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TRAITEMENT DE METASTASES AU FOIE

(54) Title: A MINIMALLY INVASIVE ISOLATED HEPATIC PERFUSION TECHNIQUE FOR TREATMENT OF LIVER
METASTASES

(57) **Abrégé/Abstract:**

A method of vascular isolation of the liver to allow regional treatment of patients with non-resectable metastases confined to the liver.



ABSTRACT

A method of vascular isolation of the liver to allow regional treatment of patients with non-resectable metastases confined to the liver.

A MINIMALLY INVASIVE ISOLATED HEPATIC PERFUSION TECHNIQUE FOR THE TREATMENT OF LIVER METASTASES

Cross-Reference to Related Applications

[0001] This Application claims the benefit of U.S. Provisional Application No. 60/488,163 filed July 18, 2003.

BACKGROUND OF THE INVENTION

Field of the Invention

[0002] The present invention relates to isolated hepatic perfusion, and more particularly, to isolated hepatic perfusion with minimally invasive techniques.

Discussion of the Related Art

[0003] Isolated hepatic perfusion (IHP) involves a method of complete vascular isolation of the liver to allow regional treatment of patients with non-resectable metastases confined to the liver. As systemic toxicity is dose limiting for most cytostatic compounds, IHP allows drug dosages that would cause fatal complications if delivered systemically. Furthermore, effective anti-tumor compounds that cannot be administered systemically because of their toxicity, such as tumor necrosis factor (TNF), can be used in IHP.

[0004] Since the development of IHP (Ausman R.K., "Development of a Technic for Isolated Perfusion of the Liver" NY State J Med, Vol. 61, pp. 3393-97 (1961)), several clinical studies have been conducted. (Vahrmeijer A.L., et al., "Increased Local Cystostatic Drug Exposure by Isolated Hepatic Perfusion: a Phase I Clinical and Pharmacologic Evaluation of Treatment with High Dose Melphalan in Patients with Colorectal Cancer Confined to the Liver", Br J Cancer,

Vol. 82, pp. 1539-46, (2000); Alexander H.R., et al., "A Phase I-II Study of Isolated Hepatic Perfusion using Melphalan with or without Tumor Necrosis Factor for Patients with Ocular Melanoma Metastatic to Liver", Clin Cancer Res, Vol. 6, pp. 3062-70, (2000); Alexander H.R., et al., "Isolated Hepatic Perfusion with Tumor Necrosis Factor and Melphalan for Unresectable Cancers Confined to the Liver", J Clin Oncol, Vol. 16, pp. 1479-89, (1998); Aigner K.R., et al., "Isolated Liver Perfusion with MMC/5-FU: Surgical Technique Pharmacokinetics, Clinical Results", Contr Oncol, Vol. 29, pp. 229-46, (1988); Hafstrom L.R., et al., "Isolated Hyperthermic Liver Perfusion with Chemotherapy for Liver Malignancy", Surg Oncol, Vol. 3, pp. 103-8, (1994); Marinelli A., et al., "Isolated Liver Perfusion with Mitomycin C in the Treatment of Colorectal Cancer Metastases Confined to the Liver", Jpn J Clin Oncol, Vol. 26, pp. 341-50, (1996); Oldhafer K.J., et al., "First Experience and Technical Aspects of Isolated Liver Perfusion for Extensive Liver Metastasis", Surgery, Vol. 123, pp. 622-31, (1998); Bartlett D.L., et al., "Isolated Hepatic Perfusion for Unresectable Hepatic Metastases from Colorectal Cancer", Surgery, Vol. 129, pp. 176-87, (2001); de Vries M.R., et al., "Isolated Hepatic Perfusion with Tumor Necrosis Factor Alpha and Melphalan: Experimental Studies in Pigs and Phase I Data from Humans", Recent Results Cancer Res, Vol. 147, pp. 107-19, (1998); Rothbarth J., et al., "Isolated Hepatic Perfusion with High Dose Melphalan for the Treatment of Metastatic Colorectal Cancer Confined to the Liver", Br J Surg Submitted). Recent studies involving IHP with melphalan and TNF- α mention impressive response rates of up to 77% and a median survival of up to 27.7 months. Alexander H.R., et al., "Isolated Hepatic Perfusion with Tumor Necrosis Factor and Melphalan for Unresectable Cancers Confined to the Liver", J Clin Oncol, Vol. 16, pp. 1479-89, (1998); Bartlett D.L., et al., "Isolated Hepatic Perfusion for

Unresectable Hepatic Metastases from Colorectal Cancer”, Surgery, Vol. 129, pp. 176-87, (2001).

[0005] A recent study by the inventors involving treatment of 71 patients with colorectal metastases by IHP with high dose melphalan demonstrated a response rate of 60% and a median survival of 28.8 months. Rothbarth J., et al., “Isolated Hepatic Perfusion with High Dose Melphalan for the Treatment of Metastatic Colorectal Cancer Confined to the Liver”, Br J Surg Submitted. These data show that IHP can be highly effective in the treatment of colorectal metastases. In addition, promising results have been obtained with IHP for liver metastases from uveal melanoma. Alexander H.R., et al., “A Phase I-II Study of Isolated Hepatic Perfusion using Melphalan with or without Tumor Necrosis Factor for Patients with Ocular Melanoma Metastatic to Liver”, Clin Cancer Res, Vol. 6, pp. 3062-70, (2000).

