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HEPATIC MICROCIRCULATION DURING TRANSIENT HEPATIC VENOUS OCCLUSION -INTRAVITAL MICROSCOPIC OBSERVATION USING HEPATIC VEIN CLAMP MODEL IN THE MOUSE -

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INDEXING WORDS

hepatic congestion; hepatic dysfunction; multiple organ failure, cardiopulmonary bypass

The purpose of this experiment was to evaluate the etiology of hepatic dysfunction in patients difficult to wean from cardiopulmonary bypass. We hypothesized that increased central venous pressure and subsequent hepatic congestion during weaning from cardiopulmonary bypass would lead to hepatic dysfunction. To induce hepatic congestion in mice, we clamped the hepatic vein for fifteen min, and observed the microcirculation of the liver using an intravital microscope during clamping and the following 30 min of reperfusion.

During reperfusion, non-reflow phenomenon, leukocytes adhesion to the wall of sinusoids, erythrocytes sludging, acute swelling of hepatic cells and narrowing of sinusoids were observed. These phenomena were indicative of warm ischemia-reperfusion injury of the liver itself. Based on these findings we concluded that, after repeated episodes of warm ischemia and reperfusion of the liver, hepatic cells would be damaged, and finally hepatic dysfunction was induced. To prevent hepatic dysfunction, repeated attempts to wean the patient from cardiopulmonary bypass should be avoided and increases central venous pressure should be prevented by early use of cardiopulmonary support.

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INTRODUCTION

Cardiopulmonary support system (CPS) or ventricular assist device (VAD) has been widely applied for the patients who could not be weaned from cardiopulmonary bypass. However, the mortality rate of these severe cardiogenic shock patients is still high. Approximately 45% of reported patients were weaned from circulatory assistance, and 25% survived to discharge. [1)] The main causes of death were bleeding, renal failure, sustained ventricular failure and multiple organ failure (MOF). We supposed that increased central venous pressure and subsequent hepatic congestion during weaning from cardiopulmonary bypass would lead to hepatic dysfunction. In this study, it was impossible to make a cardiopulmonary bypass model using mice, we prepared an acute hepatic lobe congestion model by clamping a hepatic vein and observed the hepatic microcirculation.

MATERIALS AND METHODS

Five Japanese ICR mice weighing 30g were used. All animals were kept in clean cages under a constant temperature of 20 ℃ for 2weeks before the experiment. They received humane care in compliance with " Principles of Laboratory Animal Care" formulated by the Institute of Laboratory Animal Resources and the "Guide for the Care and Use of Laboratory Animals published by the National Institute of Health. Anesthesia was induced by subcutaneous injection of Ethyl carbonate(1.7g/kg). After transverse laparotomy, the portal and hepatic veins of the anterior right lobe were identified and isolated to clamp using micro clamp. The anterior right lobe was placed on the stage of the microscope, and the liver surface was covered with plastic foil to keep it moist and prevent surface injuries. The intravital microscopic study was performed using an intravital microscope (REITZ, Panphoto), and microcirculation of the lobe was observed under a magnification of 250 x. Images were recorded using a SVHS video recording system (Sony, Tokyo, Japan).

Following observation of the normal microcirculation of the liver, the hepatic vein of the anterior right lobe was clamped for fifteen minutes with micro clamp to induce hepatic congestion. After that the hepatic vein was unclamped. During clamping and the following 30 min of reperfusion, the microcirculation of the liver was observed.

RESULTS

Microcirculation of the liver was observed in three of five mice. There were no marked differences among the three mice.

Normal microcirculation of the liver

From the direction of the blood stream, the central and portal veins in the lobule were identified. Erythrocytes moved within the sinusoids from the portal vein to the central vein. Sometimes leukocytes were found moving together with the erythrocytes. Neither adhesion of the leukocytes to the sinusoidal wall nor sludging of the erythrocytes within the sinusoids was observed (Fig. 1.). Hepatic cells were clearly identified.

Microcirculation of the congestive and reperfused liver

When the hepatic vein was clamped, blood flow through the central vein stopped, after a while, that of the portal vein also stopped. Hepatic cells did not change during clamping. Following unclamping of the hepatic vein, it took a while for the flow to restore. Within two or three min, erythrocytes began to move here and there. Within ten min, blood flow was recognized in most of the sinusoids, however the velocity of the red cells differed markedly from one sinusoid to another. In some places, leukocytes were seen rolling or stuck to the endothelium of the sinusoids. In another places, sludging of erythrocytes due to occlusion by the leukocytes accumulation were recognized. In these sinusoids, stasis of the blood flow was recognized. Hepatic cells were prominently swollen and the sinusoids were apparently narrowed compared to normal condition (Fig.2.).

