SEMMELWEIS EGYETEM

DOKTORI ISKOLA

Ph.D. értekezések

2895.

MARKUS U. BOEHNERT, M.D.

A folyadék- és elektrolitháztartás szabályozásának élet- és kórélettan; Keringés és vérnyomás szabályozás

című program

Programvezető: Dr. Zsembery Ákos, egyetemi tanár

Témavezető: Dr. Kóbori László, egyetemi tanár

Machine Perfusion and its Impact on Liver Transplantation

Ph.D. Thesis

Markus U. Boehnert, M.D.

Doctoral School of Theoretical and Translational Medicine

Semmelweis University

Consultant:	László Kóbori, M.D., D.Sc.
Official reviewers:	Kristóf Dede, M.D., Ph.D.
	Kornélia Baghy, M.D., Ph.D.
Head of the Complex Examination Committee:	György Losonczy, M.D., D.Sc.
Members of the Complex Examination Committee:	Ákos Zsembery, M.D., Ph.D.
	Zoltán Járay, M.D., Ph.D.

Budapest

2023

1. Introduction

Liver transplantation is the only curative option for patients with end stage liver disease. Due to an increasing number of transplant candidates and a persistently low organ donation rate, a growing proportion of the liver transplant candidates are dying before they have a possibility to receive an organ: In 2021, 407 of 2345 patients (17%) registered for liver transplantation at Eurotransplant died. Worldwide increasing rates of metabolic and alcohol-induced liver disease predict a future growth in transplant candidate numbers: almost 40% of the population in some countries show evidence for steatosis. For the same reasons, the quality of donor liver is decreasing, making an efficient use of marginal donor livers an essential requirement.

Historically, cold storage of livers on ice has been used to conserve donor organs, causing ischemia-reperfusion injury upon re-implantation and resulting in graft failure, in particular in marginal donor livers, eg. with manifest steatosis.

Ex-vivo perfusion of explanted livers (EVLP) offers a possibility to address the growing unmet need for transplant livers by increasing the potential donor pool and permitting quality assessment of the explanted organ. While cost and technical complexity have prevented its general use, application in specialized transplant centers represents a viable strategy to bridge the anticipated gap by increasing the use of organs from deceased donors. Perfusion temperature and medium, as well as mechanical aspects such as ample liquid pressure are crucial determinants of transplantation outcome. Damage of the hepatocytes as well as the biliary tree must be minimized.

2. Objectives:

The aim of the experimental work in this thesis is to establish a large animal model to investigate the impact of different parameters of perfusion (temperature, perfusion solution) on the liver. The first study is designed to investigate the effects of normothermic perfused preservation in a clinically relevant model of combined warm and cold ischemic injury. The author determined whether hepatocyte and bile duct injury can be improved by normothermic ex vivo perfused preservation (NELVP) in comparison to cold storage (CS).

The second study compares cold storage with combined CS and subnormothermic ex vivo liver perfusion (SNEVLP) for the preservation of donation after cardiac death (DCD) liver grafts in a model of pig liver transplantation. It outlines the effects of SNEVLP in DCD grafts on hepatocyte, sinusoidal endothelial cell (EC), and bile duct injury after transplantation.

The purpose of the literature review is to investigate which perfusion settings have been applied in each liver machine perfusion technique over the last years, and examine which combination yields the best preservation outcome, especially on long-term liver preservation. The research question is: "Which settings – in terms of perfusate, mode of flow and perfusion route – are utilized in different liver machine perfusion techniques and how do they affect the preservation outcome?". In addition, the review aims in presenting liver machine perfusion devices from an engineering standpoint, describing and analyzing the technical aspects, major components and their function in the perfusion configuration. Overall, the current state of both clinical and technical knowledge on liver machine perfusion is given and the major findings are highlighted. Last but not least, the thesis provides an overview of the commercial solutions that are presently on the market or in the process of gaining approval.

3. Methods:

To investigate the ideal conditions and the impact of various parameters on the performance of normothermic acellular *ex vivo* liver perfusion in pig livers retrieved after cardiac death, a CDC model comprising male Yorkshire pigs of 30–35 kg weight was implemented. A sophisticated perfusion circuit consisting of a hard-shell reservoir, a centrifugal pump, hollow-fiber oxygenator/heat exchanger and a leukocyte filter was set up (**Fig. 1**).

