotomy. Fifth, all blood is washed from the venotomy with heparinized saline. We use 50u, but others have used 500u[11]. The heparinized saline also displaces any air in the vein and thus acts as a safeguard against thrombi and against air emboli. Similarly, the donor PV cuff is filled with heparinized saline to displace any air. Sixth, the donor lung is brought up to the field and sandwiched between cooled wet gauze sponges. The graft is positioned such that the PV cuff is not under tension or twisted when it is inserted into the recipient vein. Finally, the cuff is then inserted into the venotomy and pushed into the recipient main PV. The correct orientation is preserved by using the knot on the anastomotic cuff as an anterior landmark. It is important to make sure that the cuff projects into the main PV to avoid any constriction of the graft venous outflow. The cuff is secured with a circumferential 6-0 silk tie.

The bronchial anastomosis is created second. In small rats it can be beneficial not to clamp the bronchus to avoid cluttering the field with clamps. In this case, the bronchial anastomosis needs to be completed quickly since the native contralateral lung is not ventilated while the left bronchus is open. First, the donor lung is re-

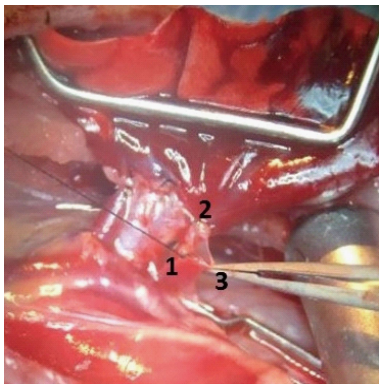

Figure 5 Triangulation of the venotomy by the superior segmental vein ligature (1), pulmonary vein back wall (2) and the tip of the flap (3) results in a wide-mouthed venotomy and serves as a safeguard that allows easy insertion of the donor cuff without tearing the recipient vessel.

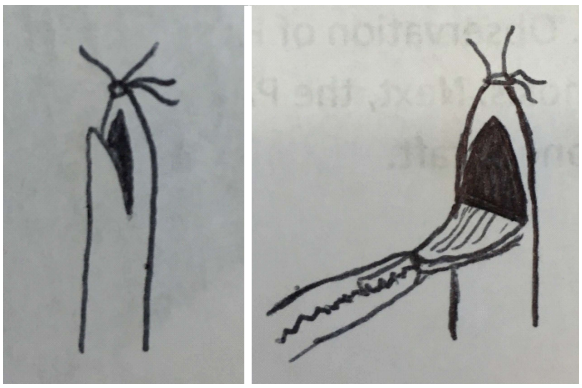

Figure 6 Oblique incision creates a V-shaped flap. Retraction on this flap with forceps results in a wide mouthed arteritomy that allows easy insertion of the donor cuff.

positioned so that there is no tension on the bronchial cuff after insertion into the bronchus. Avoiding tension prevents the cuff from slipping out of the recipient bronchus while the anastomosis is created. Second, the bronchus is incised distally between two cartilaginous rings. Intact cartilaginous ring make the bronchiotomy relatively resistant to tearing. Third, the cuff is inserted into the bronchus. The correct orientation is preserved by using the knot on the anastomotic cuff as an anterior landmark. Finally, the cuff is secured with a 6-0 silk tie. Following creation of the bronchial cuff, the tidal volume should be increased to baseline in order to accounting for the dead space of the non-perfused donor lung. Rarely, the bronchial anastomosis is constructed with sutures[4,12]. Studies with computer tomography have noted that rat bronchial anastomoses created by suturing have a trend to be wider than cuffed bronchial anastomoses, however this difference was not statistically significant[13]. We have not noted major problems with aeration of the graft if a sufficiently large cuff is used. Large cuffs can be used easily for the bronchial anastomosis since the bronchus is relative resistant to tearing.

