Recipient of 1986 Scientific Presentation Award

Isolated Total Lung Perfusion Technique for Chemotherapy

Kim M. Schavey*, Michael R. Johnston, and Hilary S. Stanbrook
*PSICOR
University of Colorado Health Sciences Center
Denver, CO

Abstract

A perfusion technique was developed in the laboratory to isolate the pulmonary vasculature from the systemic circulation to administer chemotherapy selectively to the lungs.

Dogs weighing between 20 to 30 kilograms were placed on total cardiopulmonary bypass via cannulation of the femoral artery and inferior and superior vena cava. The aorta was cross clamped and the heart arrested with crystalloid cardioplegia to minimize collateral blood flow into the pulmonary circuit. The pulmonary artery and the left atrium were then cannulated for isolated pulmonary perfusion. Cisplatin was added to the pulmonary circuit and the lungs perfused for fifty minutes at normothermia. Following termination of pulmonary perfusion, the pulmonary vasculature was flushed with Dextran, the cross clamp removed and the lungs returned to systemic circulation. Cardiopulmonary bypass was terminated and the dogs recovered.

Random biopsies demonstrated uniform drug uptake throughout the lung tissue. Simultaneous sampling of systemic drug levels showed no crossover from the pulmonary to the systemic circuit thus indicating a truly isolated perfusion technique. Systemic crossover to the pulmonary circuit from the noncoronary collateral blood flow was minimized by controlling the perfusion parameters of both circuits. Hemopoietic depression from the cytotoxic drug and lung damage from the perfusion technique were both minimal.

A technique for isolated in-situ total lung perfusion for the treatment of lung cancers has been developed which allows delivery of high drug concentrations to the tumor, thus enhancing the possibility of reaching cytotoxic levels within the tumor, while avoiding systemic toxicity.

Introduction

The occurrence of lung cancer has continued to rise steadily in the United States and has now become the leading cause of cancer death in both men and women. Aggressive surgical resection continues to provide the most promising survival rates and should be performed whenever feasible if it is thought all the cancer can be removed. Unfortunately, the majority of patients will present with advanced disease and therefore will not be appropriate for surgical resection. We must then depend on other modalities of treatment in an effort to achieve palliation or cure. To date, no other treatment modality has provided a major increase in survival. It is therefore essential that new drugs, new drug combinations and new methods of drug administration be further developed.

At present, one of the most difficult tasks to accomplish in the administration of chemotherapeutic agents has been to reach the cytotoxic drug level within the cancer cell without exceeding the toxic level to normal cells within the body. As early as 1960, an extracorporeal perfusion technique was developed to isolate and perfuse a single lung in canines which allowed a dose of chemotherapeutic agent to be delivered to the isolated lung 175 to 200 times the toxic intravenous dose. Johnston and Minchin have more recently shown that isolated in-vivo lung perfusion is technically feasible. The following preclinical study describes the perfusion technique used in an ongoing pharmacologic and toxicologic study of isolated total lung perfusion with cisplatin.

Materials and Methods

As demonstrated in Figure 1, two complete perfusion circuits were utilized. The systemic circuit was composed of a Cobe Membrane Lung and a ¾ inch A-V loop. The pulmonary circuit utilized a Cobe Membrane Lung with a ¾ inch venous line, ¼ inch arterial...
line and a recirculation line in the A-V loop on the sterile field. A crossover line, between the two venous lines of both circuits, was used for volume exchange from one circuit to another. This line was used only prior to the drug being introduced into the pulmonary perfusate. The left ventricular vent was "Y'd" into the systemic and pulmonary circuits as well as into a waste container. Separate multipurpose suction catheters were available for each circuit. Standardized tubing lengths were used on the pulmonary circuit so any drug binding by the circuit components would be equal in all experiments.

The systemic circuit was primed solely with 1500 cc Plasma-Lyte A\textsuperscript{b} and the pulmonary circuit with 1000 cc whole canine blood and 500 cc Lactated Ringers to equal 1500 cc perfusate to which one gram calcium chloride and 5000 units heparin were added. The pulmonary perfusate was recirculated and warmed to 37°C. One hundred percent carbon dioxide and sodium bicarbonate were added to the circuit to achieve physiologic gases at normothermia before pulmonary perfusion was instituted. Additional oxygen was never required to achieve a normal pO\textsubscript{2} though occasionally the blender would be turned to 21% to rid the system of excess carbon dioxide.

Conditioned dogs, weighing 20–30 kilograms and having normal preoperative hematologic and hemodynamic test results, were selected for use. Following induction with gallamine and halothane, the dogs were anticoagulated with 500 units/Kg heparin. Cannulae were placed in the femoral artery and inferior and superior vena cava (Figure 2). Arterial pressures were monitored from the opposite femoral artery and central venous pressure from the internal jugular. Complete systemic cardiopulmonary bypass was instituted, the dogs cooled to 28°C and the lungs deflated. Phenylephrine was used to maintain mean arterial pressures between 30 to 40 mmHg.

