Evaluation of Nontumorous Tissue Damage by Transcatheter Arterial Embolization for Hepatocellular Carcinoma

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ABSTRACT

The serial changes in serum hepatic enzyme activities by transcatheter arterial embolization (TAE) were analyzed in 17 patients with hepatocellular carcinoma to estimate the contribution to the value by the damage of tumor or nontumorous hepatic cells. The serum levels of relatively tumor-specific fructose 1,6-diphosphate (FDP) aldolase were elevated after TAE in the cases of both superselective and nonsuperselective TAE that were performed from the segmental and the nonsegmental hepatic artery, respectively, but we found the marked elevation of FDP aldolase in the cases of the superselective TAE. In contrast, the non-tumor-specific fructose 1-phosphate (F1P) aldolase was markedly elevated only in the cases of nonsuperselective TAE. The total amount of FDP aldolase released by TAE correlated significantly with the integrated tumorous tissue volume (P < 0.005), whereas the total amount of F1P aldolase output correlated significantly with the integrated nontumorous tissue volume (P < 0.005) as defined by lipiodol accumulation on computerized tomography scan. The consequent changes in the total nontumorous liver volumes after TAE were also analyzed by the follow-up computerized tomography scan. The nonsuperselective TAE caused the significant total nontumorous liver atrophy when compared with the superselective TAE. The progression of the total nontumorous liver atrophy correlated significantly with F1P aldolase output by TAE (P < 0.001) but not with FDP aldolase output. These results suggest that the outputs of FDP and F1P aldolase are useful to estimate the degree of the tumorous and nontumorous tissue damage by TAE, respectively, and F1P aldolase output can be used to predict the progression of liver atrophy caused by TAE.

INTRODUCTION

TAE2 causes the effective tumor necrosis of hepatic neoplasms, both primary and metastatic, by causing tumor devascularization (1). The concept of treating liver tumors by the interruption of their arterial supply was first suggested by Markowitz (2) in 1952. TAE alone or combined with chemotherapeutic agents has been considered to be an effective palliative treatment in patients with unresectable hepatic tumors (1, 3, 4). The previous study (5) showed that the serum enzyme changes by TAE could be used to estimate the size of the necrotic mass and to evaluate the effectiveness of the treatment. However, enzyme changes did not analyze the nontumorous tissue damage by TAE which could be an indicator of the adverse effect of TAE in patients with HCC. In clinical practice, we found that TAE impaired liver function, as manifested by elevation of serum transaminase levels or decrease in serum albumin and cholinesterase levels, sometimes resulting in a state of mild to moderate hepatic failure. Although the changes in the liver function after TAE appear to be responsible for not only the tumor tissue necrosis but also the damage of nontumorous liver tissue caused by TAE, there is no report concerned with the quantitative analysis of the nontumorous liver tissue damage by TAE to our knowledge.

The purpose of this study is to estimate the serial changes in serum enzyme activities released from the damaged tumor or nontumorous tissue by TAE and to measure the contribution to the value by the damage of tumorous or nontumorous hepatic cells. We mainly selected cytosolic FDP and F1P aldolase isoenzymes, because HCC has a much greater concentration of FDP aldolase and a much less concentration of F1P aldolase than nontumorous liver tissue (6, 7). We also evaluated the consequent changes in the total nontumorous liver volumes by TAE and compared the results with F1P aldolase output released by TAE.

PATIENTS AND METHODS

Patients. The first TAE was performed in all 22 patients admitted to our hospital during the period from March 1989 to June 1990. Among them, 5 patients with the diffuse type of HCC were excluded from this study because of the difficulties in calculating the tumor or the nontumorous volume by CT scan in these patients. Consequently, 17 patients with informed consent were used in this study. All of the patients had HCC associated with liver cirrhosis. There were 16 men and one woman, aged from 43 to 74 yr (61.9 ± 8.8 yr old [SD]). The diagnosis of HCC was made clinically by the characteristic appearance of ultrasonic tomography, CT scan, and angiography. Liver cirrhosis was diagnosed by laparoscopy and liver biopsy. Twelve patients had an AFP-producing tumor with serum AFP levels more than 50 ng/ml, and the other five patients had serum AFP levels less than 20 ng/ml. The superselective TAE from the second or third branch of the hepatic artery was performed in 6 patients and the nonsuperselective TAE from the proper, right, or left hepatic artery in 11 patients. As shown in Table 1, the mean age and the tumor size were not different between the two groups. The procedure of TAE was described elsewhere (4). Lipiodol was used together with Spong to calculate the integrated volumes of tumorous and nontumorous tissues.

