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Review

ARTIFICIAL LIVER: PRESENT OR FUTURE?

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SUMMARY – Modern medicine has learned to support many failing organs with machines: dialysis for kidney failure, respirators for breathing, and pacemakers and artificial heart for the heart. However, when the liver becomes too damaged to sustain life, the only medical resource is transplantation. For over 50 years, scientists and physicians have been attempting to develop an artificial liver. This article focuses upon current devices made to provide artificial liver support.

Key words: *Liver, artificial; Liver, artificial – trends; Liver failure – therapy; Liver transplantation – trends; Prognosis; Life support systems*

Introduction

The liver is a major factory in the human body. It produces many proteins, including albumin and clotting factors. It also balances the chemical environment, including glucose and amino acid concentrations, and it metabolizes or detoxifies many drugs and waste products of the body's metabolism. Because of the liver's structural complexity and functional diversity, our quest for finding an artificial replacement or semi-synthetic surrogate has been elusive. The American Liver Foundation reports that acute and chronic liver failure is the seventh leading cause of death in the United States of America (USA) (40,000 deaths in 1996). In the USA alone, it is estimated that 10 million people have some form of liver disease or impairment that results from infection, cirrhosis, drug overdose, chemical toxicity, and other causes. Approximately 750,000 patients *per* year are treated in USA hospitals for liver failure today. The increasing incidence of hepatitis C is anticipated to dramatically add to this number in the future. Over 30,000 people die of liver failure every year in the USA alone. Nearly 5,000 liver transplantations were performed in the USA in 2000, while the waiting list grew to over 17,000 patients[1]. Mortality rates are particularly high for those diagnosed with acute fulminant hepatic failure because hepatic regeneration is neither rapid enough nor sufficient to sustain the patient. Currently, the only treatment for acute liver failure is liver transplantation. Approximately 4,100 liver transplants are performed in the USA each year, but more than twice as many patients are on the waiting list. However, the supply of transplantable organs is far short of the demand. Those who qualify for a liver transplant often die while awaiting an allograft because of the scarcity of donor organs[2]. Thus there is a critical need of improved temporary liver support for potential transplant recipients as well as of patients with reversible, acute hepatitis who do not qualify for liver transplantation[3]. A multidisciplinary team of researchers from several countries of the world have developed an artificial liver device to treat patients with liver failure[4,5]. It is designed to be a bridge therapy, to support or stabilize patients until a transplantable organ becomes available or until their own liver can regenerate. In addition to acting as a bridge for patients waiting for transplants, the device will support people who need a second transplant because the first one has failed[6]. Based on this technology, the device could provide treatment for 250,000 patients admitted to hospitals in the USA each year for diseases associated with liver failure. It is estimated by the World Health Organization (WHO) that there are 1.5 million patients worldwide in need of liver

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support therapy[1]. Until now, there was no system available to solve the complications of liver failure according to the clinical practice requirements. Hemodialysis, the artificial kidney with about 60 million treatments of renal insufficiency *per* year cannot remove protein-bound toxins which must be metabolized by the liver. Other methods such as plasma perfusion over adsorbents are not accepted because of secondary complications (fibrinogen adsorption, and activation of complement)[7-11]. The best survival rates in hepatic failure have been recorded for liver transplantation[1,2,7]. However, at a cost of about 200,000 USD this is the most expensive alternative. The market for liver support is estimated to be substantial: 700 million USD in the USA and 1.4 billion USD worldwide[1]. The extracorporeal blood treatment, with the help of hepatocyte-based bioreactors, is very promising but still far from clinical acceptance[7,12,13].

Types of Artificial Liver Devices

There are two basic types of artificial liver devices: filter-based and living cell-based. The devices presently being used or tested in humans are summarized in Table 1.

Table 1. Types of artificial liver devices

Name	Manufacturer	Liver cell type	Availability
BioLogic DT/PF	HemoTherapies	None	*FDA approved
MARS	Teraklin AG	None	*FDA approved
Vitagen	Vitagen	Human liver cancer	Phase I safety study
Excorp	Excorp	Pig liver	Phase I safety study
Algenix	Algenix	Pig liver	Phase I safety study
HepatAssist	Circe Biomedical	Pig liver	*FDA approved

*Food and Drug Administration

Filter-based artificial liver

Three filter-based artificial liver devices are in use: BioLogic-DT System, BioLogic-DTPF System, and Molecular Adsorbent Recirculating System (MARS).

