Bioartificial Liver Devices

Following acute injury, the liver is normally able to regenerate and will regain its function under appropriate physiologic stimuli. Liver failure occurs when the normal regenerative process is compromised and the residual functional capacity of the damaged liver is unable to sustain life.

Orthotopic liver transplantation is the only clinically proven effective treatment for patients with end-stage liver disease, with 1- and 5-year survivals approaching 90% and 75%, respectively. However, a major obstacle to transplantation is the severe shortage of donor organs, so that many patients die while waiting for a transplantable organ and others become too sick to undergo the operation by the time the organ becomes available.

Over the last 4 decades, many attempts have been made to develop artificial liver systems that would provide temporary hepatic support for patients with liver failure. Because the liver has tremendous regenerative capacity, patients with reversible forms of liver failure may spontaneously recover if provided temporary hepatic support, thereby averting liver transplantation and the associated risks of graft rejection and immunosuppression. In other patients, temporary hepatic support could serve as a "bridge" to transplantation until a suitable organ is found.

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Duplicating the liver's complex metabolic functions that are essential for survival has been a significant challenge. Two general categories of artificial liver devices have been developed, nonbiological and biological.

The Liver Dialysis Unit, developed by HemoCleanse, Inc. (West Lafayette, IN), uses the nonbiological method of hemodiadsorption. This technique is similar to hemodialysis, except that the dialysate solution is replaced with a suspension of pulverized sorbents. Toxins pass across cellulosic membranes from blood to the sorbent suspension, where they bind to small particles of charcoal or resin.

This device has received market clearance by the U.S. Food and Drug Administration for the treatment of acute hepatic encephalopathy due to fulminant hepatic failure or acute-on-chronic liver disease.

A multicenter, prospectively randomized clinical trial of this device was conducted, enrolling 56 patients with fulminant hepatic failure or acute-on-chronic liver failure and with grade II to IV hepatic encephalopathy, who received liver dialysis treatments for 6 hrs daily. This study showed a significant improvement in recovery of hepatic function or improvement for transplant in patients with acute-on-chronic liver failure, but not in patients with fulminant disease.

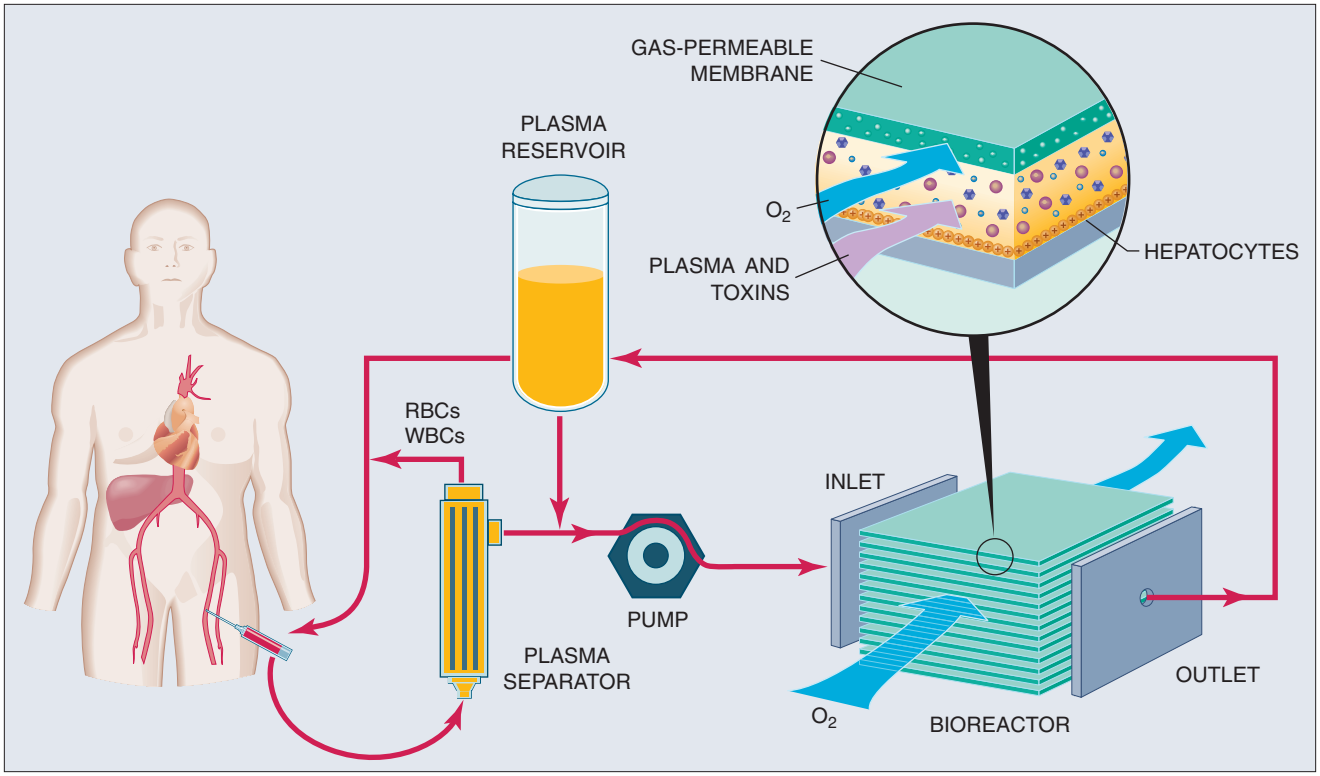
The Molecular Adsorbent Recirculating System, developed by Teraklin AG (Rostock, Germany), is another nonbiological liver support device using selective hemodiafiltration with countercurrent albumin dialysis. An albumin impregnated membrane allows the removal of albumin-bound toxic metabolites, such as bile acids and endogenous benzodiazepines, which may precipitate encephalopathy and multiorgan failure.