[0006] A major disadvantage of the current IHP is that it is a demanding and technically difficult procedure with considerable morbidity and mortality, mostly related to the invasive nature of the surgical procedure itself. Moreover, adhesion formation makes this procedure non-repeatable. Since a single 1-hour treatment by IHP with melphalan is already very effective, as shown by the high response rates in recent studies, Alexander H.R., et al., “Isolated Hepatic Perfusion with Tumor Necrosis Factor and Melphalan for Unresectable Cancers Confined to the Liver”, J Clin Oncol, Vol. 16, pp. 1479-89, (1998); Rothbarth J., et al., “Isolated Hepatic Perfusion with High Dose Melphalan for the Treatment of Metastatic Colorectal Cancer Confined to the Liver”, Br J Surg Submitted, repetitive treatment with IHP would be very attractive. This might enhance anti-tumor response and survival rates. To make the current IHP procedure less laborious and

broaden the applicability of IHP the development of a less invasive, repeatable IHP technique is needed.

[0007] A less invasive IHP approach was tested in Yorkshire pigs (60 kg), whereby the liver was isolated from the systemic circuit using an occlusion stent-graft and balloon catheters.

Intrahepatic pressure was controlled by reversion of the blood flow through the liver during IHP, i.e. inflow through the hepatic veins and outflow through the portal vein (PV), and by applying negative pressure (suction) at the PV.

[0008] Tests with varying pressures applied at the PV revealed a clear relation between the suction pressure at the outflow site (PV), intrahepatic pressure and systemic leakage of ^{99m}Tc. A leakage-free IHP was obtained in seven separate experiments.

[0009] Recent results from phase I/II studies involving surgically isolated hepatic perfusion (IHP) as a treatment for non-resectable metastases confined to the liver showed good response rates: a median life expectancy of approximately 30 months and even several 5-year survivors. Isolated hepatic perfusion using minimally invasive techniques is thus feasible in pigs when the intrahepatic pressure is controlled. This technique may be used in human patients. However, because IHP is an invasive, technically difficult, non-repeatable and demanding operation. A less invasive alternative for surgical IHP is preferred.

SUMMARY OF THE INVENTION

[0010] In current surgical IHP, clamping the suprahepatic caval vein SCV and cannulating the infrahepatic caval vein ICV are the most time-consuming aspects of the procedure because extensive surgical exploration is needed. Occluding the suprahepatic SCV with an occlusion

stent-graft and the ICV with a balloon catheter relieves some of the time constraints of the procedure. In addition the stent-graft and balloon catheter occlusion techniques contributes to a leakage-free, minimally invasive IHP with flow rates comparable to known surgical IHP procedures.

[0011] Unfortunately, complete vascular isolation cannot be achieved by just occluding the major liver vessels due to the existence of numerous venous collaterals. Increased intrahepatic pressure during IHP inevitably results in unacceptable leakage from the isolated circuit through collaterals to the systemic circulation. These collaterals can be easily ligated during a surgical IHP, but obviously not with minimally invasive techniques.

[0012] To achieve a leakage-free minimally invasive IHP according to the systems and methods of the invention, intrahepatic pressure is controlled. Leakage through hepatic collaterals to the systemic circulation could be prevented if the intrahepatic pressure is kept low. Applying negative (suction) pressure at the outflow site helps to achieve the desired low intrahepatic pressure. Unpublished experiments by the inventor's have shown that reversion of the blood stream through the isolated liver allows better intrahepatic pressure control compared to the normal perfusion direction. Therefore, the invention reverses the blood stream through the isolated liver (i.e., inflow occurs through the hepatic veins and outflow occurs through the portal vein (PV)) and applies negative (suction) pressure at the PV (the outflow site) to control the intrahepatic pressure. An additional advantage of reversion of the bloodstream through the liver during IHP is an increased tumor/liver uptake ratio of arterially administered drugs, which might reduce IHP related hepatotoxicity. Rothbarth J., et al., "Reduced Liver Uptake of Arterially

Infused Melphalan During Retrograde Rat Liver Perfusion with Unaffected Liver Tumor Uptake”, J Pharmacol Exp Ther, Vol. 303, pp. 736-40, (2002).

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] These and other features, aspects, and advantages of the invention will become better understood with regard to the following description appended claims and accompanying drawings wherein:

[0014] Figure 1A schematically illustrates the first phase of the IHP experiments in the pig model.

[0015] Figure 1B schematically illustrates an occlusion stent-graft according to the invention.

[0016] Figure 2 illustrates inflated balloon catheters in the infrahepatic caval vein ICV (thick arrow) and portal vein PV (thin arrow), and the cast of the Histoacryl® and Lipiodol® mixture (arrow-head) in the hepatic and splenic artery.

[0017] Figure 3 graphically illustrates intraportal pressure with and without suction pressure applied at the PV ($\pm$ SD) ($n = 5$). *Statistical difference between IHP with and without suction pressure ($P < 0.05$).

