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Technique Article

Percutaneous Assisted Venous Return Isolated Limb Perfusion

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Abstract: Isolated limb perfusion (ILP) is a short term therapy used in conjunction with or without hyperthermia to deliver chemotherapeutic agents to localized areas, thus avoiding the severity of side effects caused by systemic administration. The most common treatment approach is hyperthermic isolated limb perfusion (HILP) with increased oxygenation of the chemotherapeutic perfusate for treatment of melanoma, soft tissue sarcoma, or synovial sarcoma. HILP traditionally involves open surgical dissection and direct cannulation. This approach involves significant morbidity including blood loss, infection, and nerve and blood vessel trauma. Isolated limb infusion (ILI) has been proposed as a less invasive procedure to reduce the morbidity and isolation complications of ILP. However, the warming and recirculation rates of ILI are inferior to traditional ILP. We describe a minimally invasive technique of angiographically placed percutaneous cannulae with vacuum assisted return for HILP. The extracorporeal circuit is comprised of a traditional hardshell oxygenator/reservoir and accommodates all acid base management strategies. This technique allows superior circulation of chemotherapeutic agents with minimal morbidities and can be performed on an outpatient or limited stay basis. **Keywords:** isolated limb perfusion, hyperthermia, assisted venous return. *JECT. 2009;41:231–234*

Isolated limb perfusion (ILP) was first described by Krementz et al. in 1956 (1). The addition of hyperthermia was later added to potentiate the effect of isolated high dose chemotherapeutic agents with hyperoxemia and vasodilatation of the perfused vasculature (2). Hyperthermic isolated limb perfusion (HILP) became the standard for surgical treatment of recurring melanoma to a limb. The technique generally involves surgical cannulation of the affected limb through direct visualization and isolation from systemic circulation by the external application of a tourniquet. After confirmation of isolation from systemic circulation, the isolated limb is warmed via the extracorporeal circuit until a desired tumor temperature is reached. Chemotherapeutic agents are added and circulated through the limb for a prescribed time period before removal with a copious exchange transfusion washout protocol (3).

Complications of HILP include bleeding, exposure to homologous blood products, surgical site infection, vascular damage, and difficulty in obtaining a high degree of isolation. Blood flow rates typically described with HILP follow the "Rule of 9" (3). This rule is based on a percentage of calculated cardiac output to the affected limb, 9% to arms and 18% to legs. Achievement of this flow rate requires surgical placement of appropriately sized cannula. Typical cannula sizes are 12–16 French for arterial cannulation and 16–20 French for venous. Cannulation site infections and complications account for the highest (13%) morbidity rate associated with HILP (3).

A simplified method of ILP was described by Thompson et al. in 1994 and termed isolated limb infusion (ILI) (4). Simplified extracorporeal circuits for ILI which negate the need for a pump or oxygenator/reservoir system have been described by McDermott et al. (5). ILI consists of a high efficiency blood heat exchanger and a syringe to circulate chemotherapeutic agents through the isolated limb. Percutaneous placed catheters in the femoral vessels avoid surgical cut down and significantly reduce morbidity (5). The simplified extracorporeal circuit eliminates the need for a heart lung machine, reduces operating room costs and the number of personnel needed. Due to the low flow, low pressure, technique of ILI, easier isolation and less leakage of toxic chemotherapeutic agents with resulting leucopenia are reported (5).

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Circulation of the affected limb during ILI is achieved manually with a syringe alternating between aspiration and injection. Blood flow rates are low and are limited by the speed of the operator. As a consequence, tumor warming rates are reduced and hyperthermia is primarily reliant on topical warming. Significant hypoxia and acidemia are experienced with ILI (5). Although the induced hypoxia is theorized to improve chemotherapeutic agent uptake, it does limit the time of vascular isolation and increases the systemic metabolic acid load post reperfusion.

Percutaneous assisted venous return isolated limb perfusion (PAVRILP) is a hybrid procedure that incorporates the benefits of HILP (higher flow rates, higher tissue temperature, and blood gas control), with the benefits of the less complex ILI (percutaneous cannulation, improved isolation, and reduced blood exposure). This technique incorporates many common perfusion practices such as reduced prime extracorporeal circuits, vacuum assisted venous return, and peripheral or remote cannulation of a target vessel.