The pulmonary artery and the left atrium were then cannulated. A pressure catheter and temperature probe were placed in the pulmonary artery through and distal to the cannula. Venting took place from the apex of the left ventricle. At this stage, all drainage from the left ventricular vent and multipurpose suction catheter were directed into the systemic circuit. The aorta was cross clamped and 15 cc/Kg crystalloid cardioplegia delivered into the aortic root. In the presence of an incompetent aortic valve, the vent drainage should be routed into the waste line to prevent further systemic hemodilution.

Pulmonary perfusion was then instituted and the circuit checked prior to the addition of cisplatin. Proper cannula placement was verified as severe lung damage can occur immediately if the pulmonary artery pressure rises above the physiologic from poor venous drainage. The system must also be checked for volume loss or gain from systemic leakage. Following completion of the pulmonary perfusion trial run, any excess volume gain in the pulmonary circuit may be removed by using the crossover line.

Twenty milligrams of cisplatin was added to the pulmonary perfusate over the next three to five minutes and recirculated for an additional five minutes. Pulmonary perfusion was initiated by completely unrestricted the venous return and beginning infusion slowly while watching for venous return. Flow was gradually increased to 1500 cc/minute on all dogs.

\textsuperscript{b} Travenol Laboratories, Inc., Morton Grove, IL 60015
and maintained for the entire perfusion time of 50 minutes. Physiologic pulmonary artery pressures at a mean less than 25 mmHg were maintained. Once pulmonary perfusion was instituted, the suction catheter and vent were routed into the pulmonary circuit to prevent systemic contamination with the drug. Subsequent cardioplegia doses of 10 cc/Kg were infused and then drained into the waste container to prevent excessive dilution of the drug. Drug levels were drawn from the pulmonic and systemic perfusate every ten minutes and volume changes in either circuit noted on the venous reservoir of the Cobe Membrane Lungs. Random biopsies were then taken at 15, 30 and 50 minutes into the perfusion run to document drug levels within the lung tissue.

To terminate pulmonary perfusion, the arterial line was clamped and the venous line left open. The pulmonary vasculature was then flushed with one liter of 40% Dextran in 0.9% NaCl using the cardioplegia system which was connected to the pulmonary artery line via a stopcock. The cross clamp was removed, the pulmonic cannulae removed and the dogs rewarmed. The vent and suction catheter were routed back to the systemic circuit at this point. To prevent possible contamination, the pulmonic lines were removed from the sterile field. When the heart recovered, systemic bypass was terminated and all pressure lines removed when the dogs were stable. Upon extubation, the dogs were placed in an intensive care unit that was warmed, humidified and oxygenated. Postoperative hematologic and hemodynamic studies were done at weekly intervals until sacrifice at sixty days.

Results

Systemic and pulmonic laboratory results are noted in Table 1. Hemodilution, reflected by a drop in hematocrit to as low as 16 percent, was directly influenced by poor urine output resulting from low systemic perfusion pressures. Blood transfusions were delayed until post-bypass hemoconcentration occurred following diuresis. Due to the dilutional effect from the systemic to pulmonic crossover via the bronchial circulation, pulmonic perfusate hematocrits were noted to slowly decrease with time. All blood gases were temperature corrected with pCO₂ lower at a core temperature of 28°C than at normothermia systemically. Pulmonary blood gases were maintained in the normothermic physiologic range to prevent vasoconstriction and decreased capillary perfusion which, if allowed to occur, would decrease drug levels within the lung tissue. Potassium levels did not rise significantly even though some hemolysis was noted in the pulmonary samples. Mean systemic and pulmonary blood flows and pressures are found in Table 2. Low flow, low pressure perfusion techniques were practiced systemically to minimize the volume crossover from the systemic circulation into the pulmonary circuit via the bronchial circulation. The pulmonary blood flow was maintained at 1500 cc/minute on all dogs to simplify kinetic studies on a recirculating system. Figure 3 reflects the relationship between bronchial blood flow into the pulmonary circulation and the length of perfusion. Due to the small population studied and uncontrolled outside variables, a statistically significant correlation could not be demonstrated between systemic flows and pressures, pulmonic flows and pressures and bronchial crossover into the pulmonary circuit. It was seen experimentally however, that the crossover volume decreased over time when systemic pressures and flows were dropped. This has also been demonstrated by other authors. Of the seven dogs perfused with cisplatin, no deaths were attributed to the direct effects of the drug (diminuting pulmonary edema and the inability to extubate.) One dog exsanguinated through the arterial line and another died following premature extubation during a postoperative study. Hemodynamic and hematopoietic studies in all dogs were normal postoperatively. Lung biopsies demonstrated uniform drug uptake throughout the lung. As expected, minor adhesions were noted at the time of autopsy.

