

## Isolated hepatic perfusion: a regional therapy for liver cancer

Zhi-Wei Yang and Ge-Liang Xu

Harbin, China

**BACKGROUND:** Many treatments have been proposed for non-resectable primary or secondary hepatic cancer but the results have been disappointing. Isolated hepatic perfusion (IHP) was attempted five decades ago but it has been accepted recently after spectacular tumour responses were obtained by several phase I-II trials.

**DATA SOURCES:** An English-language literature search using MEDLINE (2003), Index Medicus (2003) and bibliographic reviews of books and review articles. IHP and its history and recent clinical application.

**RESULTS:** IHP offers unique pharmacokinetic advantages for locoregional chemotherapy and biotherapy. Surgical isolation of the liver and percutaneous techniques using balloon occlusion catheters are reliable and safe. They appear to have significant efficacy even in patients with advanced tumor burden or those with tumors refractory to other types of therapy.

**CONCLUSION:** IHP which has been developed in recent years is becoming a promising strategy for the treatment of unresectable liver cancer.

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**KEY WORDS:** isolated hepatic perfusion; liver carcinoma; regional chemotherapy

### Introduction

For a long time, surgical resection has been the major treatment of patients with liver cancer.<sup>[1]</sup> Most patients with such disease have been in their middle or terminal stage when they are diagnosed, and the number of patients with resectable tumor is less than 20%. Thus non-surgical therapy for unresectable liver cancer plays an important role.<sup>[2]</sup> Generally patients with

primary or metastatic liver cancer need chemotherapy, but systemic chemotherapy is not effective. A number of regional therapies in clinical trial share the advantages of intensified therapy at the site of tumor while minimizing or eliminating unnecessary systemic exposure to toxicity. One of such approaches is vascular isolation and perfusion, known also as isolated hepatic perfusion (IHP), by which the liver is treated with large-dose chemotherapy and/or biological agents under hyperthermic conditions. Although only a few of centers have reported substantial experience with this procedure, it appears to be significantly efficacious even in patients with advanced tumors or those with tumors refractory to other therapies.<sup>[3]</sup>

### Development of IHP

IHP mainly involves isolating the hepatic circulation from the general systemic circulation by occluding blood vessels around the liver. By utilizing the extracorporeal circulation equipment consisting of a reservoir, heat exchanger and oxygenator, for infusing perfusate containing high concentrations of chemotherapeutic drugs into a catheter cannulated in the hepatic artery and/or portal vein, hepatic vein outflow is collected with a cannula in the intrahepatic vena cava and returned to the perfusion circuit (Fig. 1). With such continuous rotative, durative perfusion, chemotherapeutic agents of high concentration delivered to the region can kill tumor cells. Simultaneously, the hepatic circulation being isolated entirely from the general systemic circulation can greatly alleviate or avoid drug toxicity by preventing the distribution of cytotoxic agents through the systemic circulation.<sup>[4,5]</sup>

Regional organ perfusion of cell inhibitor was designed first by Klopp in 1950, and further developed by Ryan and Greech in the late 1950s. They studied experimentally isolated organ perfusion of chemotherapeutic drugs associated with the extracorporeal circulation equipment. In 1960 Aust and Ausman utilized IHP to treat liver neoplasm, which is a primary test for this technique in clinical application. It was shown to be technically difficult to isolate the hepatic circulation and perfuse the liver while maintaining hemodynamic stability in the host animal. Leakage of the perfusate from the hepatic

**Author Affiliations:** Department of General Surgery, Heilongjiang Provincial Hospital, Harbin 150036, China (Yang ZW); Department of General Surgery, Anhui Provincial Hospital, Hefei 230001, China (Xu GL)

**Corresponding Author:** Zhi-Wei Yang, MD, Department of General Surgery, Heilongjiang Provincial Hospital, Harbin 150036, China (Tel: 86-451-5655061 ext 4062; Email: zhaoliangyan2003@163.com)

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into the system circulation was also common and it caused severe general toxic effects. Hence animal experiments and clinical research on IHP chemotherapy were not carried out at that time, but the technique of IHP was widely used in research into physiological function, pathological transformation, anabolism and catabolism of the liver, attempting to perfuse and preserve donor liver in liver transplantation. During this period, the methods for regional therapy of hepatic malignancies such as hepatic artery infusion (HAI) were established, while the techniques of liver transplantation and extracorporeal circulation turned to be mature, and the biological behaviors of liver tumor were recognized stage by stage, all of which furthered the progress of IHP.