[0018] Figure 4 is a chart illustrating ^{99m}Tc counts/sec in the isolated circuit (left y-axis) and systemic circulation (right y-axis) during experiments in which the suprahepatic caval vein SCV is occluded by a surgically placed clamp wherein no leakage of ^{99m}Tc to the systemic circulation was detected when suction pressure was applied at the PV, but massive leakage of ^{99m}Tc occurs when no suction pressure is applied at the PV.

[0019] Figure 5 illustrates a distal end of a retrievable occlusion stent-graft (thin arrow) sealing the SCV wherein hepatic veins and isolated segments of the SCV are filled with a contrast agent (thin arrow-heads) injected via the balloon catheter in the SCV (thick arrow).

[0020] Figure 6 is a chart illustrating ^{99m}Tc counts/sec in the isolated circuit and systemic circulation during experiments in which the surgically placed clamp occluding the SCV is replaced by the retrievable occlusion stent-graft.

[0021] Figure 7 is a table illustrating values for the balloon catheters and occlusion stent-grafts and other aspects according to the invention.

DETAILED DESCRIPTION OF THE INVENTION

[0022] Surgical IHP, i.e. treatment of liver metastases during complete vascular isolation, with melphalan has proven to be effective for the treatment of colorectal metastases confined to the liver. To make the current IHP procedure less laborious and to broaden the applicability of IHP, a less invasive and repeatable IHP technique according to the invention has been developed.

Isolated hepatic perfusion using percutaneous balloon catheters in pigs, in which the portal vein PV is surgically clamped and the liver is perfused hypoxically via the hepatic artery HA using the hepatic veins for outflow is known. van Ijken, M.G., et al., "Isolated Hypoxic Hepatic Perfusion with Tumor Necrosis Factor-Alpha, Melphalan, and Mitomycin C using Balloon Catheter Techniques: a Pharmacokinetic Study in Pigs", Ann Surg, Vol. 228, pp. 763-70, (1998).

[0023] The invention provides a different strategy in which IHP with an extracorporeal veno-venous bypass is achieved using a balloon catheter and an occlusion stent-graft instead of

extensive surgical exploration. The strategies and devices used by the invention are thus a minimally invasive IHP alternative. Leakage-free IHP is feasible with the methods of the invention by controlling the intrahepatic pressure. To achieve this intrahepatic pressure control, the blood flow through the liver is reversed (i.e., inflow occurs through the ICV, outflow occurs through the PV) and negative (suction) pressure is applied at the PV. Thus, reversion of the blood stream through the liver allows good pressure control in the liver. Pressure control in the liver helps minimize, or ideally prevent drug leakage to the systemic circuit through collaterals as a result of overpressure in the isolated circuit.

[0024] The reversion of the blood stream through the liver is different than the methods used in known surgical IHP procedures. The lack of vascular valves in the hepatic and portal veins enables this short-time partial reversion of the blood stream. Significantly, liver function (AST, ALT, LDH and PNP activity) and glutathione levels were not affected by partial reversion of the blood stream through the liver. Compagnon P., et al., "Effects of Hypothermic Machine Perfusion on Rat Liver Function Depending on the Route of Perfusion", Transplantation, Vol. 72, pp. 606-14, (2001). In addition, as the intrahepatic pressure can be controlled during IHP, non-physiological pressure changes can be prevented. Therefore, the safety and efficacy of short-term reversion of the blood stream through the liver is enhanced.

[0025] During conventional surgical IHP, melphalan is infused in the HA. As liver tumors are almost exclusively vascularized arterially, the reversion of the venous blood stream through the liver does not detrimentally affect the tumor's response or exposure to the chemotherapy, i.e. anti-tumor efficacy is maintained. This has been confirmed by a study in a rat model, showing that tumor uptake of arterially infused melphalan is independent of perfusion direction.

Rothbarth J., et al., "Reduced Liver Uptake of Arterially Infused Melphalan During Retrograde Rat Liver Perfusion with Unaffected Liver Tumor Uptake", J Pharmacol Exp Ther, Vol. 303, pp. 736-40, (2002). Moreover, results of the same study showed that uptake in the liver is significantly reduced after partial reversion of the blood stream. This result is presumably because melphalan only reaches the periportal zone during reversed perfusion. Accordingly, reversion of the bloodstream with HA infusion of chemotherapy might even result in less liver uptake of cytostatics, thereby reducing hepatotoxicity.

[0026] The techniques of the invention are ready for a phase I study in patients. The HA and the PV may be accessed with percutaneous techniques in order to achieve a fully percutaneous IHP. As these techniques are well known in interventional radiology, the application of percutaneous access to the HA and PV in IHP is also expected to be feasible and readily understood and appreciated by one skilled in the art. Azoulay D., et al., "Resection of Nonresectable Liver Metastases from Colorectal Cancer After Percutaneous Portal Vein Embolization", Ann Surg, Vol. 231, pp. 480-6, (2000); and Casteneda-Zuniga W.R., et al., Interventional Radiology, Baltimore: Williams and Wilkins, (1991).