The PA anastomosis is created third. First, the donor lung is again re-positioned to allow creation of the PA anastomosis without tension. Second, the artery is clamped proximally to control inflow into the segment that will be used to construct the anastomosis. Third, a V-shaped arteriotomy is made as close to the tie as possible to maximize the available length for anastomosis (Figure 6). This creates a wide mouthed arteriotomy. Fourth, the PA lumen is flushed with heparinized saline to remove any clots that may have formed in the occluded vessel and to displace any air. Similarly, air is displaced from the donor PA cuff by filling it with heparinized saline. The apex of the V-shaped flap provides a convenient handle for retraction to open a wide mouthed arteriotomy. Fifth, PA cuff is inserted into the PA. The correct orientation is preserved by using the knot on the anastomotic cuff as an anterior landmark. Finally, the cuff is secured with a circumferential 6-0 silk tie. Insertion of the PA cuff is easier than insertion of the venous cuff because the PA is elastic and far less prone to tears.

After all anastomoses have been completed, the old recipient lung is removed by cutting PA, bronchus and PV distal to the new anastomoses. This removes tension from the hilar vessels and allows the donor graft to sit in the orthotropic position. The donor lung is recruited by occluding the ventilator outflow in order for approximately 3 breaths. Recruitment of the graft before the clamps are released decreases the pulmonary vascular resistance of the donor lung and ensures homogenous reperfusion. The PV clamp is released first. This allows observation of retrograde blood flow through the cuff into the donor PV and segmental PV branches. Observation of PV backflow is an important safeguard for the quality of the venous anastomosis. Second, the PA clamp is released. This results in an immediate blush that indicates perfusion of the donor graft. Observation of a blush is an important safeguard for the quality of the arterial anastomosis.

CONCLUSION

Development of the cuff technique for lung transplantation by Mizuta popularized this model[2]. This technique was evolved by adding important safeguards to shorten the learning curve and result in more reproducible outcomes by providing safeguards against complications. This review describes highlight technical safeguards that were previously described and also describes the following new safeguards as improvements to the technique for lung transplantation: The use of anatomical landmarks to avoid twisting of the everted donor PV and bronchus in the cuff, the use of the cuff tie as a landmark to avoid twisting of the anastomotic cuffs with regards to the recipient vessels, distal ties on the recipient vessels to achieve a bloodless field and triangulation of the venotomy to avoid PV tearing.

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ORIGINAL ARTICLE

Observational Study

Cumulative positive fluid balance is a risk factor for acute kidney injury and requirement for renal replacement therapy after liver transplantation

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Abstract

AIM

To analyze whether fluid overload is an independent risk factor of adverse outcomes after liver transplantation (LT).

METHODS

One hundred and twenty-one patients submitted to LT were retrospectively evaluated. Data regarding perioperative and postoperative variables previously associated with adverse outcomes after LT were reviewed. Cumulative fluid balance (FB) in the first 12 h and 4 d after surgery were compared with major adverse outcomes after LT.

RESULTS

Most of the patients were submitted to a liberal approach of fluid administration with a mean cumulative FB

over 5 L and 10 L, respectively, in the first 12 h and 4 d after LT. Cumulative FB in 4 d was independently associated with occurrence of both AKI and requirement for renal replacement therapy (RRT) (OR = 2.3; 95%CI: 1.37-3.86, *P* = 0.02 and OR = 2.89; 95%CI: 1.52-5.49, *P* = 0.001 respectively). Other variables on multivariate analysis associated with AKI and RRT were, respectively, male sex and Acute Physiology and Chronic Health Disease Classification System (APACHE II) levels and sepsis or septic shock. Mortality was shown to be independently related to AST and APACHE II levels (OR = 2.35; 95%CI: 1.1-5.05, *P* = 0.02 and 2.63; 95%CI: 1.0-6.87, *P* = 0.04 respectively), probably reflecting the degree of graft dysfunction and severity of early postoperative course of LT. No effect of FB on mortality after LT was disclosed.

CONCLUSION

Cumulative positive FB over 4 d after LT is independently associated with the development of AKI and the requirement of RRT. Survival was not independently related to FB, but to surrogate markers of graft dysfunction and severity of postoperative course of LT.

Key words: Liver transplantation; Fluid balance; Acute kidney injury

Core tip: Whether fluid overload is an independent mediator of adverse outcomes on early postoperative liver transplantation (LT). The influence of fluid accumulation on morbidity and mortality after LT has not been well evaluated up to now. This study aims to analyze whether fluid management influences the early postoperative outcome after LT. Cumulative positive fluid balance (FB) over 4 d after LT influence the development of acute kidney injury and it is a risk factor for the requirement for renal replacement therapy. Survival is not independently related to FB but to surrogate markers of graft dysfunction.