Acellular NEVLP was performed with 3 L of Steen solution, a buffered extracellular solution containing dextran and albumin was used. The perfusate did not contain any serum or blood components, or oxygen carriers. The perfusion was performed at normothermic temperature (38°C, pig core temperature) and 100% O2 was connected to the oxygenator. In the NEVLP group, the liver was stored for 4 h on ice, followed by NEVLP for additional 8 h. Control group livers were continuously stored for 4 h or 12 h on ice. At the end of the preservation time, all three groups were perfused *ex vivo* with diluted pig blood for an additional period of 12 h as a surrogate model of transplantation. ALT and total bilirubin were used as readouts. Conservation of the vascular structure was assessed by computer tomography (CT) angiography. Histology was assessed following H&E staining.

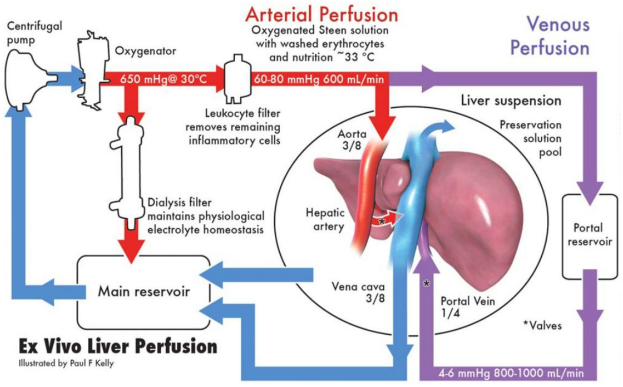

Figure 1: Exemplary setup of the subnormothermic acellular *ex vivo* liver perfusion using Steen solution plus washed erythrocytes as perfusate at 33°C

To study the efficacy of subnormothermic acellular *ex vivo* liver perfusion (SNEVLP), the same animal model was used as in the prior experiments. However, Steen solution was complemented with washed erythrocytes to achieve a hematocrit of 10% to 12%. In the previous experiment, the author had used a completely acellular perfusion solution without any blood components for normothermically perfused organ preservation. However, acellular perfusion was associated with decreased liver function and inferior long-term survival after pig liver transplantation. Therefore, in the second, subnormothermic study, the perfusion technique was modified by using leukocyte-depleted, washed erythrocytes as oxygen carriers. The liver was perfused at 33°C rather than at 38°C. In the SNEVLP group, the liver was stored for 4 hours on ice (the time frame was designated to simulate the transport time from the donor hospital to the recipient hospital), followed by

SNEVLP for 3 hours at 33°C and then CS for 3 hours (10-hour total preservation time). In the control group, the grafts were continuously stored for 10 hours on ice. At the end of the preservation time, orthotopic pig liver transplantation was performed with an active portojugular shunt. AST, ALT, total bilirubin, □-galactosidase (a measure of Kupffer cell activation) were measured. Bile fluid was analyzed for lactate dehydrogenase (LDH) content as a marker of bile duct injury. Liver histology was analyzed by H&E staining, apoptosis was quantified by cleaved caspase-3 staining.

The literature review was performed according to the guidelines of the Cochrane Collaboration.

4. Results:

Acellular normothermic ex vivo perfusion: Taken together, the results show that normothermic liver perfusion with an acellular perfusion solution resulted in improved arterial perfusion, decreased hepatocytes injury and reduced markers of bile duct injury in a pig model that mimics DCD liver transplantation: Cold stored versus NEVLP grafts had higher ALT levels (350 ± 125 vs. 55 ± 35 U/L; $p < 0.0001$, **Fig. 2A**), decreased oxygen extraction (250 ± 65 mmHg vs. 410 ± 58 mmHg, $p < 0.01$) and increased hepatocyte necrosis (45% vs. 10%, $p = 0.01$). Levels of bilirubin, phospholipids and bile salts were fivefold decreased, while LDH was sixfold higher in cold stored versus NEVLP grafts. Hepatic artery (HA) perfusion was decreased (twofold), and bile duct necrosis was increased (100% vs. 5%, $p < 0.0001$) in cold stored versus NEVLP livers. Following transplantation, mean serum AST level was higher in the cold stored versus NEVLP group (1809 ± 205 U/L vs. 524 ± 187 U/L, $p < 0.05$, **Fig. 2B**), with similar bile production (2.5 ± 1.2 cc/h vs. 2.8 ± 1.4 cc/h; $p = 0.2$). NEVLP improved HA perfusion and decreased markers of liver duct injury in DCD grafts.