The BioLogic-DT System (HemoTherapeutics, Inc., San Diego, CA, USA) is a simple, sorbent-based extracorporeal hemodioabsorption system indicated for treatment of acute hepatic failure with encephalopathy or serious drug overdose[14,15]. The DT system utilizes a 2 L sorbent suspension that surrounds the membranes of a cellulosic or cuprophane plate dialyzer. This provides a much higher sorbent surface area and greater biocompatibility than conventional sorbent hemoperfusion columns. Changes in pressure of the sorbent suspension actuate the membranes to pull blood from a single-lumen venous catheter, pass it through the dialyzer, and return it through the same catheter at 200-250 mL/min. The sorbent suspension contains 140 g of powdered charcoal (1-75 m diameter with 2,400 m^2 surface area/g) and 80 g of cation exchanges (125 m diameter). The system can selectively remove hepatic toxins of less than 5,000 daltons with moderate protein binding, e.g., aromatic amino acids, glutamine, mercaptans, spermidine, putrescine, phenols, bile acids, lactate, false neurotransmitters such as glutamate and octopamine, neural inhibitors such as GABA, benzodiazepine-like substances, short chain fatty acids, ammonium, potassium, and magnesium. Urea is removed only modestly. The sorbent suspension is preloaded with glucose in order to return glucose to the patient while removing the various organic and inorganic toxins from the blood[16]. Automated monitoring of blood flow, temperature, fluid balance, air bubbles, and dialyzer integrity provides a high standard of safety. According to the manufacturer's instructions, no routine anticoagulation is required[12] (Fig. 1).

Numerous toxins produced in hepatic failure, including bilirubin, intact endotoxins, and cytokines such as TNF-a, IL-1b and IL-6, are strongly protein-bound or lipid-bound. These toxins are expecially important in patients with fulminant hepatic failure[17]. The clearance of these toxins is limited or prevented by the molecular weight cutoff of the membranes of dialysis, hemofiltration systems, and BioLogic-DT system. For these reasons, an add-on module to the DT system with the capability to remove protein-bound toxins and large molecular weight toxins including cytokines and bilirubin has been created[18].

