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# Complete Recovery of Deep Coma by Hemodiafiltration Using a Protein Leaking Polymethyl-Metacrilate (PMMA) Membrane

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## Introduction

It has recently been hypothesized that middle molecular weight substances (MW 1500 – 5000) inducing hepatic coma are present in the plasma of patients with fulminant hepatic failure (FHF) (1). Although hitherto developed artificial liver support systems (ALSs) are shown to be effective in reversing hepatic coma in mild FHF, they are of a limited value in the treatment of hepatic encephalopathy brought about by severe and long term FHF. Based on the assumption that the limited effectiveness of the ALSs in severe FHF is due to their inefficiency in removing the middle molecules, we have pioneered the method of hemodiafiltration (HDF) using a newly developed polymethyl-metacrilate (PMMA) membrane. PMMA has a higher permeability in the middle molecular range than does a polyacrilonitril (PAN) membrane. PMMA HDF induced a complete recovery from deep coma and long-term survival in a patient with severe acute liver failure.

## Methods

### Patient

A 35-year-old female photographer was admitted to Tokyo University Hospital on 14 Nov. 1984 because of liver function abnormality, including ascites and fever prevalent 4 months prior to admission. Physical and laboratory examinations revealed advanced liver function impairment with the presence of various auto-antibodies. Based on the assumed diagnosis of autoimmune hepatitis, the administration of 100 mg predonisolone daily was instituted. In spite of this treatment, the patient's liver function progressively deteriorated. Disturbances of consciousness first occurred on 7 Dec. 1984, and it promptly aggravated to Grade IV on 12 Dec. At this time, labora-

tory examinations revealed serum protein to be 5.9 g/dl, total bilirubin 22.4 mg/dl, total cholesterol 79 mg/dl, fibrinogen 67 mg/dl, prothrombin time (PT) 17.3%, antithrombin III 21%, prealbumin 5 mg/dl, alpha 2 HS glycoprotein 18 mg/dl, plasma tyrosine 505 nmol/dl, phenylalanine 584 nmol/ml, methionine 21 nmol/ml, and the molar ratio of branched chain amino acids to aromatic amino acids 0.67, indicating the presence of severe liver failure.

### Artificial liver support

ALS was performed a total of 19 times from 12 Dec. 1984 to 2 Jan. 1985 until the patient died. ALS included one plasma exchange (PE), two PEs followed by PMMA hemodialysis (HD), 6 PEs followed by PMMA hemodialysis (HD) and 10 performances of PMMA HDF with the infusion of 15 or 20 packs of fresh-frozen plasma (FFP). Blood was drawn from the saphena magna and returned to antecubital vein after treatment. PE was carried out using Plasmaflo. PMMA HD and HDF were performed using PMMA membrane hollow fibers (BK series, Toray Industries, Inc. Tokyo, Japan) (2). We had already assessed the biocompatibility of the PMMA membrane experimentally using dogs with acute liver failure, and concluded that the membrane was highly biocompatible even in cases of severe liver failure (3). In vitro studies show that the membrane is highly permeable in the middle molecular range. PMMA HDF was performed using a dialysis apparatus (Model TR-700, Toray Industries, Inc.) for 3 hours. The flow rate of dialysate (using a commercially available acetate buffer for artificial kidney) was 500 ml/min and that of ultrafiltration (balanced by the intravenous infusion of an electrolyte solution) 200 ml/hour. Because a considerable amount of serum albumin was known to be lost during PMMA HDF, 30 to 50 g of human albumin was administered during the treatment.

## Results

Figure 1 summarizes the clinical course after the start of ALS. Although the patient transiently exhibited minimum body movements after PE, her coma progressed to Grade V on 13 Dec. 1984. After two PEs followed by PMMA HD, the patient became responsive to pain stimulus and calling. Prompt recovery from coma was observed after one performance of PE with PMMA HDF. She began talking to her family from 16 Dec. and disorientation disappeared after 18 Dec. PE was discontinued on 21 Dec. and replaced by the continuous infusion of 15 or 20 packs of FFP. A Grade III coma which reappeared on 27 Dec. following the interruption of PMMA HDF and disappeared after the treatment was resumed. The patient died on 2 Jan. 1985 of rapidly developed respiratory failure induced by acute pneumonia. The autopsy revealed massive hepatic cell necrosis caused by extensive hepatic vein thrombosis. Findings suggestive of liver regeneration were not observed. No major adverse effects considered attributable to PMMA HDF were observed.

Serial determination of PT and serum prealbumin level, parameters of liver protein synthesis, disclosed that their values were low in spite of the administration of a large amount of FFP (Fig. 2, upper panel). Total bilirubin was lowered to about 10 mg/dl