Sera were collected before and 1, 2, 4, 8, 12, and 24 h after TAE and on Days 2 through 10 when enzyme activities returned to the pretreatment levels. The sera were stored at −20°C until use.

Enzyme Assays. We measured the FDP and F1P aldolase activities by the colorimetric methods that served as the basis for the procedure described in the Sigma diagnostic kit. Serum AST and ALT activities were assayed by an automatic analyzer (Hitachi Model 736; Hitachi, Tokyo, Japan). Serum AFP concentrations were also measured by a commercially available radioimmunoassay kit (Dainabot, Tokyo, Japan).

Model for Calculation of Cumulative Amounts of Enzyme Released. The model for calculation of the cumulative amounts of enzyme released from the damaged tumorous or nontumorous tissue is based on a modification of the method of Sobel et al. (8) and Norris et al. (9) originally designed for the measurement of the total creatine phosphokinase release into the circulation by myocardial infarction.

Calculation of the Integrated Volume of Tumorous and Nontumorous Tissue by the Followed CT Scan. Serial CT scans were taken with a...
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Fig. 1. Distribution of lipiodol in tumorous and nontumorous tissue as shown by CT scan on the third day (A and C) and 2 wk (B and D) after TAE. A case of the superselective TAE (A, B) and a case of the nonsuperselective TAE (C, D) is represented.

Table 1 Comparison of ages and tumor sizes between the cases of the superselective and the nonsuperselective TAE

<table>
<thead>
<tr>
<th>Type of TAE</th>
<th>No. of patients</th>
<th>Sex (M/F)</th>
<th>Age (yr) ± SD (yr)</th>
<th>Tumor size (cm) ± SD (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superselective</td>
<td>6</td>
<td>5/1</td>
<td>59.83 ± 8.4</td>
<td>5.41 ± 2.1 NS</td>
</tr>
<tr>
<td>Nonsuperselective</td>
<td>11</td>
<td>11/0</td>
<td>63.09 ± 9.2</td>
<td>4.31 ± 2.1 NS</td>
</tr>
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* Mean ± SD.
* NS, not significant (P > 0.05).

Statistical Analysis. All values were expressed as the mean ± SD. Statistical analyses were carried out by the x² test or the Student t test.

RESULTS

Serial Changes in Serum FDP and F1P Aldolase Activities by TAE. The serial changes in serum FDP and F1P aldolase activities by TAE in 17 representative cases are shown in Fig. 2. In most of the cases, the enzyme levels began to rise 4 to 8 h after TAE, peaked at 24 to 48 h, and returned to the preembolization level within 7 to 10 days. Nonsuperselective TAE caused marked elevation of the serum F1P aldolase level, whereas the serum F1P aldolase level was almost unchanged in the case of superselective TAE (Fig. 2, right). In contrast, FDP aldolase activities were markedly elevated in the superselective TAE, but relatively less elevation was observed in the nonsuperselective TAE (Fig. 2, left).

Correlation of the Total FDP or F1P Aldolase Output Released by TAE with the Integrated Tumor or Nontumorous Volume. The integrated nontumorous tissue volumes in the cases of the nonsuperselective and superselective TAE were 268.2 ± 79.8 cm³ and 91.8 ± 48.1 cm³, respectively. The difference was statistically significant (P < 0.001). The integrated tumor vol-

The natural course of liver atrophy in 26 cirrhotic patients without HCC who were admitted to our hospital during the same period. CT scans were taken just before and 1 mo, 3 mo, and 6 mo after confirming the diagnosis of liver cirrhosis by laparoscopy and liver biopsy. There were 18 men and 8 women aged from 39 to 74 yr (56.4 ± 10.5 yr old).

Somatom 2 (Siemens AG, Erlangen, Federal Republic of Germany) at 1-cm intervals. The integrated tumor area of each slice (S, cm²) was outlined as an area of accumulated lipiodol 2 wk after TAE, and the integrated volume of the inner tumor mass was calculated by planimeter (Aloka, Tokyo, Japan) with the following formula (5).

\[ V_T (\text{cm}^3) = (S_1 + S_2 + \ldots + S_n)1/C^2 \]

where C (scale ratio) is constant, and \( V_T \) is the integrated tumor volume.

In the same way, we outlined the area of accumulated lipiodol on the third day CT scan in which lipiodol was distributed in both tumorous and nontumorous tissue according to the distributing pattern of the vessel where the tip of the catheter was inserted (Fig. 1). The integrated nontumorous tissue volume was calculated by subtracting the volume of tumor mass from the total integrated volume.