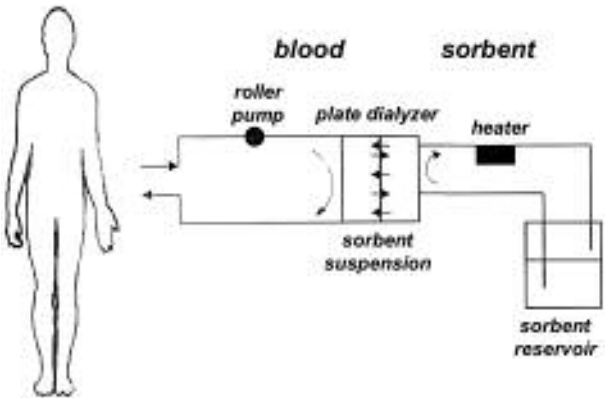

Fig. 1. The BioLogic-DT system

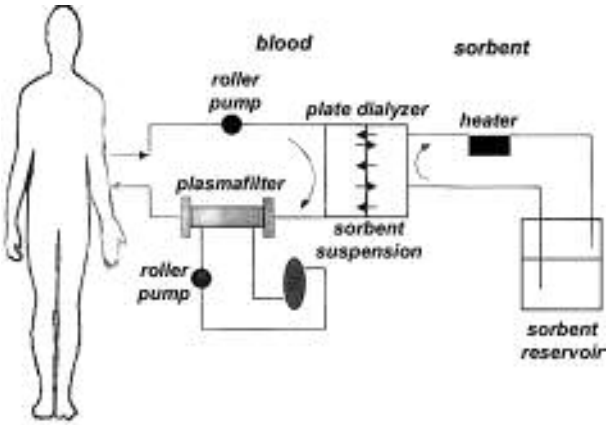

Fig. 2. The BioLogic-DTPF system

The BioLogic-DTPF System (HemoTherapies, Inc., San Diego, CA, USA) module includes a plasma-permeable hollow-fiber plasma filter placed downstream from the DT plate dialyzer, in which alternating positive and negative transmembrane pressure causes plasma to transiently pass into the PF membranes (in which direct interaction between plasma and charcoal can remove protein-bound and large molecular weight toxins), then returning it to the blood[4]. At blood flow rates of 200 mL/min, the system clears creatinine and aromatic amino acids at 120-160 mL/min, unconjugated bilirubin at 20-40 mL/min, and cytokines at 15-25 mL/min, during 6 hours of operation[19]. These liver support system used mostly in patients with acute liver failure have heavily relied on the principles of plasmapheresis, hemodialysis, and charcoal hemoperfusion[20]. These systems worked well for removal of water-soluble toxins, however, protein-bound toxins were difficult to remove. Plasmapheresis will remove these substances but with a low clearance equal only to the volume of plasma removed[19,21].

The Molecular Adsorbent Recirculating System – MARS (Teraklin AG, Rostock, Germany). This technology has been developed for the selective and very effective removal of small and medium-sized molecules from complex flu-