[0027] Experimental protocol concerning the methods and strategies of isolating the liver for treatment according to the invention was approved by the Committee on Animal research of Leiden University. According to the approved experimental protocol, Dutch Yorkshire pigs weighing approximately 60 kg were used. General anaesthesia was maintained with a O₂/N₂ (50/50) mixture with 1 to 2% Isoflurane®. Ventilation was facilitated by a muscle relaxant (Pavulon®) and an opiate (Finadyne®).

[0028] Via small incisions in the right groin and neck of the pigs, the femoral artery and internal jugular vein respectively were made accessible. Following a transverse abdominal incision the portal vein (PV) and infrahepatic caval vein (ICV) were exposed. Before cannulation, the pigs were heparinised with 3 mg/kg heparin.

[0029] As shown in Fig. 1A a total of six devices were needed to ensure hepatic isolation and venous return in this experiment whereby an isolated hepatic perfusion circuit is provided with extra-corporal veno-venous bypass. The following devices were inserted: a surgically placed suprhepatic clamp (1a); homemade balloon catheter (2) to occlude the ICV; a decompression balloon catheter (3) to stop inflow into the liver and to drain the mesenteric outflow; a catheter (4) to drain the intra-hepatic portal system; a catheter (5) to drain the outflow from the lower limbs; a catheter (6) to return blood from the extracorporeal veno-venous bypass to the systemic circulation. The hepatic artery HA is embolised with Histoacryl®. In a second phase of the IHP experiments the surgically placed suprahepatic clamp (1a) is replaced by the retrievable occlusion stent-graft (1b) shown in Fig. 1B.

[0030] Three catheters were positioned within the portal venous system: the decompression balloon catheter (3) to stop inflow into the liver and to drain the mesenteric outflow (13F retrograde cardioplegia cannula manual, model 5579, Terumo Cardiovascular Systems Corporation, Ann Arbor, Michigan, USA); the catheter (4) to drain the intra-hepatic portal system (12F Thalquick, Cook, Amsterdam, The Netherlands); and a pressure monitoring catheter (5) (5F pigtail Cordis, Roden, The Netherlands). Catheter (3) was surgically introduced, whereas catheters (4) and (5) were introduced with a Seldinger technique. The splenic vein was ligated just before entering the portal trunk.

[0031] The infrahepatic caval vein ICV was occluded caudal to the hepatic veins with a large bore balloon catheter (2) that interrupted physiological caval flow and provided inflow for the hepatic veins through a large inner lumen. This balloon catheter (2) (18F, Boston Scientific, Maastricht, The Netherlands) was surgically introduced into the ICV superior to the level of the renal veins.

[0032] The SCV was either surgically clamped (Fig. 1A) or sealed with a retrievable occlusion stent-graft (1b) (Fig. 1B) (22F Wallstreet with standard graft, JOMED, Helsingborg, Sweden) from the jugular approach. To simplify the procedure and because hepatic artery HA cannulation was not essential for the experimental purposes the hepatic artery HA was occluded instead of achieving a low-perfusion state with a balloon catheter, as would be done in practice in the clinical setting. The common hepatic artery was embolised proximally with a 3 ml 1:1 mixture Histoacryl® (Braun, Melsungen, Germany) and Lipiodol® (Lipiodol-Ultrafluide, laboratoire Guerbet, Aulnay Sous-Bois, France). The splenic artery (not shown) can be embolised in the same fashion to prevent splenic congestion.

[0033] The balloon catheters (2) and (3) in the ICV and PV, respectively, were connected to a lung machine (10) (Cobe VPCML oxygenator, Cobe Cardiovascular, Inc, Arvada, CO, USA) consisting of two independent roller pumps (Cobe/Stöckert, model 10-30-00, Munich, Germany). An extracorporeal veno-venous bypass was established by connecting the mesenteric outflow catheter (3) and a catheter (5) in the left femoral vein (22 Fr. Cannula DIITF022L, Edwards Lifesciences LLC, Irvine, CA, USA) to a catheter (6) in the right axillary vein (18 Fr. 7326 perfusion cannula, Lifestream International, The Woodlands, TX, USA). The veno-venous

bypass was supported by a centrifugal pump (20) (Medtronic BIO-Medicus, Inc, Eden Prairie, MN, USA) and primed with 700 ml saline (0.9%).

[0034] The perfusion medium consisted of intrahepatically trapped blood and 700 ml Gelofusine® (Vifor medical SA, Sempach, Switzerland). Only materials that are applicable in patients were used. The artisan will appreciate that all interventional radiological procedures may be guided by fluoroscopy (BV 300 Plus Philips Medical Systems, Best, The Netherlands).

[0035] After insertion, all balloons were inflated. Once a hemodynamic stable situation was achieved and maintained, leakage was first visually checked by injecting a contrast agent (Telebrix 350, Laboratoire Guerbet, Aulnay-sous-bois France) in the mesenteric bed and the isolated ICV segment. Leakage of perfusate into the systemic circuit was monitored by adding 2×10 MBq ^{99m}Tc -pertechnetate (^{99m}Tc) to the isolated circuit and the radioactivity level in both the systemic and isolated circuit was subsequently measured as previously described and set forth in more detail in Runia R.D., et al., "Continuous Measurement of Leakage During Isolated Liver Perfusion with a Radiotracer", Int J Rad Appl Instrum B, Vol. 14, pp. 113-8, (1987).