In the 1980s, the theory of regional chemotherapy had been established on the conception that dose of drugs is a critical factor for cancer chemotherapy. Experiments in vivo confirmed that dose-response curve of most drugs was steep or more sensitive tumors respond to drugs of higher concentrations. IHP is able to deliver cytotoxic agents of high concentration to the organs loading neoplasm without leakage of drugs to the systemic circulation. Drug doses that would cause severe toxicities if delivered systemically can be confined to the liver by IHP, resulting in the ability to intensify treatment to the cancer-burdened region of the body. Again, scientists were interested in IHP chemotherapy. Researchers in the USA, Japan, the Netherlands and Germany performed IHP on animals, focusing on: (1) the impact of hyperthermic isolation perfusion chemotherapy on normal liver and liver tumor; (2) the development of techniques for isolation perfusion using a double lumen cannula for intracaval shunt, which is intended to simplify the process of operation; and (3) continuous monitoring of leakage of perfusate into the systemic circulation by adding radionuclide to the isolated circulation and the system, indicating IHP is more dependable and safe.

Since 1990, researchers in different countries have modified the techniques of IHP. Following the establishment of various experimental animal models, professionals began to investigate the effect of chemotherapeutic drugs of different concentration on normal hepatic function and on liver tumor. In IHP a variety of drugs were used, including 5-Fu, mitomycin, adriamycin, cisplatin, melphalan and biological regulator or tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). In perfusion, one single drug was replaced by several drugs in combination. Analyzing the pharmacokinetics, concentration of drugs in hepatic tissues as well as pathological changes of the liver ensured the better use of drugs with optimal concentration, endurable dose, and compatible approach in IHP. Rat model with hepatic neoplasm was adopted with emphasis shifting from the isolated effect to tumor response and animal survival. The result was compared with that of regional chemotherapeutic technique like HAI, which

had been used clinically.<sup>[6,7]</sup> To simplify the surgical procedure of IHP, shorten the time of operation, lessen possible syndrome and improve curative effect, large experimental animals such as pigs and dogs were used. Following the classic double-bypass technique, simpler methods were developed for the treatment of patients with liver cancer (Fig. 2). With the development of techniques of interventional radiology, the techniques of IHP were renewed constantly toward minimally invasive techniques. Ku et al<sup>[8]</sup> reported percutaneous isolation of the hepatic veins by a double-balloon catheter and extracorporeal chemofiltration hepatic venous isolation and charcoal hemoperfusion (HVI-CHP) of the drugs in

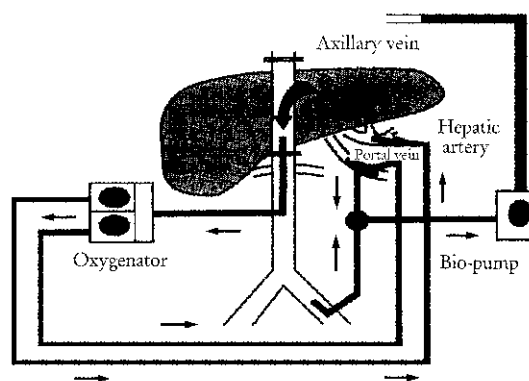


Fig. 1. Perfusion circuit with extracorporeal veno-venous bypass (Semin Surg Oncol 1998;14:262-268.).

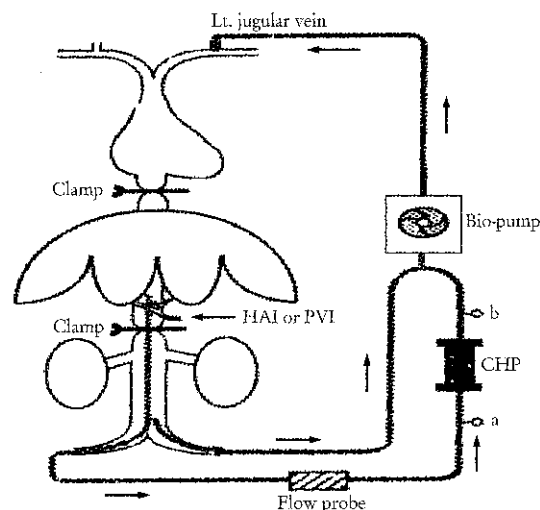
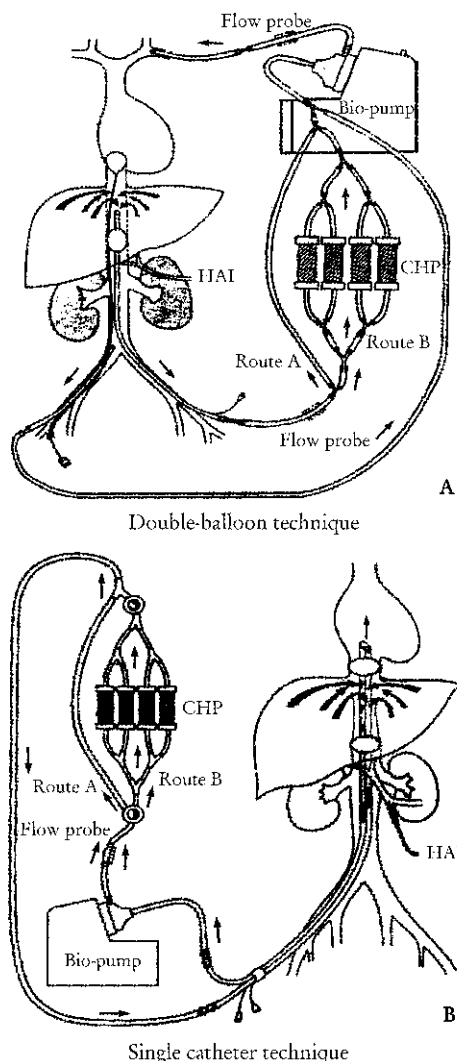