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INTRODUCTION

It is well recognized that fluid overload in critically-ill patients may lead to anasarca, pulmonary edema, abdominal compartment syndrome (ACS) and also multiple organ dysfunction due to its deleterious effect in tissue perfusion[1-3]. In this regard, positive fluid balance (FB) has been shown to be associated with adverse outcomes in patients admitted to the intensive care unit (ICU) with sepsis and septic shock[4-6], acute respiratory distress syndrome (ARDS)[7,8], acute kidney injury (AKI)[9-15] and cancer[16]. Conversely, positive FB was also linked to increased morbidity and mortality after abdominal surgery[17-19], including esophagectomy[20], open aortic aneurysm repair[21] and rectal cancer surgery[22]. In most of these reports cumulative FB in the first 4 d were reliable indicators of worse outcomes in clinical[4] and surgical[21] ICU patients. On the contrary, restrictive fluid administration policies have led to a reduction in overall morbidity, including AKI, and increased survival in surgical[23-26] and medical[9,27,28] patients in the ICU. Few data is available in the literature concerning the impact of positive FB in the postoperative course of liver transplantation (LT)[29-32]. Some authors have described an increased frequency of postoperative pulmonary morbidity[29-32] and ileus[31] that could be prevented with restrictive administration of fluids[30,31]. No association between FB and AKI or survival after LT was disclosed in those aforementioned studies[29-32].

The aims of the present study were analyze whether cumulative positive FB is associated with the occurrence of AKI, requirement for renal replacement therapy (RRT) and 28-d mortality after LT.

MATERIALS AND METHODS

One-hundred twenty one patients submitted to LT at the Portuguese Hospital of Salvador, Bahia, Brazil who underwent surgery in a period of 5 years were retrospectively evaluated. All medical and surgical charts as well as electronic files were reviewed by a single observer in order to collect data regarding perioperative and postoperative variables, previously associated with adverse outcomes after LT, including demographics; etiology of liver disease; indication for LT; severity of liver disease assessed by MELD and Child-Pugh scores; perioperative parameters such as cold ischemia time, duration of surgery, need for inotropic support, FB and use of vasoactive drugs; Acute Physiology and Chronic Health Disease Classification System (APACHE II) score, peak lactate, AST and ALT levels; occurrence of postoperative complications, including early allograft dysfunction (EAD) and primary graft non-function (PGNF), biliary strictures or leaks, hepatic artery thrombosis or stenosis, AKI and requirement for RRT, acute rejection, sepsis and septic shock; cumulative FB in the first 12 h and 4 d; length of stay (LOS) in the ICU and in the hospital; mortality and causes of death in the first 28 d. The patients were evaluated in a single admission, when they entered the hospital to be transplanted

Child-Pugh, MELD and APACHE II scores were calculated as previously described[33-35]. Early allograft dysfunction was defined according to the definition of Olthoff *et al*[36] and PGNF was defining as EAD

Table 1 Baseline characteristics before liver transplantation (*n* = 121)

Male sex	106 (88%)
Age (yr)	50 ± 13
Etiology of chronic liver disease	
Hepatitis C	39 (32%)
Hepatitis C and alcoholic liver disease	12 (10%)
Alcoholic liver disease	36 (30%)
Cryptogenic and/or non-alcoholic steatohepatitis	10 (8%)
Hepatitis B	4 (3%)
Cholestatic liver disease	6 (5%)
Autoimmune hepatitis	4 (3%)
Others	10 (8%)
Indication for liver transplantation	
Decompensated cirrhosis	93 (77%)
Hepatocellular carcinoma	28 (23%)
Severity of liver disease at admission	
Child-Pugh score	9 ± 2
MELD score	18 ± 6

Data are expressed as mean ± SD. MELD: Model for end-stage liver disease.