Several studies have shown that this device is able to lower serum levels of bilirubin and ammonia and improve the grade of hepatic encephalopathy. A few controlled studies performed in patients with acute liver failure or acute-on-chronic liver failure have indicated that albumin dialysis may improve survival. The results of two multicenter trials are expected by 2005.

In an effort to develop liver assist devices that provide synthetic and metabolic functions that are inadequately replaced in nonbiological-based systems, various biological-based approaches have been investigated. The hybrid bioartificial liver device, in which functional hepatocytes are housed in a man-made synthetic device, can overcome some of the problems seen in other forms of liver support.

These devices, with their metabolically active hepatocytes, can provide a broader range of liver-specific functions compared to nonbiological-based systems. However, for a bioartificial liver device to function optimally, it must maintain the hepatocytes in an environment that allows them to perform stable liver-specific functions.

In general, a bioreactor is inoculated with hepatocytes, and the patient's blood or plasma circulates through the device. The ideal bioreactor design would maximize mass transfer to the hepatocytes, allowing nutrients, including oxygen, and toxins from the patient's blood or plasma to reach the hepatocytes. The treated blood or plasma, including metabolites and synthetic products, is then returned to the patient's circulation. Achieving this task requires a large surface area for cell attachment with uniform cell distribution and flow.



The extracorporeal bioartificial liver perfusion circuit. The patient's circulation is connected to the plasma separator by venous catheters. Plasma is perfused through the bioreactor and then recombined with the blood cells and returned to the patient. Although several bioreactor configurations are undergoing clinical trials, the design shown is a stacked, flat-plate bioreactor module with internal membrane oxygenation that is currently under development at Massachusetts General Hospital.

Although it has been suggested that hollow-fiber devices are subject to substrate limitations due to the relatively large diameter of the fibers as well as the transport resistances associated with the fiber wall, most devices undergoing clinical trials are based on hollow-fiber technology.

The Extracorporeal Liver Assist Device, by Vital Therapies, Inc. (La Jolla, CA), is a hollow-fiber device that uses human hepatoblastoma (C3A) cells loaded into the extracapillary space, with the patient's blood flowing through the capillary lumina.

Although initial studies showed that the device was safe for clinical use and provided metabolic support to patients with late-stage liver failure, demonstrating efficacy has been more difficult. In a clinical trial of 24 patients with acute liver failure, half of whom were assigned to treatment with the device and the other half to the control group, no clinical survival benefit was seen. This finding was partly explained by the fact that the control group had a higher than expected survival.

A phase II trial with this device has been stopped due to lack of funding but will resume in 2004.

The HepatAssist (Circe Biomedical, Inc., Lexington, MA) hollow-fiber device uses porcine hepatocytes attached to collagen-coated dextran microcarriers. These hepatocytes are loaded into the extracapillary space, and patient plasma then flows through the capillary lumina. Within the flow loop is a charcoal adsorption column, which removes certain organic compounds from the plasma prior to contacting the hepatocytes.

A phase I clinical trial showed that this device could serve as a bridge to liver transplantation in patients with acute liver failure. A recent clinical study using the HepatAssist device with cryopreserved porcine hepatocytes showed significant neurological improvement in acute liver failure patients awaiting transplantation.

