Extension of Right Portal Vein Embolization to Segment IV Portal Branches

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Hypothesis: Routine embolization of segment IV, combined with right portal vein embolization (PVE), has been suggested in patients who are candidates for right trisegmentectomy to induce higher and faster hypertrophy of segments II-III. Our objective was to compare hypertrophy of segments II-III induced by PVE with and without extension to segment IV in patients undergoing major hepatectomy.

Methods: Twenty-six consecutive patients were prospectively evaluated; the future remnant liver volume was calculated using the portal phase of spiral computed tomographic scans before and 3 to 4 weeks after right PVE (group R, n=13), which was extended to segment IV branches in 13 patients (group L).

Results: Twenty patients (76.9%) underwent the scheduled hepatic resection. Of the 6 patients who did not undergo the planned operation, 5 showed disease progression; in 1 patient (group L), there was an insufficient increase of the future remnant liver volume due to the presence of embolizing material in the left lobe. The mean±SD time between PVE and volume measurements was 31.8±9.3 days. The overall mean±SD future remnant liver volume increase was 53.1%±24.8%; the increase for segment IV was significantly higher in group R than group L. The mean±SD post-PVE volumes of segments II-III and the rate of volume increase were similar in the 2 groups: group R, 348.4±83.1 cm³ and 67.8%±30.8%, respectively, vs group L, 391.2±78.05 cm³ and 56.1%±35.1%, respectively (P=.20 and P=.40).

Conclusion: Extension of embolization to segment IV portal branches should not be routinely used because a similar volume increase of segments II-III can be simply achieved by right PVE.

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There is growing evidence that hypertrophy of the estimated future remnant liver (FRL) induced by portal vein embolization (PVE) reduces the risk of hepatic failure after major liver resection and increases the resectability rate.1-5 Recently, Hemming et al6 compared 2 groups of patients with similar tumor burden, operation complexity, and predicted FRL volume and observed a significantly lower rate of liver failure among patients who underwent PVE vs those who did not. The procedure seems particularly helpful in subjects with chronic liver disease.7

Portal vein embolization is a safe, minimally invasive procedure, and major complications have rarely been reported in the literature; however, of concern is the accidental migration of the embolizing substance to parts of the liver that need to be preserved.8,9 Routine embolization of segment IV combined with right PVE has been suggested in patients who are candidates for right trisegmentectomy to induce higher and faster hypertrophy of the remnant liver. This approach may, however, increase the risk of accidental occlusion of the left portal branches, thus precluding surgery.10

The aim of our prospective study was to verify the potential benefit of extending right PVE to segment IV portal branches in patients who were candidates for a right trisegmentectomy.

METHODS

PATIENTS

From September 2000 to January 2003, 26 patients (10 women) with liver or bile duct cancer who were candidates for major hepatic resection but had an estimated FRL volume that was too small (<25% in patients with a normal liver or ≤30% in those with nonnormal liver) underwent PVE at our institution. Their mean±SD age was 61.2±10.4 years (range, 32-73 years).

Indications for surgery were as follows: liver metastases in 8 cases; Klatskin tumor in 8; peripheral cholangiocarcinoma in 4; hepatocellular carcinoma in 3; gallbladder cancer in 2;...
and hemangiopericytoma in 1 case. Diabetes mellitus was present in 5 patients. Of the 8 patients with colorectal liver metastases, 6 underwent oxaliplatin-based neoadjuvant chemotherapy. Histological examination of the liver biopsy specimens obtained at a distance from the tumor to assess the overall state of the parenchyma revealed a normal liver in 11 cases (42.3%), fatty liver disease (≥20% steatosis) in 8 cases (30.8%), and chronic liver disease in 7 cases (26.9%).

STUDY DESIGN

We analyzed all consecutive patients who underwent right PVE with extension (group L, 13 patients) or without (group R, 13 patients) to segment IV portal branches. Patients were prospectively assigned to 1 of these 2 groups: group L when the type of liver resection planned before PVE was a right trisegmentectomy and group R when the scheduled operation was a right hepatectomy (9 patients) or when, despite planning an extended hepatectomy, segment IV embolization was not technically feasible or hazardous (4 patients). The risk factors were similar between the 2 groups (Table 1).