Table 2 Intraoperative and postoperative features of the patients submitted to liver transplantation (*n* = 121)

Cold ischemia time (min)	520 ± 170
Duration of surgery (min)	333 ± 104
Use of blood products	77 (63%)
Number of packed red blood cell units	1.9 ± 3.1
Use of vasoactive drugs (norepinephrine)	38 (31%)
Peak of arterial lactate in the first 24 h (mmol/L)	2.3 ± 2.0
APACHE II score 24 h after admission	15 ± 4
Peak of AST levels (U/L)	3058 ± 4820
Peak of ALT levels (U/L)	1357 ± 1542
Postoperative complications	
Early allograft dysfunction	26 (22%)
Primary graft non-function	7 (6%)
Biliary strictures and/or leaks	5 (4%)
Arterial thrombosis or stenosis	5 (4%)
Acute rejection	32 (26%)
Sepsis or septic shock	38 (31%)
AKI	87 (72%)
AKI type 1	0
AKI type 2	44 (36%)
AKI type 3	43 (36%)
RRT	26 (22%)
Fluid balance (mL)	
Intraoperative	3829 ± 1904
Cumulative FB in the first 12 h	5473 ± 2417
Cumulative FB in the first 4 d	10956 ± 5117
Length of stay in ICU (d)	12 ± 11
Length of stay in the hospital (d)	19 ± 12
Mortality	11 (9%)

Data are expressed as mean ± SD. APACHE II: Acute Physiology and Chronic Health Disease Classification System; AKI: Acute kidney injury; RRT: Renal replacement therapy; FB: Fluid balance; ICU: Intensive care unit.

leading to death or retransplantation. The definition of AKI was based on The Kidney Disease Improving Global Outcomes (KDIGO) criteria published 2012[37]. Patients were evaluated by a nephrologist when dialysis was indicated. Fluid balance was defined as the difference between oral intake and/or intravenous fluid administration and urine output. Other potential causes for fluid losses including nasogastric aspirates, vomiting or diarrhea were not recorded. All patients received either normal saline or Ringer's lactate solution. Cumulative FB was calculated arbitrarily 12 h and 4 d after LT in order to evaluate the impact of fluid administration early in the postoperative period and thereafter after the initial phases of volume resuscitation. Cumulative FB in those chosen periods after admission to the ICU were also previously associated with adverse outcomes in other reports[4,26,30].

Cumulative FB in the first 12 h and 4 d after surgery were compared with three major adverse outcomes after LT, including the occurrence of AKI, requirement for RRT and 28-d mortality, as well as the other aforementioned variables previously known to influence morbidity and mortality after LT.

All patients granted informed consent at hospital admission. The study was approved by the Ethics Committee in Research of the Portuguese Hospital of Salvador, Bahia.

Statistical analysis

Descriptive analysis was performed. Continuous variables were expressed as mean ± SD and categorical variables as proportions. Univariate analysis of perioperative and postoperative parameters was tested using χ^2 test or the Fisher exact probability test when appropriate. Continuous variables were compared using the Mann-Whitney test[38]. Multivariate analysis using stepwise logistic regression was performed to evaluate the specific effect of each predictor[39]. Variables included in the multivariate model were those that achieved significance level of $P < 0.20$ in the univariate analysis. P value equal or less than 0.05 were considered significant. 95% confidence intervals were reported, when appropriate. The analysis of the residues was included in the steps of the logistic regression. All statistical analysis was performed using SPSS version 17.0 for Windows (SPSS Inc, Chicago, IL, United States).

RESULTS

Baseline clinical and laboratory data of those 121 patients included in the study are depicted in Table 1. Briefly most of the patients were males with a mean age of 50 ± 13 years and had decompensated cirrhosis (77%) due to hepatitis C and or alcoholic liver disease (72%) with mean Child-Pugh and MELD, respectively, of 9 ± 2 and 18 ± 6 (Table 1). The perioperative and postoperative information concerning the clinical course of those subjects are summarized in Table 2. Median cold ischemia time and duration of surgery were 520 ± 170 and 333 ± 104 min respectively. High peak AST and ALT levels were observed (Table 2) and the frequencies of EAD and PGNF encountered were 22% and 6%, respectively. Cumulative FB observed in the first 12 h and 4 d were, respectively, 5573 ±

Table 3 Comparison of baseline, intra-operative and postoperative features of patients submitted to liver transplantation according to the presence of acute kidney injury