A multicenter phase II/III randomized trial of this device was in progress at 20 U.S. and European sites and included patients with FHF and primary graft nonfunction. An interim report indicated a

survival advantage in patients with FHF who received treatment with the bioartificial liver device. However, in May 2003, Circe Biomedical ceased operations due to lack of funding.

The Bioartificial Liver Support System, developed by Excorp Medical (Oakdale, MN), is a hollow-fiber device that uses porcine hepatocytes embedded in a collagen matrix. The patient's blood is perfused through the capillary lumina.

A phase I study using this device to treat four patients with acute liver failure and acute-on-chronic liver failure indicated that the device was well tolerated by the patients, although no conclusions regarding efficacy could be drawn. Results of the phase I/II trail are pending.

The LiverX2000 (Algenix, Inc., Minneapolis, MN) uses a hollow-fiber module in which porcine hepatocytes are entrapped in a contracted collagen gel within the fiber lumina, thereby creating a third space. This third space is perfused with medium while blood flows in the extracapillary space. The rationale for this design is that the gel-entrapped hepatocytes can receive nutrients from the flowing medium in the third space as the blood circulates through the extracapillary space. This device is currently in phase I/II trials.

In the design of bioartificial liver devices, maximizing oxygen transport to the hepatocytes is critical for optimal performance. To improve oxygenation, some designs use hollow fibers as conduits for oxygen delivery.

The Modular Extracorporeal Liver System (Charite, Campus Virchow-Klinikum, Berlin, Germany) consists of a CellModule, DetoxModule, and DialysisModule. The CellModule is a bioreactor in which discrete bundles of woven capillary membranes enter and leave the bioreactor, forming a three-dimensional structure. The hepatocytes are distributed in a collagen matrix on the membrane framework, and the extracapillary space is perfused with plasma. The capillary bundles allow independent oxygen supply and plasma inflow and outflow.

The DetoxModule is for albumin dialysis to remove albumin-bound toxins, and the DialysisModule is for hemofiltration.

A phase I clinical trial using only the CellModule bioreactor component, containing porcine hepatocytes, in eight patients with acute liver failure revealed that the extracorporeal liver support with this bioreactor was safe and well tolerated. Also, all treated patients were successfully bridged to transplantation.

In a recent case report, a patient with primary graft nonfunction was treated for 79 hours with this system, using primary human hepatocytes isolated from discarded transplant organs, and was successfully bridged to re-transplantation.

The Academic Medical Center Bioartificial Liver (developed at the University of Amsterdam, The Netherlands) uses a three-dimensional, spirally wound polyester matrix for hepatocyte attachment with integrated hollow fibers for oxygen delivery to the cells. In contrast to other designs, this system uses direct contact between the patient's plasma and the matrix-attached hepatocytes to improve bidirectional mass transfer.

In Italy, this device seeded with primary porcine hepatocytes is currently undergoing phase I trials in patients with acute liver failure. Of the first seven patients treated, six were successfully bridged to liver transplantation, and one showed improved liver function and did not need a transplant. No adverse events were noted.

In an effort to maximize oxygen availability to the hepatocytes and to reduce mass transport limitations, researchers here at the Center for Engineering in Medicine at Massachusetts General Hospital have recently developed a microchannel flat-plate bioreactor with an internal gas-permeable membrane through which oxygen is supplied. The hepatocytes are attached to a collagen-coated glass substrate and are in direct contact with the perfusing medium.

A gas-permeable membrane separates the liquid compartment from the oxygenating gas compartment. This design allows oxygen delivery to the hepatocytes to be decoupled from the medium flow, thereby allowing oxygen delivery and flow to be studied independently.

Using this design, we showed that stable hepatocyte function is dependent on adequate oxygen delivery to the hepatocytes and reduced shear stress on the hepatocytes. A scaled-up version of this bioreactor seeded with porcine hepatocytes was tested in a D-galactosamine rat model of liver failure. A significant reduction was seen in the plasma ammonia level and prothrombin time, and animal survival at 7 days was significantly improved in treated rats.

In the future, it is likely that the most effective extracorporeal liver support systems will combine the features of albumin dialysis and hemodiadsorption with cell-based devices. The challenges in advancing these systems will be met by combining the expertise of biomedical engineers, cell biologists, and physicians. Once these systems are developed, rigorous evaluation of them must be standardized through randomized controlled trials to determine their safety and efficacy for specific patient populations.

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