Serial Changes in the Total Nontumorous Liver Volumes after TAE. Since the accumulated lipiodol in the integrated nontumorous liver tissue disappears time dependently, we calculated the total nontumorous liver volume before and 1 mo, 3 mo, and 6 mo after TAE by subtracting the tumor volume from the total liver volume as described before. In addition to the 17 representative patients, we also analyzed the natural course of liver atrophy in 26 cirrhotic patients without HCC who were admitted to our hospital during the same period. CT scans were taken just before and 1 mo, 3 mo, and 6 mo after confirming the diagnosis of liver cirrhosis by laparoscopy and liver biopsy. There were 18 men and 8 women aged from 39 to 74 yr (56.4 ± 10.5 yr old).
Fig. 2. Serial changes in the serum FDP and F1P aldolase levels after TAE. The thick lines and the thin lines represent the cases of nonsuperselective TAE and superselective TAE, respectively.

Fig. 3. Correlation of the total FDP aldolase output with the integrated tumor or nontumorous tissue volume. FDP aldolase output correlated significantly with the apparent tumor volume ($P < 0.005$) but not with the nontumorous tissue volume ($P > 0.05$).

Fig. 4. Correlation of the total F1P aldolase output with the integrated tumor or nontumorous volume. F1P aldolase output correlated significantly with the nontumorous volume ($P < 0.005$) but not with the tumor volume ($P > 0.05$).

Table 2  FDP/F1P aldolase output ratio in superselective and nonsuperselective TAE

<table>
<thead>
<tr>
<th></th>
<th>Superselective TAE ($n = 6$)</th>
<th>Nonsuperselective TAE ($n = 11$)</th>
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<tbody>
<tr>
<td>FDP/F1P ratio</td>
<td>$5.0 \pm 1.0^{*ab}$</td>
<td>$2.6 \pm 1.0$</td>
</tr>
</tbody>
</table>

* Mean ± SD.

** P < 0.005.

Table 2  FDP/F1P aldolase output ratio in superselective and nonsuperselective TAE

Volumes were not different between the two groups ($134.7 \pm 105.3$ versus $205.2 \pm 176.9$ cm$^3$, $P = 0.31$). The total enzyme output of FDP aldolase correlated significantly with the tumor volume but not with the nontumorous volume (Fig. 3). In contrast, the total enzyme output of F1P aldolase correlated significantly with the nontumorous volume but not with the tumor volume (Fig. 4). When the FDP/F1P aldolase output ratio in the superselective TAE was compared with that in the nonsuperselective TAE, the ratio in the superselective TAE was significantly greater than that in the nonsuperselective TAE ($P < 0.005$; Table 2).

Correlation of the Total ALT or AST Output Released by TAE with the Integrated Tumor or Nontumorous Volume. Serum levels of ALT and AST began to rise 4 to 8 h and returned to pretreatment levels within 7 to 10 days after TAE. When the total outputs of these enzymes were compared with the tumor or the nontumorous volume, the total ALT output correlated significantly with the nontumorous volume ($P < 0.05$) but not with the tumor volume. The total AST output correlated with both the tumor ($P < 0.05$) and the nontumorous volume ($P < 0.005$; Fig. 5).

Serial Changes in Serum AFP Levels after TAE. Serial changes in serum AFP levels after TAE were determined in 12 patients with serum AFP concentrations more than 50 ng/ml before TAE and expressed as a percentage of the value before TAE (Fig. 6). Serum AFP levels rose to their highest level.
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Figure 5. Relationship between total ALT or AST output and the integrated tumor or nontumorous tissue volume after TAE. ALT output correlated with nontumorous volume ($P < 0.05$) but not with the tumor volume, whereas AST output correlated with both the tumor and the nontumorous volume ($P < 0.05$ and $P < 0.005$, respectively).

![Graphs showing correlation between total ALT or AST output and tumor/nontumorous tissue volume](image)

Figure 6. Serial changes in serum AFP levels after TAE. The thick lines and the thin lines represent the cases of nonsuperselective TAE and superselective TAE, respectively. The values are expressed as a percentage of the pretreatment values.

![Graph showing serial changes in serum AFP levels after TAE](image)

Within 6 h after TAE and gradually decreased thereafter. In superselective TAE, the serum AFP level decreased to less than nearly a half of the pretreatment values on the seventh day, whereas it did not in the nonsuperselective TAE.