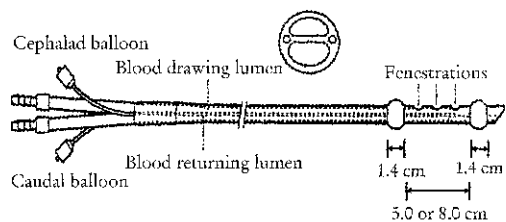
Fig. 2. Experimental design of the HVI-CHP system. Catheters were introduced into the retrohepatic inferior vena cava (IVC) and infrahepatic IVC from the right and left femoral veins, respectively. A catheter placed in the retrohepatic IVC was connected to a CHP filter and pumped to the left jugular vein together with infrahepatic IVC blood. HVI was achieved by clamping the suprahepatic and infrahepatic IVC. Hepatic venous blood flow rate was measured by an electromagnetic flow probe placed in the extracorporeal circuit (Cancer Res 1998;58:3339-3343.).



**Fig. 3.** Schematic illustration of the double-balloon technique (A) and the single catheter technique (B) for HVI-CHP. In both techniques, HAI of adriamycin was performed at a dose of 100 mg/m<sup>2</sup> for 15 minutes, and hepatic venous blood was isolated and solely directed through the CHP filters. HVI-CHP was maintained for 20 to 30 minutes after initiating drug infusion. Arrows indicate direction of blood flow (Am J Surg 1997;173:103-109.).

circulation (Fig. 3A). The technique of percutaneous hepatic isolated perfusion (PIHP) with four-lumen/double-balloon and extracorporeal chemofiltration used by Ku et al not only simplified the procedure of IHP but also made it repeatable (Figs. 3B and 4).<sup>[9]</sup> Ku et al reported the curative effect of PIHP; eleven (52%) of 21 patients in the single PILP group and 7 of 8 patients (88%) in the repeated PILP group had partial or complete response. The median durations of response in the responding patients were 6 and 21 months in the single and repeated PILP groups, respectively. The 1- and 2-year survival rates (single vs. repeated) were 57% vs 88% and 29% vs 70%, respectively.<sup>[10]</sup>

Meanwhile, IHP has aroused the interest of Chi-



**Fig. 4.** Diagram of the 4-lumen/2-balloon catheter. A cross sectional view is illustrated (Am J Surg 1997;173:103-109.).

nese researchers. Early in 1990, Wang and coworkers<sup>[11]</sup> at Zhongshan Medical University, Guangzhou, China reported isolated perfusion of pig liver in vivo. In this experiment, a single-balloon-triple-lumina catheter was used in intracaval shunting, with a large high dose of 5-Fu perfused exclusively through the hepatic artery. In Tongji Medical University, Wuhan, China, Xia et al also studied the changes in concentration of drugs in rat liver tissue, general circulation, inflammatory medium, and liver morphology.<sup>[12-14]</sup> In April 1997, Xiangya Hospital of Hunan Medical University cooperated with the American National Cancer Institute accomplished IHP for a patient with liver cancer.<sup>[15]</sup> Later 1999 at this hospital researchers assisted by Japanese specialists, treated three patients with terminal unresectable liver cancer under HVI-CHP by the 4-lumen/2-balloon technique. Postoperative recovery of the patients was uneventful, and long-term curative effect is under observation.<sup>[16]</sup>