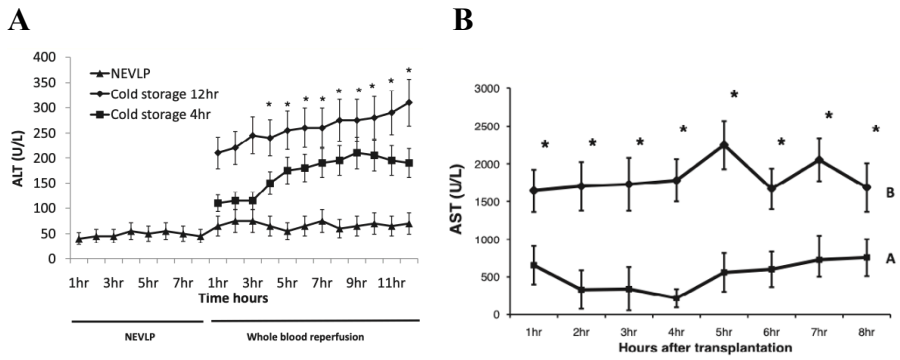

Figure 2: Normothermic ex vivo liver perfusion (NEVLP) reduces liver damage during storage ex vivo and improves liver damage following transplantation in vivo.

A. During normothermic perfusion ALT levels remained within the range of normal pig ALT levels (40– 60 U/L). The NEVLP preserved livers had a minimal ALT increase after blood reperfusion. In contrast, cold static preserved livers had a five- to sixfold increase of ALT compared with the NEVLP group (n = 6, ANOVA, *p < 0.001 at each time point 4 or 12 h cold vs. NEVLP).

B. AST as a marker of liver injury following orthotopic pig liver transplantation using DCD grafts.

Group A received a DCD liver graft with combined cold storage (4 h) and NEVLP (4 h), while in

group B the DCD graft treated with 8 h cold storage only. AST was significantly reduced with NEVLP preservation (n = 6, *p < 0.05, Student's t-test).

Subnormothermic ex vivo perfusion results: Long-term survival (7 days) after transplantation was similar between the SNEVLP and CS groups (60% versus 40%, P = 0.13). No difference was observed between SNEVLP- and CS-treated animals with respect to the peak of serum INR, factor V, or AST levels within 24 hours. Post-transplant SNEVLP animals had decreased serum ALP and serum bilirubin levels in comparison to cold storage (CS) animals. In addition, LDH in bile fluid was lower in SNEVLP pigs versus CS pigs (14 ± 10 versus 60 ± 18 μmol/L, P = 0.02). Bile duct histology revealed severe bile duct necrosis in 3 of 5 animals in the CS group but none in the SNEVLP group (P = 0.03). Serum levels of galactosidase, a marker of Kupffer cell activation, were significantly

lower in SNEVLP grafts versus CS grafts between 2 and 6 hours after reperfusion, and this indicated reduced Kupffer cell activation with SNEVLP preservation (**Fig. 3A**). At 3 hours after transplantation, hyaluronic acid (HA) serum levels were significantly reduced in SNEVLP livers versus CS livers (1077 ± 711 versus 2476 ± 364 ng/mL, P = 0.01), and this indicated improved EC function in SNEVLP DCD grafts (**Fig. 3B**).

The author concludes that sequential SNEVLP protects DCD liver grafts against sinusoidal endothelial cell (EC) injury and decreases bile duct necrosis after liver transplantation. DCD liver grafts represent a large donor pool, which could significantly improve the current donor shortage.