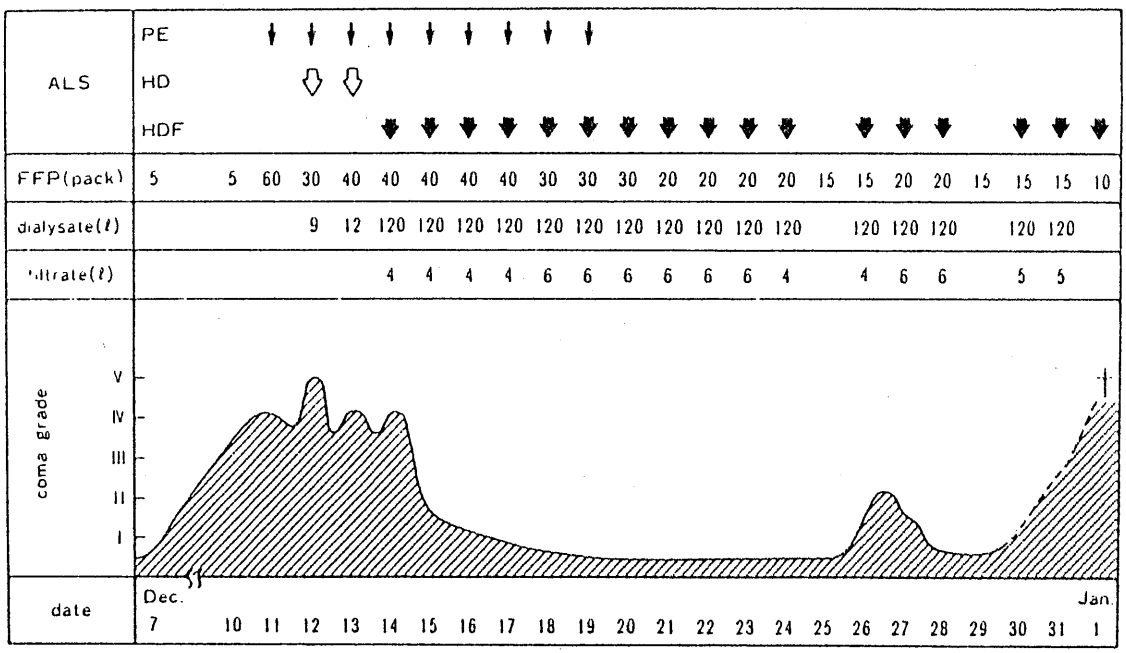


Fig. 1. Clinical course after the start of artificial liver support (ALS). ALS included plasma exchange (PE, ↓ ), poly-methyl metacrilate (PMMA) membrane hemodialysis (HD, ⇩ ) and PMMA hemodiafiltration (HDF, ⬇ ). Numbers in FFP section represent packs of fresh-frozen plasma (FFP) consumed each day.

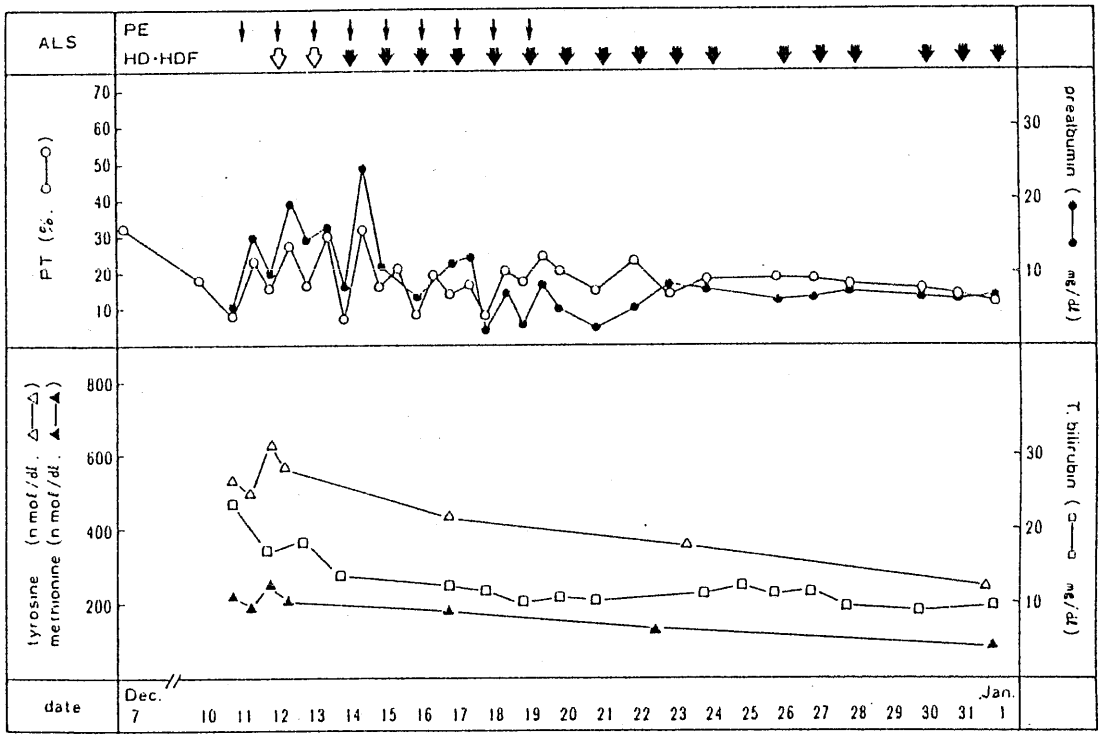


Fig. 2. Changes in plasma level of prothrombin time (PT) and prealbumin (upper panel) and total bilirubin, tyrosine and methionine (lower panel) during the course of artificial liver support.

from 16 Dec. because of the removal of 120 mg of total bilirubin on average by one performance of PMMA HDF. Although plasma tyrosine and methionine decreased by 50%, they were still above their normal ranges (Fig. 2, lower panel).

## Discussion

Seven years' experience with PE has shown us that although PE is effective in the treatment of coma brought about by mild FHF, it frequently ends in early brain death as the result of deepening coma caused by severe FHF. Our analytical study as to the effect of PE discloses that although PE is effective in supplying depleted plasma components synthesized by the liver, it is of limited value in the removal of accumulated toxic substances with a large body pool (4). Introduction of PMMA HDF was at first intended to augment the capability of PE to relieve hepatic coma by additionally removing putative coma-inducing middle molecules. After recognizing that PMMA HDF has the sufficient capability to sustain the patient in clear consciousness, we discontinued PE and replaced it with continuous FFP dripping.

Although, unfortunately, the patient died of acute pneumonia 19 days after the start of the ALSs, she might have survived long enough for the liver to regenerates provided due care was taken of complications. PMMA is expected to become a promising alternative mode to existing artificial liver support systems.

### References

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