### Clinical application of IHP

At present, clinical trial is still in its phase I-II.<sup>[17,18]</sup> For many years, the development of liver surgery and liver transplantation has increased the reliability of hepatic venous isolation and the security of IHP by monitoring leakage via radiative isotope in the systemic circulation.<sup>[19]</sup> In recent years, a great deal of animal experimental research have been involved in the use of different techniques of IHP and various drugs such as 5-FU, mitomycin, adriamycin, cisplatin, melphalan, and TNF- $\alpha$ . Specialists of the Netherlands, the USA, Japan and Germany have conducted clinical trials of IHP in the treatment of patients with liver cancer.<sup>[20,21]</sup>

Patients who are subjected to IHP have to meet the following criteria: unresectable advanced primary or metastatic carcinoma proved clinically, including multi-metastasis to the two lobes and the portal vein; carcinoma confined to the liver; carcinoma in the advanced or metastatic stage after treatment of other regional methods such as HAI, percutaneous ethanol injection (PEI); eligible laboratory tests should show a serum bilirubin level of less than 2 mg/dl, a 15-minute indocyanine green retention rate of less than 35%, a serum aspartate aminotransferase (AST) concentration of less than 300 IU/dl,

and a platelet count of more than 50 000/mm<sup>3</sup>, and a creatinine level less than or equal to 1.5 mg/dl. No pre-existing heart diseases and kidney failure occur, nor ascites, hepatic encephalopathy and esophageal veins caused by portal hypertension.<sup>[9]</sup> None of the patients have received any cytotoxic chemotherapy for at least 4 weeks before IHP.<sup>[10]</sup>

A phase II trial of IHP in patients with colorectal metastasis to the liver was performed in Leiden University Medical Center, Germany.<sup>[22]</sup> Seventy-one patients with unresectable colorectal carcinoma underwent IHP with a large dose of melphalan (200 mg) for 1 hour. Four of these patients died within 30 days after IHP, giving an operative mortality rate of 5.6%. Sixteen patients (22.5%) experienced grade 3–4 hepatotoxicity 1 week after IHP, which was transient and resolved within 3 months. The tumor response rate (complete or partial remission) was 59%. The median time to progression was 7.7 months (range 2.3–31.4 months). The overall median survival of patients after IHP was 28.8 months, with a 3-year survival rate of 37%.

Clinical practice proved that total hepatic isolation, effective washout after perfusion, safe anesthesia and intensive postoperative care are the critical factors for a successful IHP.

Classic IHP is time-consuming and traumatic. Occlusion of the major vessels around the liver, heparinization of blood and perfusion of a large dose of chemotherapeutic drugs may influence hemodynamics blood coagulation, and liver function. Savier et al<sup>[23]</sup> performed IHP in 10 patients, of whom one experienced hepatic artery thrombosis and 3 severe neutropenia. Minor complications included ascites and pleural effusion, but no death occurred 2 months after IHP. It can not be ignored that IHP does influence the function of the liver. Apart from chemotherapeutic drugs, ischemic or reperfusion injury should be reduced to minimal. The component of perfusate as well as the flow rate and pressure of perfusion must be different according to the use of different techniques and perfusion approaches. Appropriate physiological state of and protective effect on normal liver cells can be achieved. The perfusate commonly used clinically includes Ringer's lactate, equilibrium liquid, haemaccel liquid and isotonic brine and its capacity is about 1000 ml. The pressure and flow rate should be kept in a steady state after appropriate adjustment. Perfusion time ranges from 30 to 60 minutes, and the range of temperature should be controlled within 36–42 °C. Irreversible liver damage may be caused by longer time of perfusion or higher temperature.

## Problem and prospects

In clinical application, some problems need to be solved. First, IHP is generally used to treat patients with

unresectable liver cancer. If it is used as a preoperative or postoperative accessorial therapeutic method, its effect on regenerative function of the liver should be clarified. Second, the relation between the range of perfusion temperature, the dose of drugs and area of hepatectomy has not been defined in IHP. Third, long-term curative effect of IHP in treating liver cancer is not clear whether it is superior to other regional therapies or is effective in combination with other treatments. Fourth, how to reduce the syndrome caused by IHP is also a problem.

Isolated limb perfusion has been considered effective in patients with melanoma<sup>[24]</sup> and those with local aggressive soft-tissue sarcoma,<sup>[25]</sup> and the number of clinical research on IHP is increasing. Several clinical trials of phase I–II indicate that IHP can yield a high tumor response rate, and have unique pharmacokinetic advantages over regional chemotherapy and biotherapy for liver cancer.<sup>[26,27]</sup> With the recognition of biological behaviors of liver tumor, IHP chemotherapy combined with tumor resection, hyperthermochemotherapy, hypoxia, and biological regulation is of great potentiality in the treatment of liver cancer.<sup>[28,29]</sup>

## Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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