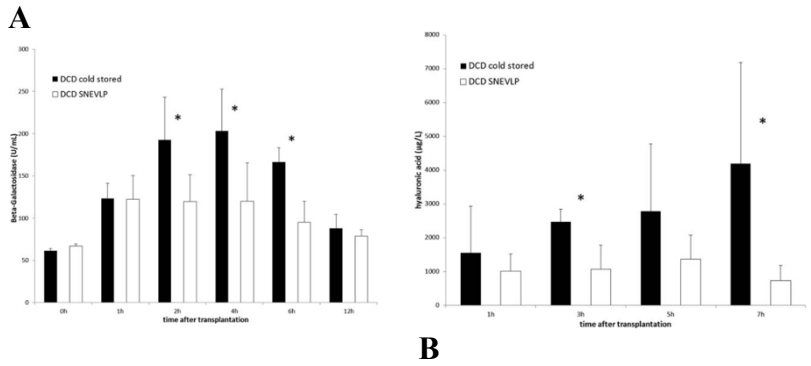

Fig. 3: Subnormothermic *ex vivo* perfusion (SNEVLP) reduces Kupffer cell activation and sinusoidal endothelial cell injury after liver transplantation

A: □-Galactosidase serum levels after DCD liver transplantation as a marker of Kupffer cell activation. -Galactosidase levels were decreased in pigs receiving an SNEVLP graft versus CS DCD graft in the reperfusion phase between 2 and 6 hours (n = 5 for each group, *P < 0.05).

B. HA serum levels were evaluated after transplantation in CS- and SNEVLP-treated groups as a marker of HA clearance by ECs. Animals receiving a CS DCD liver graft had increased HA levels in comparison with pigs receiving a DCD graft preserved with the SNEVLP protocol (n = 5 for each group, *P < 0.05).

Literature review

Literature research on normothermic machine perfusion demonstrated that it is indeed a widely used MP technique, which is generally compared to CS as the "gold standard". In all cases, the comparison indicates that livers preserved with NMP displayed lower levels of AST, ALT and LDH, less histological damage and no or insignificant necrosis compared to CS. Furthermore, biliary tree and hepatocyte integrity as well as bile production and composition are maintained during perfusion. Livers preserved with subnormothermic machine perfusion (SNMP) exhibit lower AST, ALT and LDH levels than cold storage, higher ATP and energy levels as well as more bile production compared to those that underwent CS. Oxygenated perfusates were utilized in all the included papers. It is noteworthy that albeit acellular hemoglobin-based oxygen-carrying (HBOC) solutions have been used in experimental systems, all systems presently in clinical application use blood as oxygen carrier.

5. Conclusions

The work presented in the first experimental section this thesis shows that normothermic liver perfusion with an acellular perfusion solution resulted in improved arterial perfusion, decreased hepatocellular damage, and reduced markers of bile duct injury in a pig model that mimics donation after cardiac death (DCD) liver transplantation. The current technology for normothermic perfusion requires equipment that is difficult to transport and run under mobile conditions. Thus, for the foreseeable future liver grafts will likely be flushed at the donor center with a cold preservation solution and then transported back to the transplant center for normothermic perfusion and storage. These steps will result in a cold ischemia time of approximately 3–5 h before normothermic perfusion can be initiated. To simulate "real-life" conditions, 4 h of cold static storage were added to the normothermic perfusion group. No blood cells or serum were used in the perfusate of the first model to minimize the potential adverse effects of inflammatory mediators during perfusion. In addition, using a blood free perfusate potentially minimizes the potential risk of intrahepatic clotting, breakdown of erythrocytes and infection risks associated with a blood perfusate.

Preservation of DCD grafts by initial cold storage and subsequent normothermic perfused preservation improved arterial flow, decreased bile duct hypoxia and prevented bile duct injury. These findings indicate that bile duct injury occurs after reperfusion and can be

prevented by using the right preservation conditions despite severe ischemia during DCD retrieval.