Total Nontumorous Liver Atrophy after TAE. The total nontumorous liver volumes were estimated by the follow-up CT scans 1, 3, and 6 mo after TAE and compared with the natural course of liver atrophy in 26 cirrhotic patients without HCC (Table 3). The nonsuperselective TAE resulted in significant total nontumorous liver atrophy, when compared with the superselective TAE and the natural course of liver cirrhosis. The degree of total nontumorous liver atrophy caused by the superselective TAE was not different from liver atrophy in the natural process of liver cirrhosis.

Relation of the Percentage of the Total Nontumorous Liver Atrophy with the Total FDP or F1P Aldolase Output Released by TAE. Since FDP and F1P aldolase were mainly released from the tumor and the nontumorous tissue of the liver, respectively, we analyzed the correlation of the percentage of the total nontumorous liver atrophy 1 mo after TAE with the total of these enzyme outputs (Fig. 7). The percentage of liver atrophy correlated significantly with the total F1P aldolase output ($r = 0.867, P < 0.001$) but not with the total FDP aldolase output ($r = 0.316, P > 0.05$).

DISCUSSION

Although three fourths of the total hepatic blood supply are provided by portal vein, the hepatic artery provides 40 to 60% of the oxygen supply to the liver (10). Popper et al. (11) reported that the portal vein plays only a secondary role as a source of oxygen supply. The limited amount of oxygen supply to the liver by the portal blood flow is not sufficient to prevent liver necrosis by the interruption of the hepatic arterial perfusion (11). To date, several reports revealed the various complications of TAE (12–16). However, the quantitative analysis of the nontumorous liver damage by TAE in patients with HCC has not been reported previously. In this study, we evaluated the adverse effect of TAE on nontumorous liver tissue.

Although there are several factors in TAE, as for example, size of the tumor, position of the catheter tip, appropriate feeding artery, size of the Spongel particle, volume of the Spongel material, and blood flow of the feeding vessels, we considered the position of the catheter tip, the appropriate feeding vessel, and the fixed size and volume of the Spongel material for our study. We found marked elevation of serum FDP aldolase activities in the superselective TAE and relatively less elevation of serum FDP aldolase activities in the nonsuperselective TAE. These results coincided with the more significant decline of serum levels of AFP in the cases of superselective TAE than that in the nonsuperselective TAE. In contrast,
serum F1P aldolase activities were significantly elevated in the cases of the nonsuperselective TAE. We also found that the total enzyme outputs of FDP aldolase and F1P aldolase correlated significantly with the tumorous and nontumorous tissue volumes, respectively, and that the FDP/F1P aldolase output ratio in the superselective TAE was significantly greater than that in the nonsuperselective TAE. These results indicate that the nonsuperselective TAE causes the increase in the release of F1P aldolase from the damaged nontumorous liver tissue. In fact, the occlusion of segmental tumor feeding vessels by embolic materials is more selective than that of nonsegmental vessels where the embolic materials are distributed in a scattered fashion and entered into the intrahepatic branches of the other major hepatic arteries.

Unlike the previous report (5), we did not find correlation of the total ALT output with tumor tissue volume. The total AST output correlated with not only the tumor but also the nontumorous tissue volume. We also found that the serum AST and ALT activities after TAE were higher in the nonsuperselective TAE. The total nontumorous liver atrophy ratio in the superselective TAE was significantly greater than that in the nonsuperselective TAE. These results indicate that the nonsuperselective TAE causes the increase in the release of F1P aldolase from the damaged nontumorous liver tissue. In fact, the occlusion of segmental tumor feeding vessels by embolic materials is more selective than that of nonsegmental vessels where the embolic materials are distributed in a scattered fashion and entered into the intrahepatic branches of the other major hepatic arteries.

The nontumorous liver damage caused by TAE was followed by the consequent development of the nontumorous liver atrophy, as were 26 control cirrhotic patients without HCC. There was no difference of liver atrophy between the superselective TAE and the natural course of liver cirrhosis. In contrast, the nontumorous liver atrophy caused by the nonsuperselective TAE was more progressive than that caused by the superselective TAE and the natural course of liver cirrhosis. This progression of liver atrophy after proximal TAE is mainly responsible for the nontumorous parenchymal damage, because the progression of the nontumorous liver atrophy correlated significantly with the total F1P aldolase output released by TAE.

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Thus, we reported here, nonsuperselective TAE causes significant nontumorous liver damage, impairing the reserved function of the liver, resulting in the subsequent development of liver atrophy after TAE. We also suggest that the measurement of serum FDP and F1P aldolase activities can be used to evaluate the degree of tumor necrosis and nontumorous tissue damage by TAE, respectively, and the elevation of serum F1P aldolase levels after TAE is useful to predict the subsequent development of liver atrophy.

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