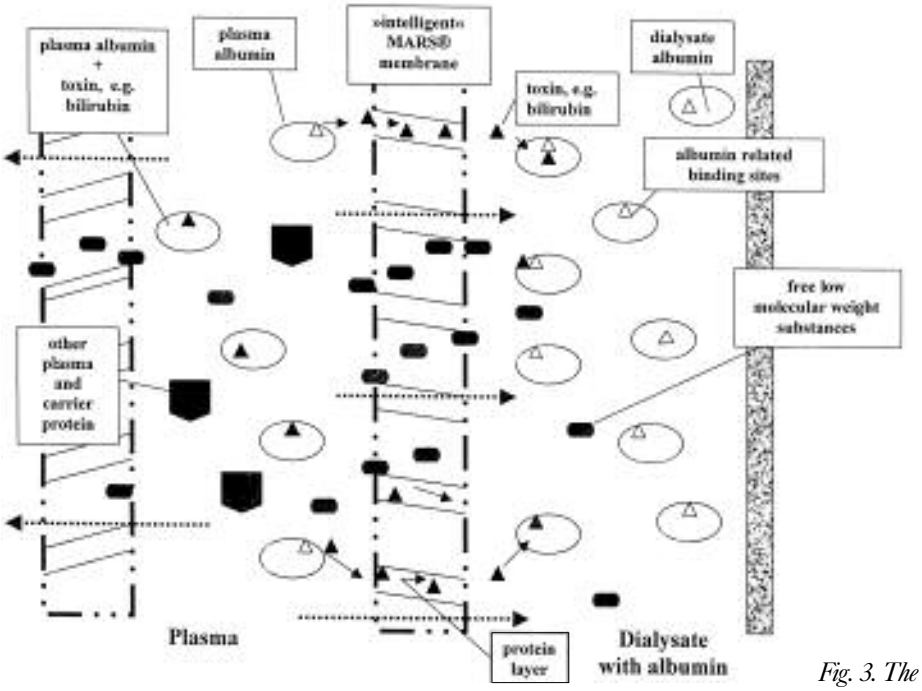

Fig. 3. The 'intelligent' MARS membrane

ids (e.g., blood). If these undesired substances are bound in a ligand-like manner to desired molecules of the fluid, their selective separation may be especially difficult. One medical example of such a need is a life-threatening liver insufficiency, when lipophilic, protein-bound toxins accumulate in the patient's blood due to inadequate detoxification by the liver. By the MARS technology, these lipophilic, protein-bound toxins are adsorbed continuously to one side of a special semi-permeable membrane that is constantly cleaned by selective molecular adsorbents (e.g., carrier proteins) from the other side by binding these toxins in a ligand-like manner. The molecular adsorbents are on-line regenerated by deligandization and recirculated[22]. MARS combines the specific removal of the toxins of liver failure (albumin-bound toxins) with the removal of water soluble toxins as in hemodialysis by 'intelligent' membrane transport – no removal of valuable and essential substances and proteins. This is a new combination of kidney and liver dialysis[23]. The patient's blood flows through a catheter and an extracorporeal circuit with a hemodialyzer containing a special hollow-fiber membrane. The other side of this membrane is cleansed by a recirculating albumin solution. Albumin is the natural carrier molecule in the blood for substances we want to remove, and has high selectivity and biocompatibility. High availability of free binding sites increases the efficiency of the transmembranous transport[24]. Since the 'liver toxins' are transported by protein binding, this mechanism produces the driving force for these toxins to pass the MARS membrane.

The washing solution is then on-line regenerated in a closed circuit (hepatic detoxification), and is itself dialyzed by a buffered aqueous solution (renal detoxification). After this regeneration, the membrane can be cleansed again by the purified albumin solution[25]. The MARS system is characterized by a very effective removal of protein bound and water soluble toxins. Substances like albumin, clotting factors, immunoglobulins and antithrombin III cannot cross MARS membranes because their molecular weight is too high. Investigations of different hormones such as T3, T4, etc. show that there is no significant loss in their blood concentration during treatment. In terms of drugs, several investigations are under way[26].

With MARS system, the fluid, electrolyte and acid-base balance can be very successfully managed. The ligandin-like binding proteins of MARS mimic the biologic detoxification process of hepatocytes. The advantage of MARS is its cost effectiveness due to recycling of toxin binding proteins.

The artificial liver support therapy systems are applicable in a variety of hospital sections, e.g., internal medicine, surgery, infectious diseases, intensive care units, and first of all at liver transplantation centers. Possible indications for artificial liver support therapy are shown in Table 2.

Endogenous accumulation of protein-bound toxins becomes life threatening especially in patients suffering from liver diseases who develop additional organ failure (e.g., kidney failure). A clinical example is that of jaundice, which indicates bilirubin accumulation[34,35]. It is often com-

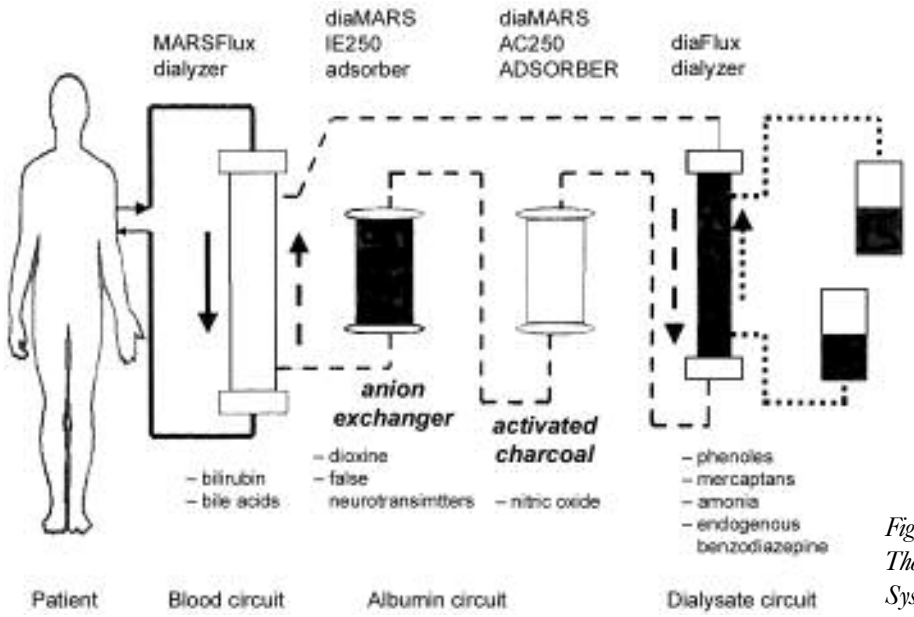

Fig. 4.
The Molecular Adsorbents Recirculating System (MARS).

