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Hepatic Hemodynamics and Arterial Ketone Body Ratio
in patients with chronic liver diseases
（慢性肝障害患者における肝血行動態と動脈血中ケトン体比に関する研究）
Transcatheter Hepatic Arterial Drug Infusion Therapy for Hepatocellular Carcinoma

Effect on the Arterial Ketone Body Ratio

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The arterial ketone body ratio (acetoacetate to β-hydroxybutyrate) was measured in 15 patients with chronic liver disease before and after the infusion of antineoplastic drugs or embolic agents (gelatin sponge or iodized oil) into the hepatic artery. The arterial ketone body ratio decreased after hepatic angiography and decreased further at 15 min after infusion therapy. When the arterial ketone body ratio decreased to 1.0 or less on at least one occasion after infusion therapy, the ratio after hepatic angiography was always 1.35 or less. Such patients developed marked systemic symptoms like fever and severe liver dysfunction. Ascites also developed in three patients in whom the arterial ketone body ratio was reduced to 0.7 or less at 24 h after infusion therapy. The arterial ketone body ratio improved at 3-7 days after infusion therapy. In the seven patients treated with gelatin sponge embolization, the ratio at 3-7 days after therapy was actually higher than that before angiography.

Key words: Arterial ketone body ratio; redox; transcatheter arterial embolization

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The infusion of various drugs into the hepatic artery is currently widely used in the diagnosis and treatment of liver tumors. In particular, transcatheter arterial embolization (TAE) plays a major role in the treatment of patients unable to undergo surgery for primary hepatocellular carcinoma (1, 2). This is because normal liver cells receive a dual blood supply from the portal vein and hepatic artery, while hepatocellular carcinoma cells receive most of their blood supply from the hepatic artery (3). However, in patients with advanced liver cirrhosis or with tumor infiltrating the portal vein, hepatic failure after drug infusion can be a problem, and death due to hepatic insufficiency has also been reported (1). However, no definitive guidelines are yet available to determine whether it is safe to infuse drugs into the hepatic artery.

According to the redox theory proposed by Ozawa et al. (4-6), the arterial ketone body ratio (AKBR; acetoacetate to β-hydroxybutyrate) indicates both hepatic mitochondrial function and the hepatic functional reserve because it is proportional to the hepatic energy charge. In this study we measured the AKBR before and after the infusion of drugs into the hepatic artery, to determine whether it was a useful variable for predicting posttreatment hepatic insufficiency.

PATIENTS AND METHODS

The subjects were 15 patients with chronic liver disease. Their clinical profiles, diagnoses, indocyanine green test (ICG-K) values, and treatments are shown in Table I. In patients with liver cirrhosis (LC) and chronic hepatitis (CH) the diagnosis was based on liver biopsy, laparoscopy, angiography, and laboratory data. Informed consent to participate in this study was obtained from all patients.

Angiography of the celiac artery, common hepatic artery, and superior mesenteric artery was performed by the Sel-dinger method. After arteriography, hepatic venography was performed using a 7 Fr occlusion balloon catheter (Meditech, Inc., Watertown, Mass., USA), which was introduced into the hepatic vein via the femoral vein. A volume of 140-160 ml of contrast medium (Iopamiron®, Schering AG, Berlin, Germany) was injected for angiography. Drugs and/or embolic agents were then injected into the common hepatic artery, proper hepatic artery, right hepatic artery, or left hepatic artery via a catheter. The drugs and embolic agents included mitomycin C (Mitomycin-C®; Kyoma Hakko Kogyo, Tokyo, Japan), 5-fluorouracil (5-FU®; Hoffmann-La Roche, Basel, Switzerland), doxorubicin hydrochloride (Adriamycin®, Farmitalia Carlo Erba, Milano, Italy), iodized oil (Lipiodol®, Andre Guebert, Aulnay-Sous-Bois Cedex, France), and gelatin sponge (Spong®; Yamanouchi, Tokyo, Japan). The doses of iodized oil, mitomycin C, 5-fluorouracil, and doxorubicin hydrochloride were 5-10 ml, 10-20 mg, 250 mg, and 10-30 mg, respectively. Half to a whole gelatin sponge block was used, with the sponge being cut...
Effect of dobutamine on the arterial ketone body ratio and portal blood flow velocity in cirrhosis

Kajimura K, Moriyasu F, Kimura T, Okuma M, Mori K, Ozawa K.
Effect of dobutamine on the arterial ketone body ratio and portal blood flow velocity in cirrhosis.

Abstract: We studied the relationship between the portal blood flow velocity and the arterial ketone body ratio in patients with chronic liver disease receiving a dobutamine infusion. We used an ultrasonic Doppler duplex system to evaluate the portal blood flow velocity. Dobutamine was given intravenously at 5 μg/kg/min for 20 min. Dobutamine infusion induced smaller changes in the portal blood flow velocity and ketone body ratio in liver cirrhosis than in chronic hepatitis. The existence of shunts and the poor increase of the cardiac index in response to dobutamine explained the limited improvement of portal blood flow velocity in cirrhosis patients. The ketone body ratio was improved by dobutamine in cirrhosis patients whose portal blood flow velocity was increased by more than 10%, while this ratio decreased when the increase of it was less than 10%. There was no change in portal oxygen extraction in the cirrhosis group, and portal oxygen uptake only increased when the portal blood flow velocity rose by more than 10%. Dobutamine should only be used to treat liver failure if the portal blood flow velocity is increased by more than 10% or the arterial ketone body ratio is improved by a test infusion.

Abbreviations used in this paper: AKBR (arterial ketone body ratio), CH (chronic hepatitis), CI (cardiac index), FHVP (free hepatic venous pressure), POE (portal oxygen extraction), POU (portal oxygen uptake), LC (liver cirrhosis), PBVF (portal blood flow velocity), WHVP (wedged hepatic venous pressure).

Since the liver consumes an enormous amount of energy in order to carry out its various functions, the energy-producing capacity of hepatic mitochondria may be said to represent the hepatic functional reserve. The hepatic ketone body ratio (acetoacetate/β-hydroxybutyrate) is normally in equilibrium with the ratio of the oxidized and reduced forms of free nicotinamide adenine dinucleotide (free NAD+/NADH ratio) in the mitochondria (1). Since acetacetate and β-hydroxybutyrate can pass freely across the cell membrane, and since there is a close relationship between the ketone body ratio of hepatic venous blood and that of arterial blood, the arterial ketone body ratio (AKBR) reflects the hepatic mitochondrial redox state (2, 3). Evidence has been accumulating that the AKBR is an accurate parameter for evaluating hepatic function (4) and is related to the metabolic basis of multiple organ failure (5). In addition, the metabolic aspects of chronic liver disease have recently been analyzed by investigating diurnal fluctuations of the AKBR and the blood glucose level (6).

Hepatic blood flow has a close correlation with the hepatic ATP level (7, 8). The cellular level of ATP decreases rapidly in ischemic liver, and interruption of hepatic blood flow causes a reduction in the AKBR due to inhibition of the oxidation of NADH via mitochondrial oxidative phosphorylation. Catecholamines influence hepatic blood flow,