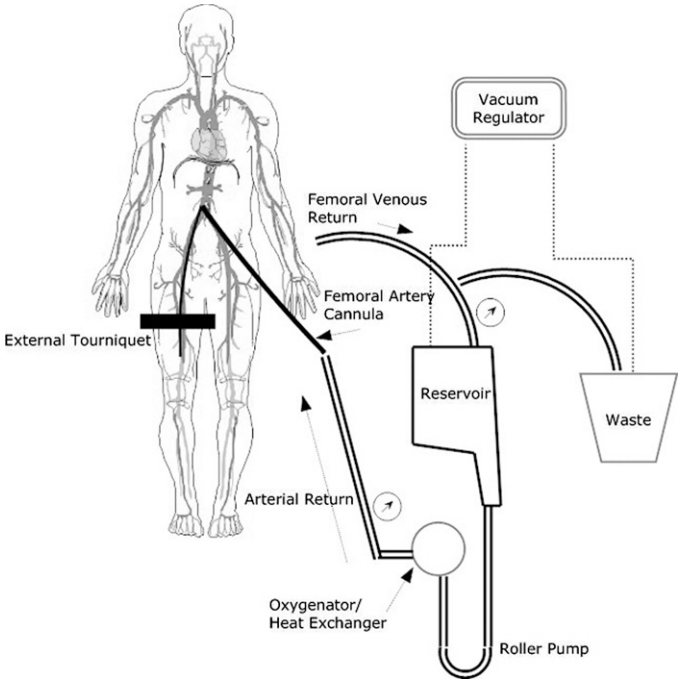

Figure 1. Schematic of PAVRILP circuit with contralateral percutaneous cannulation.

DESCRIPTION

The PAVRILP circuit consists of a pediatric RX05 oxygenator with vacuum assist venous return (VAVR) reservoir (Terumo Cardiovascular, Ann Arbor, MI) and a ¼ inch Smart™ coated perfusion circuit (Sorin USA, Arvada, CO). The circuit was assembled on an SIII heart lung machine (Sorin-Stockert Gmbh, Germany) which provides temperature, line pressure, level, and bubble monitoring. Vacuum regulation is provided by a VAVD controller (Maquet Cardiopulmonary AG, Germany) and water supply for both the extracorporeal circuit and patient blanket are provided by a Hemotherm™ heater cooler (Cincinnati Sub-Zero, Cincinnati, OH).

After assembly of the circuit, the heat exchanger is leak tested and the circuit is primed with 250 mL of Plasmalyte A (Baxter, Chicago, IL). Two thousand international units (IU) of porcine heparin (APP Pharmaceuticals LLC, Schaumberg, IL) are added to the prime. The prime is recirculated and warmed with the heater set to 42°C. The venous line of the PAVRILP circuit has a ¼ inch wye connector with 10 inches of ¼ inch tubing proximal to the venous inlet of the oxygenator. The short stub is connected to a standard suction waste container (Cardinal Health, Dublin, OH). The vacuum supply line is also wyed with one leg to the vent port of the oxygenator reservoir and the other to the waste collection reservoir. Both are connected to a vapor collection trap and then the vacuum controller (See Figure 1). This arrangement allows uninterrupted conversion from circulation in the PAVRILP circuit to waste collection during the washout phase simply by moving two clamps.

Since surgical exposure is not being performed, the patient is placed under a light general anesthesia. A systemic heparin dose of 5000 IU is administered. Activated clotting time (ACT) is determined to be greater than 250 seconds. Additional heparin is administered as required. Temperature probes (Genesee Biomedical, Denver, CO) are placed in the medial limb and respective tumor. The entire limb is wrapped in a water bath hyperthermia blanket, attached to the heater cooler set at the maximum water temperature of 42°C.

The contralateral femoral artery and vein to the affected leg are percutaneously cannulated with a 9 French × 100 cm Super Arrow-Flex® percutaneous sheath introducer set (Arrow International, Inc., Reading, PA). The catheters are guided into the affected limb and placement is angiographically confirmed. Placement is distal to a previously placed pneumatic tourniquet and proximal to the tumor location. Return from both cannula is tested by manual aspiration.

After confirmation of placement, the pneumatic cuff is inflated and 5000 IU of heparin is injected into each cannula. The cannulae are connected to the extracorporeal circuit via ¼ inch male perfusion adapters (Medtronic, Minneapolis, MN) and circulation is immediately begun. Vacuum assist is gradually increased to negative 40 mmHg to achieve an average flow rate greater than 350 mL/min. An ACT of the recirculating limb perfusate is confirmed and maintained at greater than 480 seconds with additional heparin boluses if needed. Gas flow to the oxygenator is

determined by the planned chemotherapeutic agent and surgeon preference.

Isolation of the limb is confirmed by injecting 1 mL of 10% fluorescein dye into the circuit. After recirculation for 5 minutes, the limb is then inspected at the tourniquet site with an ultraviolet Woods lamp to illuminate the adsorption of the dye by the vessels and dense tissue. With good isolation a clear demarcation is evident at the tourniquet site. Poor isolation is observed by fluorescence of the tissue proximal to the tourniquet. If leakage is suspected, pressure is increased in the tourniquet or an additional Esmarch bandage tourniquet is placed.