The second experimental section of this thesis demonstrates that subnormothermic ex vivo liver perfusion (SNEVLP) at 33°C using an acellular perfusate containing washed erythrocytes as oxygen carrier protects DCD liver grafts against sinusoidal EC injury and decreases bile duct necrosis after liver transplantation. DCD liver grafts represent a large donor pool, which could significantly improve the current donor shortage. Unfortunately, DCD liver transplantation is associated with a high risk (20%-40% of cases) for ischemic-type bile duct injury. This has resulted in strict selection criteria for DCD grafts, and therefore they are often declined based on donor age or warm and cold ischemia times. A better preservation technique is urgently required to protect bile ducts in DCD liver grafts, and thus to make this donor group more broadly available for liver transplantation. In previous studies, acellular perfusion was associated with decreased liver function and inferior long-term survival after pig liver transplantation. Therefore, in the second experimental study, perfusion technique was modified by using leukocyte-depleted, washed erythrocytes as oxygen carriers. Along with the addition of other active substances, the modified perfusion solution was able to decrease the activation of the inflammatory cascade substantially. Adding washed, leukocyte-depleted, and serum-free erythrocytes as oxygen carriers to the perfusate improved liver function after transplantation with similar protective effects on bile ducts in comparison with the acellular perfusate used in the first study. In summary, the second study demonstrates that organ preservation with combined CS and subsequent SNEVLP protects DCD liver grafts against ischemic-type bile duct injury and reduces EC death. Reducing the incidence of intrahepatic bile duct strictures will permit better use of DCD liver grafts, and hence increase the donor pool for liver transplantation.

While the experimental studies described in this thesis demonstrate that it is possible to replace blood as oxygen carrier with acellular solutions in normothermic as well as subnormothermic machine liver perfusion and still protect the bile ducts, all machine perfusion systems in clinical application involve the use of full blood or red-blood-cell (RBC)-based perfusates with all its drawbacks. At normothermic temperature, RBCs have to date been irreplaceable as oxygen carriers to support the metabolism of the graft by sufficient oxygen delivery. This is where the advantage of subnormothermic perfusion lies: the included studies have accomplished successful SNMP by obviating blood-based oxygen

carriers. Acellular perfusates were utilized, with Krebs-Henseleit (KH) and UW-G solutions being the most characteristic examples.

Even in 2022, the optimal temperature and timing for perfusion preservation remain controversial. Although successful trials using normothermic perfusion have been reported, NMP has the problem that higher preservation temperatures necessitate higher oxygen supply. Dissolved oxygen alone is insufficient, and oxygen carriers, traditionally total human blood or blood fractions, are required. Hence, NMP is associated with increased risk of coagulation and bacterial contamination in the perfusion circuit. Hypothermic oxygenated machine perfusion (HOPE) has at least four protective mechanisms against lethal impairment of hepatic flow in parenchymal and nonparenchymal cells: Endothelial cell effects, hepatocyte effects, mitochondrial effects culminating in ROS release, and cellular defense effects triggered by ROS. The combination of subnormothermic machine perfusion and innovative artificial oxygen carriers, such as HBOC-201 or Hemopure® promises to unite the benefits of both low temperature and cell-free perfusate: The ideal perfusion solution will contain a cell-free oxygen carrier that can be used at all temperatures, and it should have a long shelf life. In this respect, the experimental work presented in this thesis reflects the state-of-the-art as seen in the literature review. While the future of machine perfusion should definitely be acellular, clinical practice in 2022 still involves blood or blood products. Probably because of the additional cost and complexity associated with both the potential blood replacement compounds and the machinery required for SNMP.

9. Bibliography of the candidate´s publications

I. List of original publications within the topic of the PhD thesis:

Knaak Jan M., Spetzler Vinzent N., Goldaracena Nicolas, **Boehnert Markus U**., Bazerbachi Fateh, Louis Kristine S., Adeyi Oyedele A., Minkovich Leonid, Yip Paul M., Keshavjee Shaf, Levy Gary A., Grant David R., Selzner Nazia, Selzner Markus
Subnormothermic Ex Vivo Liver Perfusion Reduces Endothelial Cell and Bile Duct Injury After Donation After Cardiac Death Pig Liver Transplantation
LIVER TRANSPLANTATION 20: 11 pp. 1296-1305., 10 p. (2014)
Journal Article (Article) | Scientific |
Journal subject: Scopus - Surgery Rank: D1
Journal subject: Scopus - Hepatology Rank: Q1
Journal subject: Scopus - Transplantation Rank: Q1
IF: 4,241