Table 2. Possible indications for artificial liver support therapy

1) Acute deterioration of chronic liver failure with hyperbilirubinemia[23,27,28]
– viral hepatitis[20,27,29]
– alcoholic liver damage[3]
– hepatorenal syndrome[30,31]
2) Fulminant liver failure[19,26,27]
– viral hepatitis
– autoimmune hepatitis
– mushroom poisoning
– Wilson's disease[32]
– bridging to liver transplantation
3) Postoperative conditions[27]
– primary liver nonfunction
– aggressive tumor surgery
4) Other
– secondary liver failure due to sepsis (SIRS)[17,26]
– heart failure[27]
– acute intoxications with strongly albumin bound substances[33]

plicated with secondary injuries such as internal bleeding and decreased capacity of protein synthesis.

The beneficial clinical effects of artificial liver support therapy are shown in Table 3.

Advantages and benefits of filter-based liver support therapy are shown in Table 4.

The liver has four basic functions: excretion of a variety of toxins (especially protein-bound, such as bilirubin, cholesterol, and bile acids); metabolism of a variety of organic substances and supply of nutrients (generally not protein-bound, such as lactate and glucose), and drug biotransformation; immune and hormonal modulation (such as removal of bacteria, endotoxins, antidiuretic hormone, and cytokines); and synthesis of a number of macromolecules (clotting factors, albumin, and liver support substance). For excretion of small molecules of toxins, high permeability hemodialysis, hemofiltration, and hemoperfusion with coated charcoal were used[18]. For excretion of protein-bound toxins and large molecular weight toxins, plasmapheresis, plasma exchange, and plasma charcoal perfusion were used. For immune and hormonal modulation, plasmapheresis or plasma exchange was employed[7,8]. The first three functions can be partially but properly substituted with filter-based artificial liver support therapy devices. However, this does not improve survival in patients with severe encephalopathy, which strongly suggests that blood detoxification should be accompanied by replacement of biotransformation and liver synthetic functions. This seems possible to achieve only with the use of intact hepatocytes. The researchers call these devices bioartificial liver[42].

Table 3. Beneficial clinical effects of artificial liver support therapy

1. Support of liver function by improvement of liver excretory function liver and synthetic function
2. Regulation of blood homeostasis
3. Improvement of hepatic encephalopathy[19,36-39]
4. Reduction of jaundice[34,35,40]
5. Improvement of cardiovascular status
6. Improvement of impaired renal function (hepatorenal syndrome)[30,31]
7. Buying time for liver regeneration

The Living Cell-Based Artificial Liver (Bioartificial Liver)

Early on, the researchers realized that it would be pointless to attempt to mechanically replicate each of the liver functions. In an attempt to buy time, researchers have developed xenogeneic hepatocyte-based perfusion systems that can act as a bridge to liver allotransplantation, thereby allowing for additional time to find a suitable organ. Instead, they isolated live hepatocytes from pigs or human hepatoma hepatocytes, and incorporated them into the devices in hope that these cells would continue to perform enough of their function to make the bioartificial liver useful[43]. The metabolic support hypothesis states that while albumin-bound toxins may be important in causing

Table 4. Advantages and benefits of filter-based liver support therapy

1. Improvement of quality of life
2. Therapy of acute and chronic liver insufficiency
3. Well known principle
4. Mostly compatible with existing technology
5. Reducing mortality[20,26,27,41]
6. New therapeutic tool in addition to liver transplantation
7. Bridging to liver transplant
8. Shortening of intensive care unit stay[27]
9. Reduction of overall treatment cost