[0036] In these experiments, the SCV was surgically clamped, as in Fig. 1A, to exclude leakage from this site. To achieve intrahepatic pressure control, the blood flow through the liver (L) was reversed (inflow through the ICV, outflow through the PV) and negative (suction) pressure was applied to the PV. The negative pressure was varied from 0 to 30 mmHg and the effect on intraportal pressure, indicative of intrahepatic pressure, and leakage of ^{99m}Tc to the systemic circulation during IHP was monitored. After the data from the IHP with the surgical clamp were obtained, the experiment was stopped.

[0037] After finishing the first series of experiments, a second series of experiments was started with exactly the same set-up as shown in Fig. 1A. However, after confirmation of a leakage-free liver perfusion with ^{99m}Tc with the suprahepatic clamp, the clamp (1a) was replaced by an occlusion stent-graft (1b) of Fig. 1B. Then, a second dose of ^{99m}Tc was administered to determine whether the occlusion stent-graft (1b) could also occlude the SCV and whether identical intrahepatic pressure and leakage data could be obtained. In addition, the liver was flushed for approximately 10 minutes with 2 litres saline after perfusion to determine whether and effective wash out could be achieved with the devices and methods according to the invention.

[0038] Separate experiments using pigs were performed. One experiment was prematurely stopped because of an aberrant infrahepatic venous anatomy precluding cannulation of the ICV (i.e., interrupted ICV with hemi-asygos continuity). Otherwise, all newly developed minimally invasive materials were able to be introduced without difficulty. After isolation from the systemic circulation the liver was perfused at a flow of 300 ml/min. The flow in the veno-venous bypass ranged from 0.9 to 1.6 l/min. The pigs were hemodynamically stable during perfusion.

[0039] Referring to Fig. 2 the first set of experiments ($n = 4$) showed that the infrahepatic occlusion balloon (2) did not show any leakage as seen with contrast injections. When the SCV was surgically clamped to exclude leakage from this site (Fig. 1A), tests with varying pressures applied at the PV revealed a clear relation between the suction pressure at the outflow site and the intraportal pressure. As shown in Fig. 3, a negative pressure of 30 mmHg applied at the PV resulted in a significant decrease of the intraportal pressure to a mean of 2.4 mmHg ($P < 0.05$).

The experiments with this set-up showed a leakage-free IHP in all experiments, but only when suction pressure of 30 mmHg was applied at the PV. The artisan should appreciate that other suction pressure valves, such as between 25-35 mmHg may be applied at the PV to a suction valve of 30 mmHg is most preferable. As a result, as shown in Fig. 4, the intraportal, i.e., intrahepatic pressure, was maintained low whereas nearly instant leakage occurred when the suction pressure was not applied (Fig. 4).

[0040] In the second set of experiments the surgically placed clamp (1a) occluding the SCV was replaced by the retrievable occlusion stent-graft (1b) (Fig. 1B). The occlusion stent-graft (1b) did not reveal any leakage as seen with contrast injections (Fig. 5). As shown in Fig. 5 no contrast agent is visible in the SVC (thick arrow-head), indicating that no leakage occurs through the suprahepatic occlusion stent-graft. Three consecutive experiments confirmed the data from the first phase of experiments, i.e. leakage-free IHP with the surgically placed clamp occluding the SCV. As shown in Fig. 6, nearly identical intraheptic pressure and leakage data were obtained with the retrievable occlusion stent-graft as occurred with the clamp (1a) (Fig. 4). In either case, no significant leakage could be detected. A 10-minute wash out with saline resulted in the removal of almost all ^{99m}Tc from the isolated circuit (Fig. 6).

[0041] As shown in Fig. 6, I: no leakage to systemic circulation after first dose ^{99m}Tc is administered in isolated circuit while the SCV is occluded by a clamp; II: clamp is replaced by retrievable occlusion stent-graft, first dose ^{99m}Tc distributed in both isolated circuit and systemic circulation; III: no leakage to systemic circulation after second dose ^{99m}Tc is administered in isolated circuit while the SCV is occluded by a retrievable occlusion stent-graft; IV: almost all

^{99m}Tc is removed from the liver after flushing the liver with 2 litres saline for approximately 10 minutes.

[0042] As shown in Fig. 7, catheter occlusion diameters in the various veins may range from 20 to 40 mm for the ICV and SCV and from 15 to 25 for the PV. Catheter lengths may range from 20-30 mm for the SCV, whereas the ICV length is 80mm; and the PV length is 10 mm. The distance between the ICV catheter (2) and the clamp (1a) or stent-graft (1b) ranges from 8-12 mm. Flow-rates in the various vessels range from a minimum of 50 ml/min in the HA, to a maximum of 3000 ml/min in the femoral vein to axillary vein bypass. Other values pertinent to the invention are evident in the table set forth in Fig. 7.