	No AKI (n = 34)	AKI (n = 87)	P value
Age (yr)	51 ± 13	50 ± 12	0.643
Male sex	24 (71%)	82 (94%)	0.0001
Child-Pugh score at admission	8 ± 2	10 ± 2	0.840
MELD score at admission	17 ± 6	18 ± 6	0.868
APACHE II score 24 h after admission	14 ± 3	15 ± 4	0.142
Cold ischemia time (min)	537 ± 187	513 ± 164	0.267
Duration of surgery (min)	324 ± 131	336 ± 92	0.439
Use of blood products	59%	66%	0.490
Number of packed red blood cell units	1.0 ± 1.7	2.2 ± 3.4	0.010
Use of vasoactive drugs	6 (18%)	32 (37%)	0.032
Peak of arterial lactate in the first 24 h (mmol/L)	2.2 ± 1.4	2.4 ± 2.2	0.208
Peak AST levels (U/L)	1789 ± 1524	3535 ± 5511	0.022
Postoperative complications			
Early allograft dysfunction	3 (4%)	24 (28%)	0.019
Biliary strictures and/or leaks	1 (3%)	4 (5%)	0.567
Arterial thrombosis or stenosis	2 (6%)	3 (3%)	0.433
Acute rejection	10 (29%)	22 (25%)	0.402
Sepsis or septic shock	8 (24%)	30 (34%)	0.305
Cumulative FB in the first 12 h	4780 ± 1673	5743 ± 2610	0.050
Cumulative FB in the first 4 d	8690 ± 3463	11841 ± 5395	0.050
Length of stay in ICU (d)	8 ± 8	13 ± 11	0.087
Length of stay in the hospital (d)	15 ± 7	20 ± 12	0.001
Mortality	1 (3%)	10 (12%)	0.128

Data are expressed as mean ± SD. AKI: Acute kidney injury; MELD: Model for end-stage liver disease; APACHE II: Acute Physiology and Chronic Health Disease Classification System; FB: Fluid balance; ICU: Intensive care unit.

2417 and 10956 ± 5117 mL. AKI occurred in 87 (72%) patients, all with either type 2 (n = 44) or type 3 (n = 43) AKI. Twenty six patients required RRT 4 ± 2 d after surgery. The LOS in the ICU and in the hospital was, respectively, 12 ± 11 d and 19 ± 12 d. Eleven (9%) patients died due to PGNF (n = 7), septic shock (n = 2) and intraabdominal bleeding (n = 1) 10 9 d after surgery (Table 2).

The occurrence of AKI was associated with male sex (94% *vs* 71% of the patients without AKI, P = 0.0001), number of packed red blood cells transfused (2.2 ± 3.4 *vs* 1.0 ± 1.7 of subjects without AKI, P = 0.01), use of norepinephrine (37% *vs* 18% of patients without AKI, P = 0.032), peak AST levels (3535 ± 5511 *vs* 1789 ± 1524 of patients without AKI, P = 0.022), occurrence of EAD (28% *vs* 4% of patients without AKI) and cumulative FB in the first 12 h (5743 ± 2610 mL *vs* 4780 ± 1673 mL of patients without AKI, P = 0.05) and 4 d (11841 ± 5395 mL *vs* 8690 ± 3469 mL of patients without AKI, P = 0.05) (Table 3), but the difference remained significant in the multivariate analysis only for male sex and cumulative FB over 4 d.

In the univariate analysis, RRT was related to male sex (100% *vs* 84% in patients without RRT, P = 0.0001), APACHE II levels (18% ± 6% *vs* 14% ± 4% in patients without RRT, P = 0.03), use of blood products (81% *vs* 59% in patients without RRT, P = 0.03), use of norepinephrine (50% *vs* 26% in patients without RRT, P = 0.02), peak levels of arterial lactate in the first 24 h (3.3 ± 3.5 mmol/l *vs* 2.1 ± 1.3 mmol/L in patients without RRT, P = 0.0001), peak of AST level (6599 ± 9060 U/L *vs* 2144 ± 2157 U/L, in patients without RRT, p 0.0001), occurrence of EAD (50% *vs* 15% in patients without RRT, P = 0.0001), septic shock (58% *vs* 24% in patients without RRT, P = 0.0001), cumulative FB in the first 12 h (7146 ± 2538 mL *vs* 5014 ± 2181 mL in patients without RRT, P = 0.005) and cumulative FB over 4 d (14924 ± 7345 mL *vs* 9868 ± 3677 mL in patients without RRT, P = 0.0001) (Table 4). As expected, mortality (35% *vs* 2% in patients without RRT, P = 0.0001), LOS in the ICU (20 ± 14 *vs* 9 ± 9 in patients without RRT, P = 0.002) and in the hospital (24 ± 14 *vs* 17 ± 10 in patients without RRT, P = 0.007) were significantly increased in those patients requiring RRT (Table 4). However, only APACHE II levels, occurrence of sepsis or septic shock and cumulative FB in the first 4 d remained significant variables related to RRT in the multivariate analysis.