liver failure, patients with acute liver failure require an added metabolic assist that only liver cells can provide to help stabilize and reverse the course of liver failure. However, incorporating live cells presented a major technical challenge because the researchers needed to develop techniques to harvest and process living hepatocytes obtained from pigs. In the early stages, the researchers sacrificed a new pig for each patient, but to make the wider use of the bioartificial liver more feasible, they developed techniques to incorporate cryopreserved hepatocytes into cartridges. Cryopreservation allows for cell storage for future use and transport to treatment sites[44]. Different techniques of cell cultivation are used to keep human hepatocytes or liver cells alive by a constant supply of oxygen and 'culture medium' to feed on. The cells can survive for up to two months in these conditions[45]. Studies have shown that liver support systems based on viable hepatocytes can prolong life in animals having acute liver failure. Recent clinical trials in humans have shown very encouraging results for bioartificial liver's utilizing both porcine and human hepatocyte cultures[46]. Hepatocytes cultured into three-dimensional, tightly packed, freely suspended, multicellular aggregates or spheroids remained viable longer and had significantly higher levels of liver-specific functions compared to hepatocytes in a monolayer. Polystyrene, hydrogels, porous polyvinyl formal resin, water-soluble synthetic polymers, and porous polysulfone hollow fibers have also been reported as supports for hepatocyte cultures. These materials have either spherical shape, large surface area, exhibit large pores and high porosity, or are hydrophilic and biocompatible[47].

Three devices are undergoing initial safety trials (phase I). Two contain liver cells from a pig, whereas the VitaGen machine uses human hepatoma cells. The system uses a 100 kD molecular weight cutoff hollow fiber cartridge similar to those used in hemodialysis systems to house 60 to 100 g of primary porcine hepatocytes. The hepatocytes are isolated from 8-12 kg pigs by the collagenase perfusion technique and purified, then propagated and cultured within a bioreactor. The bioreactor consists of a hollow fiber module within which the liver cells attach to the matrix. A catheter connects the patient to the system, and blood is pumped from the patient in a manner similar to hemodialysis and undergoes plasma separation. The plasma is perfused through a charcoal column and then perfuses the hepatocyte impregnated bioreactor previously returned to the patient. The fibers act as a barrier to prevent proteins and cell bioproducts of pig cells from coming in direct contact with the patient's blood but allow for the necessary contact between the cells, so that toxins in the blood can be removed. The pore size varies depending on the report from 0.03 mm to 0.2 mm[43]. There are as yet no proven bioartificial therapies to treat patients with encephalopathy and liver failure. Review by the USA Food and Drug Administration (FDA) was necessary to assure the study uses proper mechanisms to screen and monitor

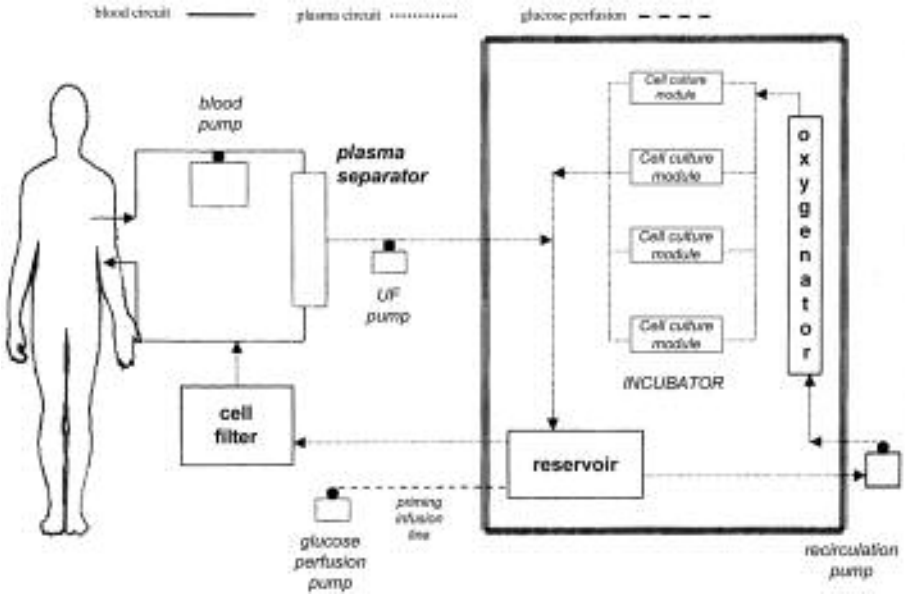

Fig. 5. The HepatAssist Bioartificial Liver System.

for potential animal viruses[48]. Experimental data demonstrate that intact viral particles are unable to cross the semipermeable membrane in the bioartificial liver for the planned use duration of 7 to 10 days[49].

The HepatAssist

(Lexington, Mass) is the only device that is beyond the safety trials.