All patients were evaluated using abdominal computed tomography (CT) performed 3 to 7 days before PVE; magnetic resonance cholangiography was performed if bile duct involvement was suspected. Portal-phase CT scans were used to assess the FRL volume in view of their best ability to depict the hepatic venous anatomy. The region of interest (ROI) was traced manually with a cursor on each CT slice and the area was determined automatically. The volume was obtained by the sum of the areas of each ROI multiplied by the scan interval. The FRL volume was calculated using the following formula:

\[
\text{FRL Volume} = \text{Volume of the FRL Before Surgery} - \text{Volume of the FRL Before PVE} \times 100/\text{Volume of the Entire Liver} - \text{Tumor Volume}.
\]

The increase in FRL volume was calculated with the following formula:

\[
(\text{Volume of the FRL Before Surgery} - \text{Volume of the FRL Before PVE}) \times 100/\text{Volume of the FRL Before PVE}.
\]

We decided to perform PVE when the FRL volume estimated on the basis of the planned hepatectomy was 25% or less in patients with a normal liver or 30% or less in those with moderate or severe steatosis or a chronic liver disease (ie, nonnormal liver). The estimated FRL volume included segment IV when right hepatectomy was the planned treatment. Once the indication for PVE was confirmed, volumes of the caudate lobe (IX-I), medial (IV), and lateral (II-III) segments were measured individually as described earlier.

The volume measurements were repeated 3 to 4 weeks after the procedure to measure volume changes for each individual segment and the percentage increase in FRL volume. If the latter was still not adequate to warrant major liver resection, liver CT and volume measurements were repeated 2 weeks later, thus allowing for further hypertrophy of the FRL.

In patients with obstructive jaundice, percutaneous transhepatic biliary drainage was performed 1 week before PVE. Our approach was to drain only the FRL volume estimated according to the planned hepatectomy; biliary decompression of the liver segments to be removed was additionally performed if jaundice persisted, irrespective of the presence of cholangitis.

TECHNIQUE FOR PVE

Portal vein embolization was performed in all cases under fluoroscopic guidance during conscious sedation. The ipsilateral approach was used when possible (22 of 26 patients) for the following reasons: (1) access to the left branches of the portal vein is usually more difficult because of the smaller size of the left lobe; (2) the risk of accidental embolization of the left portal branches is lower; and (3) the percutaneous tract can be sealed while removing the catheter at the end of the maneuver, reducing the risk of hemoperitoneum. In 4 patients with large lesions of the right liver narrowing or obstructing the posterior right portal branch, PVE was performed with a left anterior approach. The puncture of the portal vein was achieved with a 22-gauge Chiba needle. A 4F hydrophilic catheter (Radiofocus Glidecath; Terumo Europe, Leuven, Belgium) was used to catheterize the portal system. Digital subtraction portography was performed in the anteroposterior projection to visualize the portal segmental anatomy and possible anatomical variations. If embolization of segment IV was planned in addition, selective portography of the left portal branches was performed in the right anterior projection. Embolization was performed in all cases by injecting a mixture of cyanoacrylate (Glubram; GEM, Viareggio [LU], Italy) and iodized oil (Lipiodol UF; Guerbet, Roissy CDG CEDEX, France) in a 1:10 ratio through a 3-F hydrophilic microcatheter introduced through the Cobra catheter. This coaxial technique prevents glue adhesion and reduces the risk of main catheter occlusion. Embolization of the proximal part of the main right portal branch was avoided to minimize the periproctal inflammatory reaction that may hamper surgical isolation of the hepatic pedicle. Control portography was performed at the end of the procedure.

STATISTICAL ANALYSIS

Results were expressed as mean ± SD. Continuous variables were compared using the t test; categorical variables were compared using the chi-squared or Fisher exact tests, as appropriate. All analyses were performed using statistical software (SPSS for Windows 11.0.1; SPSS Inc, Chicago, Ill.). Differences were considered statistically significant at P<.05 levels.

RESULTS

PVE COMPLICATIONS AND RESECTABILITY RATE

No significant complications were observed following PVE. There was a significant transient increase in the serum aspartate aminotransferase levels and a significant decrease in the prothrombin time values 24 hours after PVE but without any clinical consequence. All parameters returned to baseline values at 7 days.