Discussion

During perfusion, there was no gas flow to the pulmonic oxygenator. Gases, in the normal range prior to perfusion, tended to remain stable during the remainder of the perfusion period due to the low oxygen consumption of lung tissue (20ul O₂/g lung/minute). Hyperoxia was avoided to prevent endothelial damage from oxygen free radicals. Hypercapnia, acidosis and hypoxia are known to be the three major causes of pulmonary vasocostric-

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Lab Results (mean ± standard deviation)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pH</td>
</tr>
<tr>
<td>SYSTEMIC</td>
<td>7.44 ± 0.10</td>
</tr>
<tr>
<td>PULMONIC</td>
<td>7.40 ± 0.10</td>
</tr>
</tbody>
</table>
Table 2
Perfusion Parameters
(mean ± standard deviation)

<table>
<thead>
<tr>
<th></th>
<th>FLOW</th>
<th>PRESSURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYSTEMIC</td>
<td>56cc/kg ± 6</td>
<td>46mm Hg ± 9</td>
</tr>
<tr>
<td>PULMONIC</td>
<td>56cc/kg ± 10</td>
<td>9 mm Hg ± 2</td>
</tr>
</tbody>
</table>

Pressures were measured in the pulmonary artery distal to the perfusion cannula, and in the femoral artery.

tion. This effect is seen whether it occurs at the pre-capillary vascular level or in the alveolus. When the pH is lowered to 7.16, the pulmonary artery pressure rises by 40 percent. When the \( \text{pO}_2 \) of the pulmonary arterial and venous blood and the \( \text{pO}_2 \) in the alveolus are all lowered to less than 25 torr, the pulmonary vascular resistance increases by 49 percent. Pulmonary gases were therefore kept in the normal physiologic range to avoid pulmonary vasoconstriction.

The lungs were kept completely deflated during perfusion because capillary closure occurs whenever alveolar pressure exceeds capillary pressure. To obtain maximum flow distribution, the pulmonary arterial pressure was kept greater than the pulmonary venous pressure which in turn is greater than the alveolar pressure. It must also be kept in mind that as the venous pressure rises, increased edema is encountered.

The pulmonary circuit was primed with whole blood rather than crystalloid solutions to decrease pulmonary edema and the wet/dry weight lung tissue ratio, even though this permitted an increased amount of metabolite binding of the drug by plasma proteins. Drug dosage was determined on drug concentration per milliliter of perfusate rather than milligram per kilogram since earlier studies have already pointed out the poor correlation between body weight, lung weight and pulmonary blood volume.

Bronchial arteries arising from the aorta, subclavian, intercostals and right internal mammary arteries make it extremely difficult to isolate or temporarily ligate them during perfusion, nor would this be necessarily beneficial. Venous flow to the pulmonary veins constitutes almost all the bronchial venous return although some drains into theazygos, hemiazygos and mediastinal veins thus minimizing pulmonic to systemic crossover. There are many direct anastomoses in man between the bronchial and pulmonary circulations. The direction of flow in the bronchial circulation depends on the pulmonary artery pressure, systemic pressure, blood flow in the pulmonary and systemic circulation, temperature and hemodilution of both perfusates; the same factors that affect flow in any vessel. Neoplastic tissue is invaded by proliferative bronchial arteries. This fact produced a controversy over the benefit of lung perfusion for bronchogenic carcinoma whose nourishment is normally received by the bronchial circulation rather than the pulmonary circulation. With an increase in anastomoses between the two circulations and the ability to control the direction of bronchial flow, perhaps adequate drug concentrations could be achieved within the primary bronchial tumor as well as metastatic tumors from bone and soft tissue sarcomas that are fed by the pulmonary circulation.

A technique for isolated in-situ total lung perfusion for the treatment of unresectable lung cancers has been developed which allows for the delivery of higher drug concentrations to the tumor mass thus increasing the possibility of reaching cytotoxic levels in the tumor while avoiding systemic toxicity. Perhaps with regression of the tumor, it might become resectable at a later date. Further studies have demonstrated drug levels within the lymph nodes which raises the possibility of therapeutic treatment of nodal spread.

This technique was successfully utilized in a patient with bronchogenic adenocarcinoma. No complications were encountered from the procedure itself and drug concentrations within the tumor were demonstrated to be cytotoxic to some cancer cells in-vitro. From all indications, this perfusion technique may provide a viable alternative for delivering chemotherapy with a more positive outcome than those previously described.

Acknowledgment

Special thanks to Cobe Laboratories, for generously providing the pump and the disposables for use in this study.
References