Currently, the HepatAssist is being studied in critically ill liver patients with less than 20% chance of surviving. If the HepatAssist is proven to work, it will be the first bioartificial liver certified by the FDA[43]. The majority of the clinical experience comes from the Cedars-Sinai Medical Center, UCLA, USA. In 1997, they reported a phase one study in 31 patients who received acute support by a bioartificial device. As a group, this therapy had beneficial effects on intracranial pressure, level of consciousness, and Glasgow Coma Score. Furthermore, there were quantifiable improvements in liver transaminases and bilirubin. Of the 21 patients who were suitable for liver transplantation, 18 were successfully bridged to the procedure[50]. Four research centers in Germany, France, Spain and the United Kingdom are involved in the work funded by the European Commission since 1998. Each country has treated different groups of patients in order to test the bioartificial liver's efficacy, and each case has proved successful. So far, 11 patients have been treated. Ten patients had acute liver failure and one patient had chronic liver failure. All the patients were successfully transferred to liver transplantation[51,52]. The bioartificial liver seems attractive in terms of cost: a liver transplant with life-long treatment costs about 500,000 euro, whereas bioartificial liver costs around 2,500 euro[13,53]. However, more trials will be necessary to convince the medical community and, importantly, health insurers that the patient's relatively good health is due to the treatment with bioartificial liver.

Today, the future is as bright as ever for artificial liver support. No less than six different systems should be in use or have been tested in clinical trials for several years. Filter-based products are commercially available; however, the published data do not indicate that these machines will significantly help the patients[54-56].

Fortunately, cell-based therapies are now in clinical trials. *In vitro* and *in vivo* experimental animal studies have shown that isolated liver cells inoculated into a hollow fiber module can prevent hepatic encephalopathy in models of hepatic failure[57]. In a large animal (pig) model, both canine and pig hepatocytes in a bioartificial liver device were shown to metabolize cyclosporine and 19-nortestosterone[58]. Six-hour bioartificial liver treatment resulted in higher blood glucose levels, and lower serum ammonia and lactate levels[59]. The degree to which chemical function was due to hepatocytes (*versus* charcoal columns or mere plasma dilution) remained unclear, and the short follow-up time between the treatment and liver transplant made the assessment of clinical benefits of this device difficult[60].

In conclusion, despite promising case reports and small series, no controlled studies of mechanical devices have ever shown a long-term survival benefit. Thus, the removal of presumed toxins seems to be insufficient to support patients with fulminant hepatic failure, and the biologic function of the liver must also be replaced. Current technologies combine mechanical and biologic support systems in hybrid liver-support devices. The bioartificial liver and extracorporeal liver-assist device are both investigated in clinical trials. Although the trials seemed to have yielded good survival data when the devices were used as a bridge to liver transplantation, the type and degree of liver support provided by these devices remain uncertain. Thus, despite decades of great progress in the field of artificial liver support, no single technique alone has as yet provided adequate liver support. A hybrid system seems to be the best option at present. Still to be determined is the best tissue to use, how much liver tissue should be used, and optimal design of the bioreactor. Most of the cell-based systems are still in safety studies. All these devices represent tangible evidence that artificial liver support will provide new treatment possibilities for this millennium.

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Sažetak

UMJETNA JETRA: SADAŠNJOST ILI BUDUĆNOST?

S. Šefer i P. Kes

Suvremena medicina je sposobna pomoću strojeva gotovo u potpunosti nadomjestiti funkciju mnogih oštećenih organa: dijalizom bubrežnu funkciju, respiratorima plućnu funkciju, a elektrostimulatorima odnosno umjetnim srcem srčanu funkciju. Međutim, kada dođe do teškog oštećenja jetre, jedino medicinsko rješenje je transplantacija. Već više od 50 godina znanstvenici i liječnici pokušavaju načiniti umjetnu jetru. Ovaj članak usredotočen je na prikaz postojećih sustava za nadomještanje funkcije jetre.

Ključne riječi: *Jetra, umjetna; Jetra, umjetna – trendovi; Zatajenje jetre – terapija; Transplantacija jetre – trendovi; Prognoza;*