<table>
<thead>
<tr>
<th>Table 1. Clinical Characteristics of the Patients*</th>
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<tbody>
<tr>
<td>Variable</td>
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<tr>
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</tr>
<tr>
<td>Age ≥70 y, No.</td>
</tr>
<tr>
<td>Diabetes mellitus, No.</td>
</tr>
<tr>
<td>Normal liver, No.</td>
</tr>
<tr>
<td>AST level, U/L, mean ± SD†</td>
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<tr>
<td>ALT level, U/L, mean ± SD†</td>
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<tr>
<td>Bilirubin level, mg/dL, mean ± SD</td>
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<tr>
<td>Prothrombin time, %, mean ± SD</td>
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<td>FRL biliary drainage, No.</td>
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</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FRL, future remnant liver; PVE, portal vein embolization; SI factor conversion: To convert bilirubin to micromoles per liter, multiply by 17.1.

*Group R was composed of patients who underwent right PVE. Group L was composed of patients who underwent right PVE extended to segment IV.

†Pre-PVE serum levels.
levels within 3 weeks (data not shown). No significant differences in bilirubin values were noted, and there was no difference between group R and group L patients.

Six patients (23.1%) did not undergo liver resection (3 in each group). In 4 cases, the decision was made on the basis of intraoperative findings: peritoneal dissemination (3 patients) or bilateral, nonresectable liver metastases (1 patient). In the remaining 2 patients, the decision was made preoperatively; in 1 patient with gallbladder cancer, the CT scan showed infiltration of the left lobe. In the remaining case (Klatskin tumor) belonging to group L, there was an insufficient increase in the estimated rate of FRL volume (15% before PVE, 18.2% at 2 months); in this case, despite patency of the left portal branch that was demonstrated at the portography performed at the end the embolization, the subsequent CT scan revealed the presence of an embolizing substance in the left lobe (Figure).

Twenty (76.9%) of the 26 patients had the scheduled hepatic resection. All 10 cases in group L underwent the planned trisegmentectomy. In group R, all patients had a right hepatectomy, extended to segment IV in 5 cases. In 12 cases (4 in group R and 8 in group L), segments IX-I were removed.

The mortality rate was 5%; 1 patient with cirrhosis in group L who underwent liver resection without pedicle clamping died of portal thrombosis 4 days after surgery.

In 2 patients, one from each group and both undergoing an extended right hepatectomy, a small cyaanocrylate thrombus was found fluctuating in the main portal trunk bifurcation and was removed during surgery without further complications.

Table 2. Variations of Liver Volume for Segments IV, II-III, and IX-I*

<table>
<thead>
<tr>
<th></th>
<th>Pre-PVE Volume, cm³</th>
<th>Post-PVE Volume, cm³</th>
<th>Rate of Volume Increase, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial segment (IV)</td>
<td>Group R 148.4 ± 52.2</td>
<td>186.2 ± 74.8</td>
<td>28.1 ± 31</td>
</tr>
<tr>
<td></td>
<td>Group L 187.4 ± 74.1</td>
<td>193.5 ± 74.3</td>
<td>5.6 ± 18</td>
</tr>
<tr>
<td>P value</td>
<td>.10</td>
<td>.80</td>
<td>.03</td>
</tr>
<tr>
<td>Lateral segments (II-III)</td>
<td>Group R 212.1 ± 55.6</td>
<td>348.4 ± 83.1</td>
<td>67.8 ± 30.8</td>
</tr>
<tr>
<td></td>
<td>Group L 258.1 ± 64.9</td>
<td>391.2 ± 78.05</td>
<td>56.1 ± 35.1</td>
</tr>
<tr>
<td>P value</td>
<td>.06</td>
<td>.20</td>
<td>.40</td>
</tr>
<tr>
<td>Segments IX-I</td>
<td>Group R 57.5 ± 59.8</td>
<td>68.2 ± 74.2</td>
<td>24.5 ± 40</td>
</tr>
<tr>
<td></td>
<td>Group L 52.6 ± 26.9</td>
<td>61.2 ± 33.2</td>
<td>28.5 ± 53.1</td>
</tr>
<tr>
<td>P value</td>
<td>.80</td>
<td>.80</td>
<td>.80</td>
</tr>
</tbody>
</table>

Abbreviation: PVE, portal vein embolization.

*Group R was composed of patients who underwent right PVE. Group L was composed of patients who underwent right PVE extended to segment IV.

**VOLUMETRIC ASSESSMENTS**

The mean ± SD time between PVE and volume measurements was 31.8 ± 9.3 days: 33.9 ± 8.6 days in group R and 29.3 ± 9.8 days in group L (P = .20).