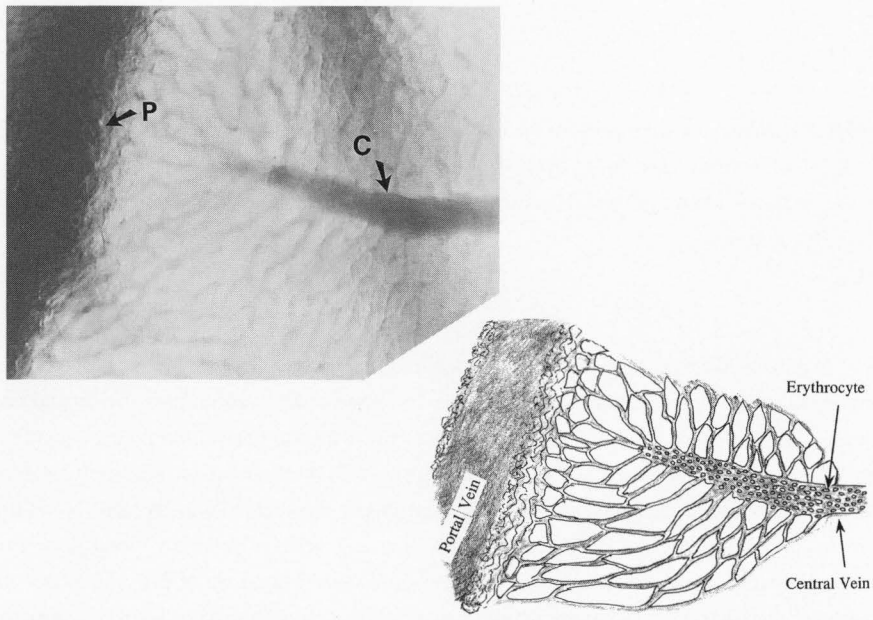

Fig. 1. Erythrocytes moved within the sinusoids from the portal vein to the central vein. Sometimes leukocytes were found moving together with the erythrocytes. Neither adhesion of the leukocytes to the sinusoids wall nor sludging of the erythrocytes within the sinusoids was observed.

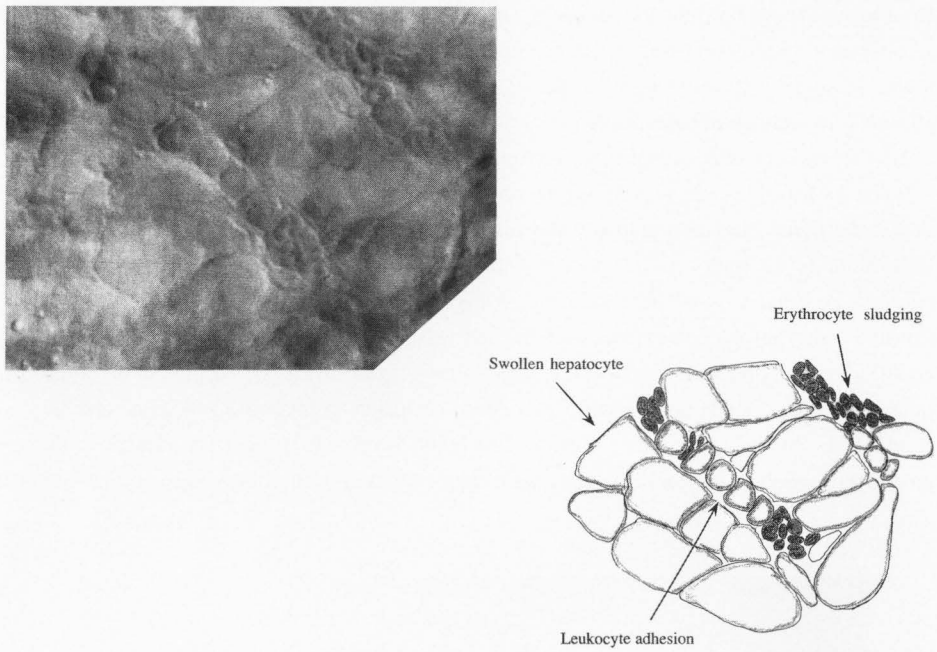

Fig. 2. Leukocytes were stuck to the endothelium of the sinusoid. In another places, sludging of erythrocytes due to occlusion by the leukocytes accumulation and stasis of the blood flow were recognized. Hepatic cells were prominently swollen and the sinusoid become narrow.

DISCUSSION

In patients difficult to wean from cardiopulmonary bypass, central venous pressure increases prominently with optimal inotropic support. An increased central venous pressure would cause an increase in blood pressure in the terminal hepatic vein, which in turn would prevent a normal flow from the terminal portal vein to the terminal hepatic vein through hepatic sinusoids. A markedly increased pressure in the sinusoids would prevent proper evacuation of oxygenated blood from the terminal hepatic arterioles. Hemostasis in this area and perhaps reversed blood flow from the terminal hepatic vein to the terminal portal vein would cause a decrease of PO_2 and induce the first metabolic disturbances .[2] Subsequently, hepatic cells would become ischemic during sustained hepatic congestion. We induced hepatic congestion in mice by clamping the hepatic vein for 15 min, and observed the microcirculation of the liver under an intravital microscope, during clamping and the following 30 min of reperfusion to look for evidence that would support our hypothesis. As already described, we observed non-reflow phenomenon, leukocytes adhesion to the wall of sinusoids, erythrocytes sludging and swelling of hepatic cells following reperfusion. These

phenomena were indicative of warm ischemia-reperfusion injury. [3] Vukovic demonstrated that hepatic and sinusoidal wall cells become swollen very fast after ischemia, as a consequence the lumen of sinusoids becomes narrow and the functional structure of Rapaport microcirculation units is significantly disturbed. [4] Muller also observed, using an intravital microscope, accumulation of leukocytes within the postischemic hepatic microvasculature associated with stasis in the sinusoids and adherence of leukocytes to the endothelial lining of post sinusoidal venules. [5]

Anyway, in patients who could not be weaned from the cardiopulmonary bypass, repeated weaning was tried with increased central venous pressure, full dose cathecolamine with IABP (intra-aortic balloon pumping), prior to cardiopulmonary support system (CPS) was applied. Just during this period, congestion and reperfusion have already progressed in the liver and disturbance of microcirculation proceeded.

In conclusion, repeated episode of warm ischemia and reperfusion of the liver would damage hepatic cells, and finally lead to hepatic failure. To prevent such an unfortunate event, repeated attempts to wean the patient from cardiopulmonary bypass should be avoided and increases of central venous pressure should be prevented by early use of cardiopulmonary support.

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