[0043] Preferably, the hub design of any catheter or stent-graft according to the invention does not limit flow rates. The catheters are preferably resistant to chemotherapy. No fast deflation is desired and average PTA is acceptable. Because a heart-lung machine is used no high pressure settings should be encountered. Negative pressures are preferably applied to the portal side so as not to collapse the catheter walls.

[0044] Although shown and described is what is believed to be the most practical and preferred embodiments of the invention, it is apparent that departures from the specific designs and methods described and shown herein will suggest themselves to those skilled in the art and may be used without departing from the spirit of the invention. The present invention is not restricted to the particular constructions described and illustrated, but should be construed to cohere with all modifications that may fall within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A method for isolated hepatic perfusion comprising:
 - isolating a liver from systemic blood circulation;
 - controlling intrahepatic pressure; and
 - infusing a chemotherapy agent to treat liver metastases.
2. The method of claim 1, wherein controlling intrahepatic pressure further comprises:
 - reversing blood flow through the liver; and
 - applying negative pressure to the liver at a portal vein.
3. The method of claim 2, wherein controlling intrahepatic pressure further comprises:
 - preventing the intrahepatic pressure from exceeding physiological intrahepatic pressure levels.
4. The method of claim 3, wherein reversing the blood flow through the liver further comprises:
 - causing inflow to occur through the infrahepatic caval vein (ICV); and
 - causing outflow to occur through the portal vein (PV).
5. The method of claim 4, further comprising:
 - clamping a suprahepatic caval vein (SCV); and
 - occluding the ICV;
 - the clamping, occluding and negative pressure combining to minimize leakage from the liver thereby isolating the liver from systemic blood circulation.

6. The method of claim 5, whereby isolating the liver comprises creating a veno-venous bypass of the systemic blood circulation using the clamping, occluding and negative pressure.
7. The method of claim 5, wherein the occluding of the ICV further comprises deploying a balloon catheter in the ICV.
8. The method of claim 7, further comprising occluding the SCV in place of the clamping.
9. The method of claim 8, wherein the occluding of the SCV is comprised by providing an occlusion stent-graft in the SCV.
10. The method of claim 7, wherein the negative pressure applied at the PV is within the range of 25-35 mmHg and preferably 30 mmHg.
11. The method of claim 9, wherein the negative pressure applied at the PV is within the range of 25-35 mmHg and preferably 30 mmHg.

Application number / numéro de demande: 2474377

Figures: 1A-1B-2-5

Pages: _____

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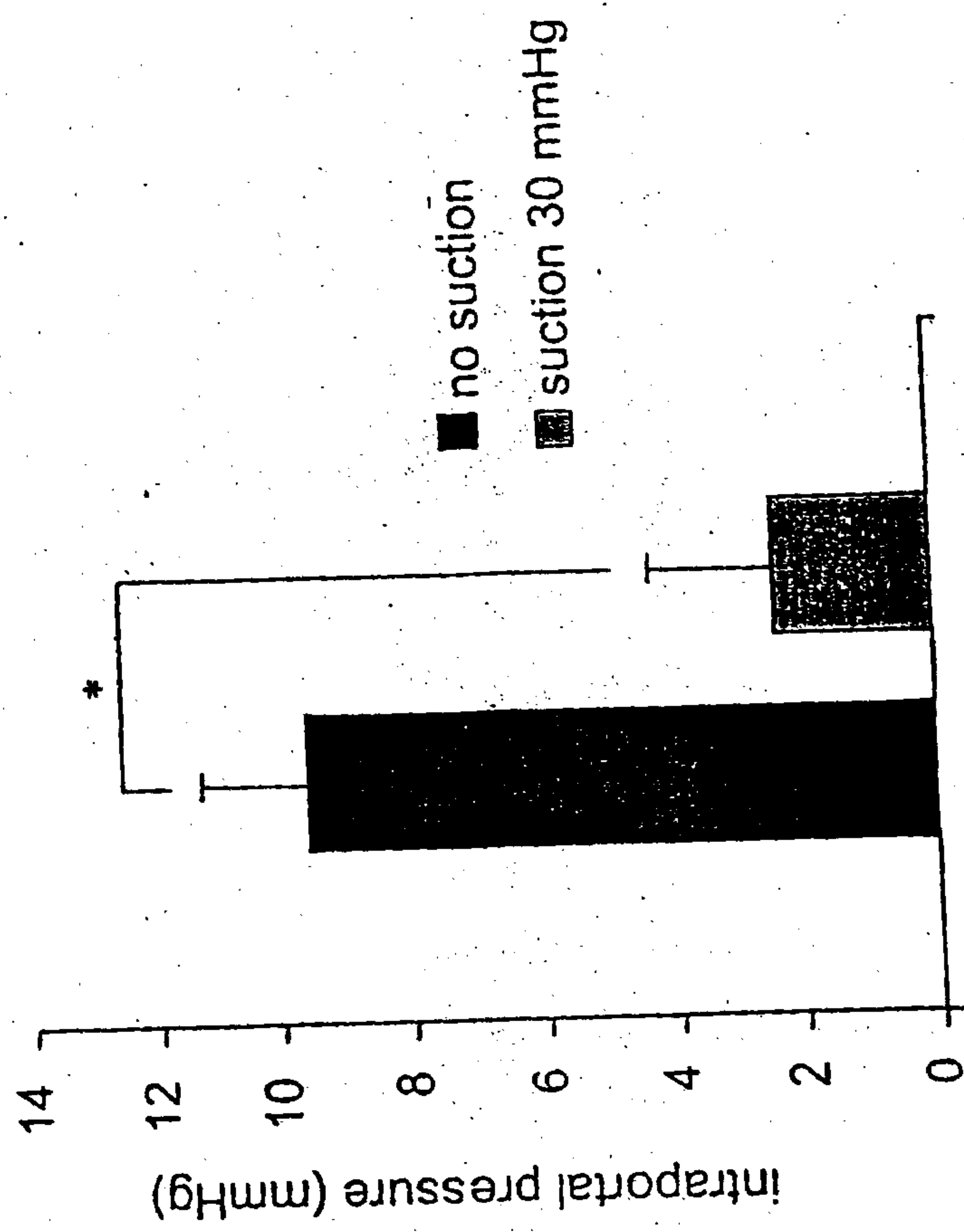