The mean ± SD estimated baseline percentage FRL volume was 20.8% ± 4.9%, and there was no statistically significant differences between group R and group L (22.2% ± 4.5% vs 19.5% ± 5.2%, respectively; P = .20). Following PVE, the mean ± SD estimated percentage FRL volume increased to 31.5% ± 7.4%; it was significantly greater in group R than group L (34% ± 6.4% vs 28.5% ± 7.3%, respectively; P = .03). The mean ± SD overall percentage FRL volume increase was 53.1% ± 24.8% by comparison with baseline levels, and it was similar between the 2 groups (54.8% ± 18.7% vs 51.4% ± 30.3%, respectively; P = .70).

The measurements of absolute volumes obtained at baseline and post-PVE and the percentage volume increase for segments II-III, IV, and IX-I are reported in Table 2. As expected, the percentage volume increase of segment IV was significantly higher in group R. The rate of segments II-III volume increase was similar in the 2 groups: 67.8% in group R and 56.1% in group L (P = .40).

**COMMENT**

Right PVE is a safe and effective way to produce FRL hypertrophy as a preparation for major hepatic resections. In experienced hands, catheterization of the portal system is a relatively simple and nontraumatic maneuver that is feasible under ultrasound or fluoroscopic guidance; however, it is essential to avoid accidental occlusion of the left portal vein, which would jeopardize operability.

The additional occlusion of segment IV portal branches has been reported by Nagino et al as a way of inducing greater FRL hypertrophy than right PVE alone in patients who are candidates for right trisegmentectomy but have a small left liver lobe. This approach requires highly trained interventional radiologists and complex proce-
dures involving the use of multilumen balloon-occluding catheters since there is a higher risk of accidental reflux of embolizing material in the left portal vein. This complication occurred in 1 of our 13 patients who underwent extended PVE; as a consequence, there was an inadequate increase of the FRL volume and the patient did not undergo the planned operation.

Thus, to routinely perform embolization of left medial portal veins, this approach should carry a clear advantage over right PVE alone in terms of FRL volume. To verify this issue, we analyzed 26 patients who underwent right PVE with or without embolization of segment IV portal branches. As expected, we found a greater increase of segment IV volume in group R but no difference was detected for volume changes in the caudate lobe. For the first time, to our knowledge, we have shown that embolization of segment IV did not increase the hypertrophy rate of segments II-III compared with that obtained by right PVE alone. As a possible explanation, we hypothesize that additional embolization of segment IV branches might not increase portal blood pressure further than right portal embolization, owing to the high compliance of the portal venous system. Following portal embolization, stretch stress in endothelial cells of the FRL is associated with release of IL-6, which has a key role as a priming factor for liver regeneration. In a study assessing the role of IL-6 after ischemic liver damage following liver resection, we found that IL-6 serum levels were similar in patients who underwent right hepatectomy with extension (n=5) or without (n=5) to segment IV (data not shown), thus providing support for our hypothesis.

Avoiding embolization of segment IV, even if a right trisegmentectomy is preoperatively planned, is also an advantage for the surgeon, who is allowed to preserve segment IV whenever intraoperative findings make this possible. As an example, we recently performed an extended right hepatectomy with preservation of segment IVb for liver metastases due to colorectal cancer, despite the planned complete resection of this segment before PVE.

We obtained a greater increase in the mean left lobe volume in our patients (mean±SD, 61.9%±32.9%) than that reported by Nagino et al (mean±SD, 37%±27%). In our opinion these differences are due both to the techniques used and to the different intervals between PVE and volume measurements in the 2 studies. In our series, cyanoacrylate was used for embolization because it is considered very effective in producing complete and irreversible vascular occlusion. De Baere et al reported a 90% increase in FRL volume after 30 days using cyanoacrylate in comparison with a 53% increase after 43 days using fibrin glue. Nagino et al used fibrin glue solutions, which are probably the least effective embolizing substances because they are reabsorbed and allow restoration of portal vein flow with time.

Hypertrophy of the FRL is known to continuously increase after PVE and the optimal timing is estimated around 4 weeks. We measured hypertrophy in our patients on average 32 days after PVE, whereas Nagino et al allowed an average interval of only 16 days before assessing hypertrophy. It has been argued that postponing hypertrophy measurement may determine a reduction in resectability rate due to disease progression. This was not the case in our series where only 5 patients (19.2%) had disease progression, 2 of them locally. This resection rate is in line with the data available in the literature.

In conclusion, we believe that extension of right PVE to segment IV should not be indicated in patients who are candidates for a right trisegmentectomy since a similar volume increase of segments II-III can be obtained by the simpler and safer embolization of the right portal branches.

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REFERENCES