In respect to mortality in 28 d (Table 5), univariate analysis revealed an association with the number of packed red blood cell units transfused (3.6 ± 6 units *vs* 1.7 ± 2.6 units in survivors, P = 0.0001), peak of arterial lactate in the first 24 h (4.9 ± 4.2 mmol/L *vs* 2.1 ± 1.4 mmol/L in survivors, P = 0.0001), peak AST levels (11289 ± 13591 U/L *vs* 2372 ± 2280 U/L in survivors, P = 0.0001), EAD (72% *vs* 17% in survivors, P = 0.0001), acute rejection (0% *vs* 29% in survivors, P = 0.03), cumulative FB in 4 d (19073 ± 9416 mL *vs* 10144 ± 3656 mL in survivors, P = 0.00001), RRT (82% *vs* 15% in survivors, P = 0.001) (Table 5), but only APACHE II and AST levels remained significant in the multivariate analysis (Table 6).

Table 4 Comparison of baseline, intra-operative and postoperative features of patients submitted to liver transplantation according to requirement of renal replacement therapy

	No RRT (n = 95)	RRT (n = 26)	P value
Age (yr)	49 ± 12	53 ± 12	0.960
Male sex	80 (84%)	26 (100%)	0.0001
Child-Pugh score at admission	9 ± 2	10 ± 2	0.800
MELD score at admission	18 ± 6	19 ± 7	0.420
APACHE II 24 h after admission	14 ± 4	18 ± 6	0.030
Cold ischemia time (min)	506 ± 166	587 ± 175	0.470
Duration of surgery (min)	322 ± 103	372 ± 102	0.500
Use of blood products	59%	81%	0.030
Number of packed red blood cell units	1.6 ± 2.7	2.7 ± 4.2	0.080
Use of vasoactive drugs	25 (26%)	13 (50%)	0.020
Peak of arterial lactate in the first 24 h (mmol/L)	2.1 ± 1.3	3.3 ± 3.5	0.0001
Peak AST levels (U/L)	2144 ± 2157	6599 ± 9060	0.0001
Postoperative complications			
Early allograft dysfunction	14 (15%)	13 (50%)	0.0001
Biliary strictures and/or leaks	3 (3%)	2 (8%)	0.292
Arterial thrombosis or stenosis	5 (5%)	0 (0)	0.290
Acute rejection	27 (28%)	5 (19%)	0.249
Sepsis or septic shock	23 (24%)	15 (58%)	0.0001
Cumulative FB in the first 12 h	5014 ± 2181	7146 ± 2538	0.005
Cumulative FB in the first 4 d	9868 ± 3677	14924 ± 7345	0.0001
Length of stay in ICU (d)	9 ± 9	20 ± 14	0.002
Length of stay in the hospital (d)	17 ± 10	24 ± 14	0.007
Mortality	2 (2%)	9 (35%)	0.0001

Data are expressed as mean ± SD. RRT: Renal replacement therapy; MELD: Model for end-stage liver disease; APACHE II: Acute Physiology and Chronic Health Disease Classification System; FB: Fluid balance; ICU: Intensive care unit.