Boehnert M. U., Yeung J. C., Knaak J. M., Selzner N., Selzner M.
Normothermic Acellular Ex Vivo Liver Perfusion (NEVLP) Reduces Liver and Bile Duct in DCD Liver Grafts
AMERICAN JOURNAL OF TRANSPLANTATION 13: 12 pp. 3290-3290., 1 p. (2013)
Journal Article (Comment, Correction) | Scientific

Boehnert M. U., Yeung J. C., Bazerbachi F., Knaak J. M., Selzner N., McGilvray I. D., Rotstein O. D., Adeyi O. A., Kandel S. M., Rogalla P., Yip P. M., Levy G. A., Keshavjee S., Grant D. R., Selzner M.
Normothermic Acellular Ex Vivo Liver Perfusion Reduces Liver and Bile Duct Injury of Pig Livers Retrieved After Cardiac Death
AMERICAN JOURNAL OF TRANSPLANTATION 13: 6 pp. 1441-1449., 9 p. (2013)
Journal Article (Article) | Scientific
Journal subject: Scopus - Pharmacology (medical) Rank: D1
Journal subject: Scopus - Transplantation Rank: D1
Journal subject: Scopus - Immunology and Allergy Rank: Q1
IF: 6,190

II. List of original publications not relating to the topic of the PhD thesis:

Takagi Kosei; Domagala Piotr; Polak Wojciech G; Ijzermans JNM; **Boehnert Markus U.**
Right posterior segment graft for living donor liver transplantation: A systematic review
TRANSPLANTATION REVIEWS 34: 1 Paper: 100510, 7 p. (2020)
Journal Article (Survey paper) Scientific
Journal subject: Scopus - Transplantation Rank: Q1
IF: 3,943

Zidan Ahmed; Sturdevant Mark; Alkhail Faisal Aba; Alabbad Saleh; **Boehnert Markus Ulrich**; Broering Dieter
The first two cases of living donor liver transplantation using dual grafts in Saudi Arabia
ANNALS OF SAUDI MEDICINE 39: 2 pp. 118-123., 6 p. (2019)
Journal Article (Article) Scientific
Journal subject: Scopus - Medicine (miscellaneous) Rank: Q3
IF: 0,917

Alotaibi Faisal; Kabbani Monther; Abaalkhail Faisal; Chorley Alicia; Elbeshbeshy Hany; Al-Hamoudi Waleed; Alabbad Saleh; **Boehnert Markus U**; Alsofayan Mohammad; Al-Kattan Wael; Ahmed Baderaldeen; Broering Dieter; Al Sebayel Mohamed; Elsiesy Hussien
Low Utility of Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography for Detecting Hepatocellular Carcinoma in Patients Before Liver Transplantation
EXPERIMENTAL AND CLINICAL TRANSPLANTATION 15 pp. 37-41., 5 p. (2017)
Journal Article (Article) Scientific
Journal subject: Scopus - Transplantation Rank: Q3
IF: 0,695

Kandel Sonja M; Meyer Henning; **Boehnert Markus**; Hoppel Bernice; Paul Narinder Singh; Rogalla Patrik
How Influential Is the Duration of Contrast Material Bolus Injection in Perfusion CT? Evaluation in a Swine Model

RADIOLOGY 270: 1 pp. 125-130., 6 p. (2014)
Journal Article (Article) Scientific
Journal subject: Scopus - Radiology, Nuclear Medicine and Imaging Rank: D1
IF: 6,867

Selzner Nazia; Liu Hao; **Boehnert Markus U**; Adeyi Oyedele A; Shalev Itay; Bartczak Agata M; Xue-Zhong Max; Manuel Justin; Rotstein Ori D; McGilvray Ian D; Grant David R; Phillips Melville J; Levy Gary A; Selzner Markus
FGL2/Fibroleukin mediates hepatic reperfusion injury by induction of sinusoidal endothelial cell and hepatocyte apoptosis in mice
JOURNAL OF HEPATOLOGY 56: 1 pp. 153-159., 7 p. (2012)
Journal Article (Article) Scientific
Journal subject: Scopus - Hepatology Rank: D1
IF: 9,858