Figure 3

Figure 4

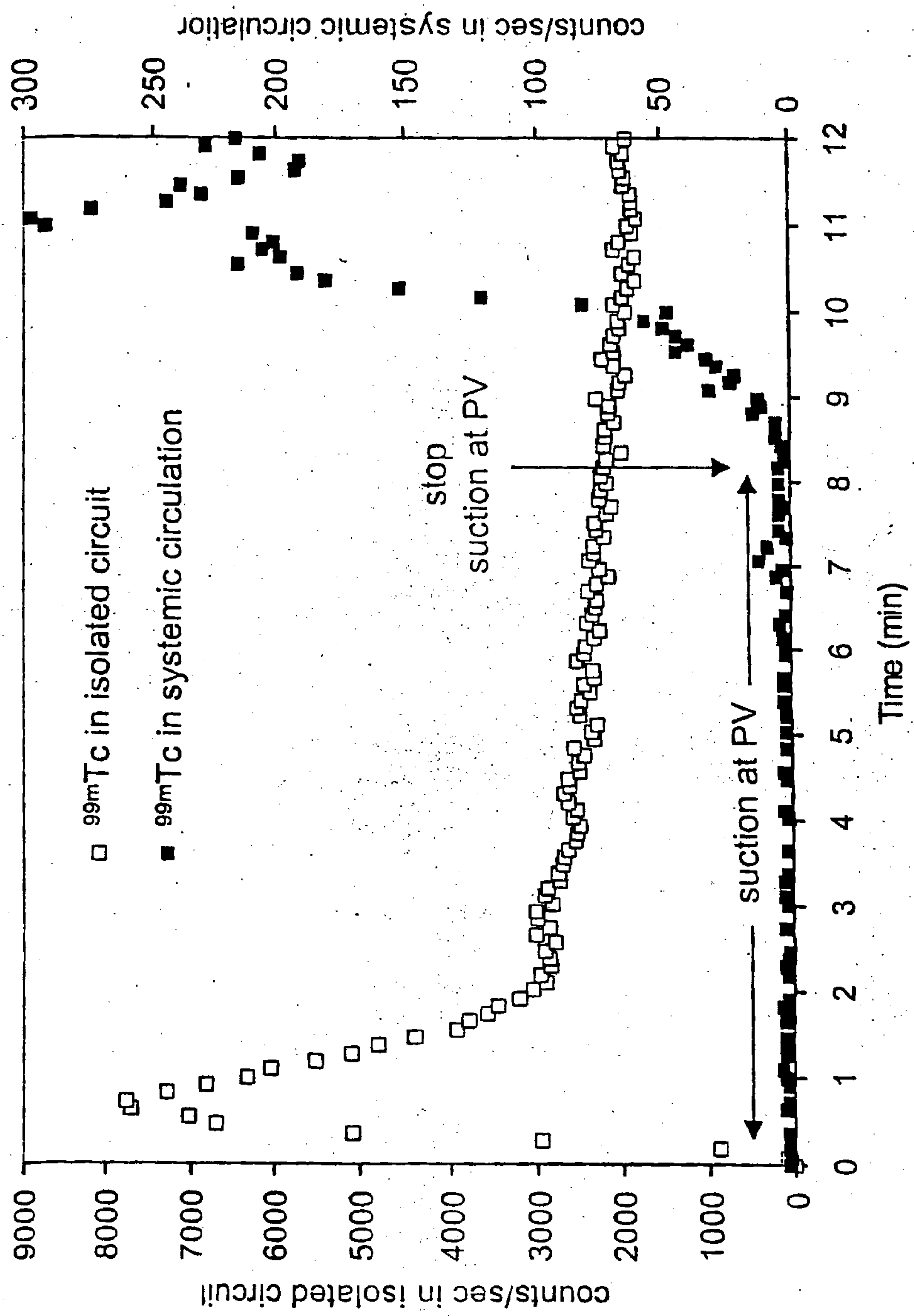


Figure 6

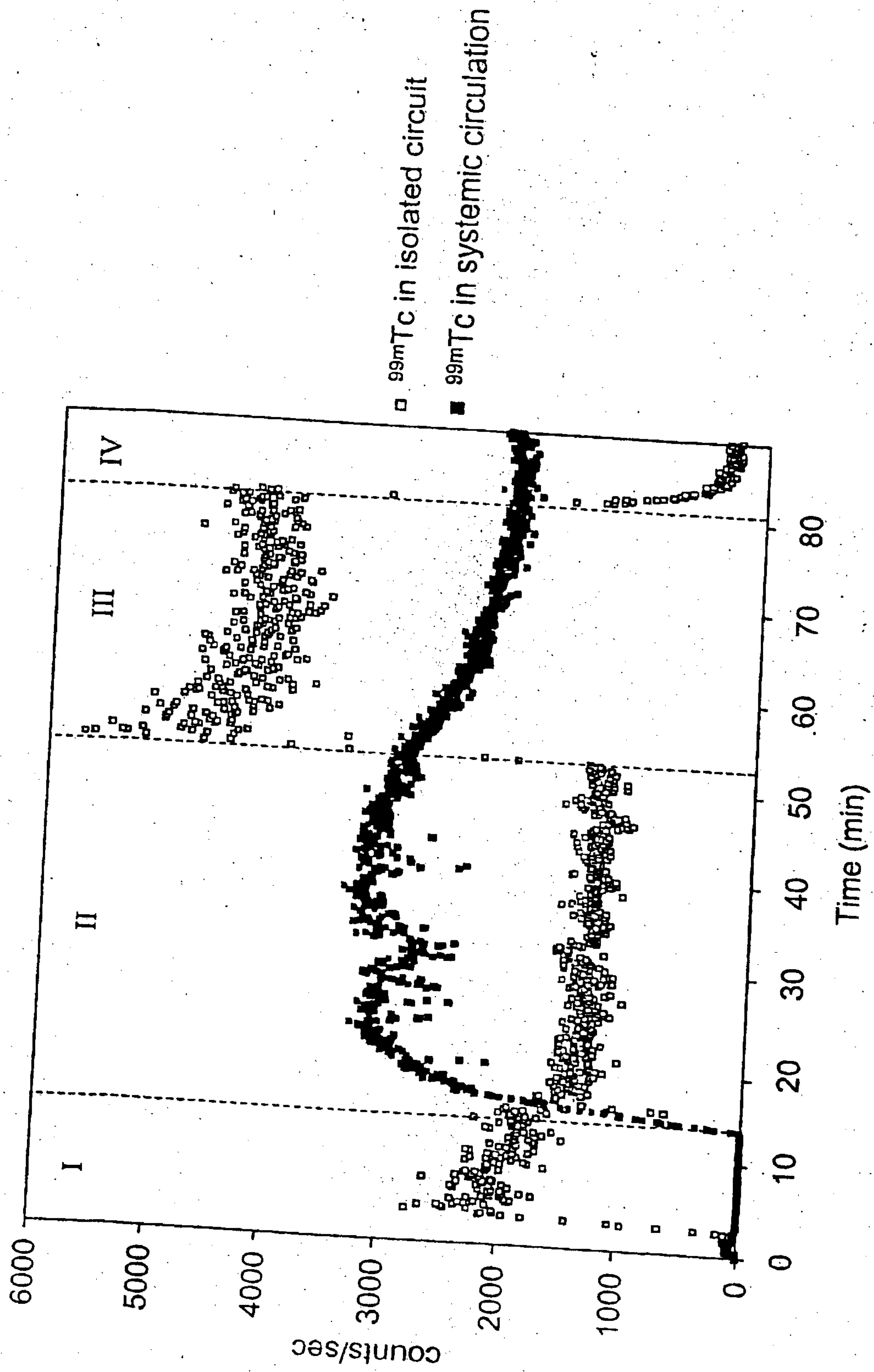


FIG. 7

EXEMPLARY DESIGN INPUT FOR LIVER PERFUSION SYSTEM

	Device	Occlusion diameter (in mm)			Length of occlusion (in mm)			Flow rate (in ml/min)			Shaft length - from hub to distal tip (in cm)	Max size Of puncture hole at site of introduction (in Fr)	
		Ave	Min	Max	Ave	Min	Max	Ave	Min	Max	Min	Max	
A	Vena cava, above renal vein	30	20	40	80			300	200	400	65	24	
B	Vena cava, above hepatic vein	30	20	40	25	20	30				65	24	
C	Portal vein, collecting from mesenteric circ.	20	15	25	10			400	300	500	25	12 to 14	
D	Portal vein, collecting from liver							400	300	500	25	12 to 14	
E	Hepatic artery (infusion only)							75	50	100	80	5	
F	Femoral vein to axillary vein bypass							2500	2000	3000	14	24	Femora vein
													axillary vein
		Ave	Min	Max									
	Distance between A and B (in mm):	10	8	12									
	(= between cranial end of occlusion A and caudal end of occlusion B - or in other words the length of space between the two occlusions)												