Table 5 Comparison of baseline, intra-operative and postoperative features of patients submitted to liver transplantation according to mortality in 28 d

	Survivors (n = 110)	Non survivors (n = 11)	P value
Age (yr)	50 ± 12	52 ± 13	0.780
Male sex	95 (86%)	11 (100%)	0.218
Child-Pugh score at admission	9 ± 2	10 ± 3	0.360
MELD score at admission	18 ± 6	19 ± 9	0.060
APACHE II 24 h after admission	14 ± 3	21 ± 6	0.060
Cold ischemia time (min)	512 ± 167	628 ± 177	0.080
Duration of surgery (min)	324 ± 98	417 ± 130	0.060
Use of blood products	64%	64%	0.620
Number of packed red blood cell units	1.7 ± 2.6	3.6 ± 6	0.000
Use of vasoactive drugs	32(29%)	6 (55%)	0.090
Peak of arterial lactate in the first 24 h (mmol/L)	2.1 ± 1.4	4.9 ± 4.2	0.0001
Peak AST levels (U/L)	2372 ± 2280	11289 ± 13591	0.0001
Postoperative complications			
Early allograft dysfunction	19 (17%)	8 (72%)	0.0001
Biliary strictures and/or leaks	5 (5%)	0	0.620
Arterial thrombosis or stenosis	5 (5%)	0	0.620
Acute rejection	32 (29%)	0	0.030
Sepsis or septic shock	34 (31%)	4 (36%)	0.740
Cumulative FB in the first 12 h	5205 ± 2233	8140 ± 2677	0.600
Cumulative FB in the first 4 d	10144 ± 3656	19073 ± 9416	0.00001
Length of stay in ICU (d)	12 ± 10	14 ± 11	0.360
Length of stay in the hospital (d)	18 ± 11	13 ± 10	0.070
AKI	77 (70%)	10 (90%)	0.140
RRT	17 (15%)	9 (82%)	0.0001

Data are expressed as mean ± SD. LT: Liver transplantation; MELD: Model for end-stage liver disease; APACHE II: Acute Physiology and Chronic Health Disease Classification System; FB: Fluid balance; ICU: Intensive care unit; AKI: Acute kidney injury; RRT: Renal replacement therapy.

DISCUSSION

Despite the development of several strategies to assess fluid responsiveness[40], fluid administration in the ICU remains largely empirical in daily practice. It is usually guided by bedside simple hemodynamic and laboratory parameters and urine output measurement. Early-goal directed therapy using large volume of

Table 6 Multivariate analysis of predictors of acute kidney injury, renal replacement therapy and mortality of patients submitted to liver transplantation

	Odds ratio	95%CI	*P* value
AKI			
Male sex	9.29	1.48-58.24	0.017
Cumulative FB in the first 4 d	2.3	1.37-3.86	0.020
RRT			
APACHE II 24 h after admission	2.5	1.36-4.62	0.003
Sepsis or septic shock	14.7	0.99-2.18	0.050
Cumulative FB in the first 4 d	2.89	1.52-5.49	0.001
Mortality			
AST levels (U/L)	2.35	1.1-5.05	0.020
APACHE II 24 h after admission	2.63	1.0-6.87	0.040

AKI: Acute kidney injury; RRT: Renal replacement therapy; APACHE II: Acute Physiology and Chronic Health Disease Classification System; FB: Fluid balance.

fluids to restore tissue perfusion in sepsis and septic shock has been shown to improve survival[41] and it is still considered today as the cornerstone of resuscitation in septic shock and sepsis-induced tissue hypoperfusion[42]. It may lead however, on the other hand, to post-resuscitation fluid overload with its detrimental effect in tissue perfusion leading to organ dysfunction and failure[1-3]. In surgical patients, fluid overload, usually assessed by cumulative FB, has been associated with impaired wound healing, ACS, postoperative pulmonary morbidity, as well as AKI with a detrimental influence not only on morbidity[1-3,10,11], but also on patient survival[13]. On the contrary, a restrictive approach on fluid administration has been shown to improve morbidity after major surgery, including LT[17,29-32], and mortality[17]. Concerning the influence of FB on the outcome of LT, other authors have shown detrimental effects of a cumulative positive FB concerning postoperative pulmonary complications and ileus[29-32]. Jiang *et al*[29], have demonstrated that a negative FB in the first 3 d after LT was linked to a decrease the frequency of early pulmonary complications. Lin *et al*[32] furthermore have described an increased incidence of postoperative pulmonary morbidity in patients submitted to LT who received a large amount of fluids and blood transfusions intraoperatively. Not surprisingly, protection from postoperative pulmonary morbidity was related to a negative FB in the first three days after LT. Later on, the same group of investigators demonstrated that employment of more than 100 mL/kg of blood transfusion intraoperatively and a FB equal or less than -14 mL/kg per day in the first three days after LT were inversely associated with postoperative pulmonary complications, when assessed by extubation time. Beneficial effects were also observed in frequency of postoperative ileus and ICU LOS. Reydellet *et al*[31] performed a before and after study comparing two resuscitation protocols after LT. The patients submitted to a liberal approach of fluid administration had significantly increased cumulative FB at 24 and 48 h when compared to their counterparts submitted to a more restricted fluid approach per protocol. Those patients submitted to a more restricted fluid approach had fewer days on mechanical ventilation and on postoperative ileus. None of the authors have investigated the influence of FB in the development of AKI after LT.