Selzner Nazia; **Boehnert Markus**; Selzner Markus
Preconditioning, postconditioning, and remote conditioning in solid organ transplantation: basic mechanisms and translational applications
TRANSPLANTATION REVIEWS 26: 2 pp. 115-124., 10 p. (2012)
Journal Article (Survey paper) Scientific
Journal subject: Scopus - Transplantation Rank: Q2
IF: 2,675

Bazerbachi Fateh; Selzner Markus; **Boehnert Markus U**; Marquez Max A; Norgate Andrea; McGilvray IanD; Schiff Jeffrey; Cattral Mark S
Thymoglobulin Versus Basiliximab Induction Therapy for Simultaneous Kidney-Pancreas Transplantation: Impact on Rejection, Graft Function, and Long-Term Outcome
TRANSPLANTATION 92: 9 pp. 1039-1043., 5 p. (2011)
Journal Article (Article) Scientific
Journal subject: Scopus - Transplantation Rank: Q1
IF: 4,003

Boehnert Markus U; Zimmermann Heinz; Exadaktylos Aristomenis K
O knowledge, where art thou?
JOURNAL OF EVALUATION IN CLINICAL PRACTICE 15: 6 pp. 1177-1179., 3 p. (2009)
Journal Article (Note, Short, Rapid communications) Scientific
Journal subject: Scopus - Health Policy Rank: Q1
IF: 1,487

Boehnert Markus U; Armbruster Franz Paul; Hilbig, Heidegard
Relaxin as a Protective Substance in the Preserving Solution for Liver Transplantation Spectrophotometric in Vivo Imaging of Local Oxygen Supply in an Isolated Perfused Rat Liver Model
ANNALS OF THE NEW YORK ACADEMY OF SCIENCES 1160 pp. 320-321., 2 p. (2009)
Journal Article (Note, Short, Rapid communications) Scientific
Journal subject: Scopus - History and Philosophy of Science Rank: D1
IF: 2,670

Boehnert MU; Armbruster FP; Hilbig H
Relaxin as a protective substance in preservation solutions for organ transplantation, as shown in an isolated perfused rat liver model
TRANSPLANTATION PROCEEDINGS 40: 4 pp. 978-980, 3 p. (2008)
Journal Article (Note, Short, Rapid communications) Scientific
Journal subject: Scopus - Surgery Rank: Q2
IF: 1,055

Boehnert MU; Hilbig H; Armbruster FP
Relaxin as an additional protective substance in preserving and reperfusion solution for liver transplantation, shown in a model of isolated perfused rat liver
ANNALS OF THE NEW YORK ACADEMY OF SCIENCES 1041 pp. 434-440., 7 p. (2005)
Journal Article (Article) Scientific
Journal subject: Scopus - History and Philosophy of Science Rank: D1
IF: 1,971

Kessler M.; **Boehnert M**; Singer M; Nicklas A
Functional monitoring in perfused liver
In: Kessler, MD; Muller, GJ (eds.) FUNCTIONAL MONITORING AND DRUG-TISSUE INTERACTION
BELLINGHAM: SPIE-INT SOC OPTICAL ENGINEERING (2002) pp. 324-331., 8 p.
Chapter in Book (Conference paper) Scientific

Singer M.; Kessler M; **Boehnert M**
Imaging of dynamic alteration of functional structures
In: Kessler, MD; Muller, GJ (eds.) FUNCTIONAL MONITORING AND DRUG-TISSUE INTERACTION
BELLINGHAM: SPIE-INT SOC OPTICAL ENGINEERING (2002) pp. 308-313., 6 p.
Chapter in Book (Conference paper) Scientific

Hensen J.; Henig A; Fahlbusch R; Meyer M; **Boehnert M**; Buchfelder M
Prevalence, predictors and patterns of postoperative polyuria and hyponatraemia in the immediate course after transsphenoidal surgery for pituitary adenomas
CLINICAL ENDOCRINOLOGY 50: 4 pp. 431-439., 9 p. (1999)
Journal Article (Article) Scientific
Journal subject: Scopus - Endocrinology, Diabetes and Metabolism Rank: Q1
IF: 2,833