Isolation is also confirmed by monitoring changes in venous reservoir volume (3). With a vacuum assisted low flow technique, leakage is more likely from the venous system to the extracorporeal system than outward to the arterial system. This is evident by increasing venous reservoir volumes. Compensation for vascular bed dilation due to hyperthermia must also be accounted for. This usually occurs early in the procedure during the tumor warming phase. Monitoring reservoir volume changes over time is a critical aspect of pressure/flow balancing (3). Once the limb temperature reaches a target of 38.5°C or greater, the change in reservoir volume per 30 minute increment is evaluated. If the volume change is greater than 10% of the total volume flow, the leakage rate is considered excessive and additional steps are taken to secure the tourniquet. Activated clotting times are measured frequently during this initial warming and stabilization phase. Since the systemic blood is not fully anticoagulated, leakage will appear as a change in the systemic to extracorporeal ACT ratio. Confirmation with the ultraviolet Woods lamp can be done early on but becomes less helpful over time due to the short half life of the fluorescein dye.

After confirmation of isolation, chemotherapeutic agents are injected into the venous reservoir and allowed to circulate. The typical regimen at this institution is 7.5 mg/L of limb volume of melphalan divided into two doses and administered 15–20 minutes apart. If dactinomycin is prescribed, the dose is 75 μg/L of limb volume administered in two half doses 15–20 minutes apart. After administration of the final dose, recirculation is continued for 60 minutes or as prescribed. Blood gases and ACT are evaluated sequentially.

At the conclusion of the limb perfusion, washout is begun by simultaneously switching the clamp from the waste container to the inlet of the venous reservoir and from the reservoir vacuum source to the waste container. This diverts the venous return directly to the waste container under the same venous return conditions. Washout is performed using Plasmalyte A at a volume of three times the perfused limb's blood volume or until the venous return is clear. The crystalloid volume is chased with 500 mL of 5% normal human albumin. Perfusion is discontinued and the arterial and venous lines clamped.

The tourniquet(s) is then released and the affected limb is reperfused. The cannula is removed and compression is applied to the site. After reperfusion, a systemic blood gas and ACT are drawn. The ACT is allowed to decrease gradually and is not reversed unless it is greater than 200 seconds. This aids in preventing limb thrombosis. Protamine may be administered if there is difficulty in achieving hemostasis at the cannula site. All equipment is disposed of following proper chemotherapeutic disposal precautions.

DISCUSSION

HILP treatment of multiple melanoma of the leg is successful with complete remission in approximately 40% of patients and partial remission in 35–40% of patients (6). Multiple applications of HILP are generally contraindicated due to the complexity of this invasive procedure. The experience with ILI is less well documented but offers the benefits of being less invasive and providing the opportunity for multiple treatments. The limitations of ILI include limited recirculation and compromised hyperthermia delivery due to the low blood flow rates. Although improvements in melphalan uptake have been reported under conditions of hypoxia and acidosis, some authors still believe hyperoxia is beneficial (3).

The use of a less invasive micro-perfusion circuit for ILP has been reported as a blood conservation strategy (7). PAVRILP combines the benefits of both the traditional HILP techniques and the less invasive ILI. Table 1

Table 1. Advantages and disadvantages of different isolated limb perfusion (ILP) techniques.

Advantages	Disadvantages
Hyperthermic Isolated Limb Perfusion (HILP)	
↑↑ Recirculation	↑ Blood loss
↑↑ Hyperthermia	↑ Infection rate
	Single application
Isolated Limb Infusion (ILI)	
Less invasive	↓ Recirculation
Simple	↓↓ Warming rates
Improved isolation	Acidemia
Repeated applications	Limited ischemic time
Percutaneous Assisted Venous Return Isolated Limb Perfusion (PAVRILP)	
↑ Recirculation	Blood flow limitations
↑ Hyperthermia over ILI	Equipment intensive
Metabolic control	
Repeated applications	

Arrows represent the relative strength or weakness of that feature associated with a specific technique.

lists the specific advantages and disadvantages to each isolated limb perfusion technique. During PAVRILP blood flow rates of 40–50% based on the "Rule of 9" guideline are achievable. Enhanced warming rates over ILI help limit total treatment times. The regional anticoagulation strategy limits protamine exposure, prevents possible limb thrombosis, and helps with cannula site hemostasis. This decreases recovery time and opens the opportunity for multiple treatments if needed. Placement of the cannula in the contralateral vessels facilitates tourniquet placement and improves isolation.

Choosing an ILP extracorporeal circuit with an oxygenator allows the perfusionist control over the metabolic management strategy. Although hypoxia increases the tumoricidal effects of drugs like melphalan, a high pO_2 potentiates the action of alkylating agents (8). The PAVRILP circuit accommodates both strategies and multiple surgeon preferences simply by selecting the appropriate ventilating gas.

PAVRILP employs common perfusion strategies of VAVR and reduced prime circuits to limit homologous blood exposure while maximizing the delivery of hyperthermic chemotherapeutic agents in a controlled environment. Limitations are due to catheter design which restricts blood flow at acceptable extracorporeal line pressures. Additional development of a percutaneous catheter with acceptable flow characteristics is needed. The use of PAVRILP is a safe alternative to the more complex HILP and enhances the features of ILI. Additional study with outcome results is warranted.

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