In the present study, most of the patients were submitted to a liberal approach of fluid administration with a mean cumulative FB over 5 and 10 L in the first 12 h and 4 d after LT. Several preoperative and postoperative variables were associated either with development of AKI and/or requirement for RRT, but only cumulative FB in 4 d were independently associated with occurrence of both AKI and requirement for RRT. Other variables on multivariate analysis associated with AKI and RRT were, respectively, male and APACHE II levels and sepsis or septic shock. Mortality was shown to be independently related to AST and APACHE II levels, probably reflecting the degree of graft dysfunction and severity of early postoperative course of LT. No effect of FB on mortality after LT was disclosed in the present study.

Although there is an increasing interest in the use of biomarkers to help identify AKI at an earlier stage, they were not used in the study. Patients with cirrhosis frequently have predisposing factors for the development of kidney diseases, such as advanced age, diabetes, and hypertension. In addition, specific liver diseases may be associated with kidney disease, such as HBV/HCV-associated glomerulonephritis or alcohol-related IgA nephropathy. In this study, the definition of AKI was based on The Kidney Disease Improving Global Outcomes criteria. This definition has been validated and it considers increases in serum creatinine from baseline known or presumed to have occurred within the prior 7 d. Early recognition of AKI in cirrhosis or in post-transplant is important in order to avoid factors that may contribute to further deterioration of renal function and to initiate appropriate management.

One of the major limitations of the present study is its retrospective design as well as the number of patients included in our cohort. We tried to control confounding variables through multivariate analysis. The authors also have to acknowledge that it is difficult to determine in such a study design whether cumulative FB may be a cause or consequence of disease severity or of AKI development, as postoperative resuscitation protocols were not standardized. However, our results do corroborate the detrimental effects of cumulative FB on the occurrence of AKI and requirement of RRT after LT, as demonstrated in several other clinical scenarios in the ICU[10-13,27,43].

In summary, cumulative positive fluid balance over 4 d after LT influence the development of AKI and is a risk factor for requirement of RRT. No effect on patient survival was independently related to FB, but to surrogate markers of graft dysfunction and severity of postoperative course of LT.

ARTICLE HIGHLIGHTS

Research background

Liver transplantation (LT) has become an option in treating a wide variety of liver diseases. Patients undergoing LT are at high risk of perioperative complications and death. Recently, there has been considerable interest in perioperative fluid therapy following major surgeries. Important question is whether fluid overload is an independent risk factor for adverse outcomes after LT. Previous reports indicate that restrictive strategy of fluids in surgical patients is beneficial. The influence of fluid accumulation on morbidity and mortality after LT has not been well evaluated up to now.

Research objectives

The aim of the study was to analyze whether cumulative positive fluid balance (FB) is associated with the occurrence of adverse outcomes after LT.

Research methods

Patients were retrospectively evaluated. In the present study, most of the patients were submitted to a liberal approach of fluid administration. Accumulated fluid balance (acFB), assessed within the first 12 hours and the 4 days following surgery, was compared with major adverse outcomes after LT.

Research results

Cumulative positive FB over 4 d after LT influences the development of acute kidney injury and it is a risk factor for the requirement for dialysis. No effect on patient survival was independently related to fluid balance.

Research conclusions

Our results show that fluid overload is a marker of severity of illness.

Research perspectives

We hope that these results may contribute to the management of liver grafted patients.

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