Role of paraoesophageal collaterals and perforating veins on outcome of endoscopic sclerotherapy for oesophageal varices: an endosonographic study

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Abstract
Background—Endoscopic sclerotherapy (EST) is an established method for controlling and preventing bleeding from oesophageal varices. However, oesophageal varices sclerose easily and require less sessions of EST in some patients while few fail to respond. This study therefore looked at changes in the vascular anatomy of the lower oesophagus and upper stomach that accompany successful sclerotherapy of oesophageal varices.

Methods—Endoscopic ultrasonography was performed in 50 patients with cirrhotic portal hypertension before (control, 20 patients) and after successful obliteration of varices with endoscopic sclerotherapy in a group of responders (EST-R, 20 patients) and in a group of non-responders (EST-NR, 10 patients).

Results—The median number and size of submucosal veins at the gastrooesophageal junction and in the lower oesophagus were significantly less in the EST-R group compared with control and EST-NR groups (p values between <0.00001 and <0.000001). Concomitantly, the number and size of paraoesophageal collaterals were significantly less in the EST-R group compared with the other two groups (p values between 0.02 and 0.00007). Perforating veins were identified in 14 (70%) patients in the control group, nine (90%) in the EST-NR group and in none in the EST-R group (p<0.001 for both controls v EST-R and EST-R v EST-NR, and p=NS, control v EST-NR).

Conclusion—Oesophageal variceal sclerosis is associated with significant reduction in the number and size of paraoesophageal collaterals and disappearance of perforating veins in the lower oesophagus.

Keywords: cirrhosis, endoscopic ultrasound, endoscopic sclerotherapy, oesophageal varices, portal hypertension.

Endoscopic sclerotherapy (EST) has become an established method of treatment of bleeding oesophageal varices in patients with portal hypertension.1-3 It is, however, unclear why varices sclerose easily in some patients and not in others, and also why they recur rapidly in some who show initial sclerosis and obliteration. Factors affecting these variables have been studied, but are still unclear.4-7 Lin et al7 found that EST is less effective in treating patients with oesophageal variceal haemorrhage who have severe paraoesophageal collaterals. McCormack et al8 have shown that oesophageal varices are not always the main pathway for portal to systemic shunting and that most shunting occurs at a deeper level. Therefore it seems that the ultimate outcome of EST may be influenced by the paraoesophageal collaterals and perforating veins.

The vascular anatomy of the lower oesophagus and upper stomach especially in patients with portal hypertension was initially determined by injection of contrast or casting agents into blood vessels of resected postmortem specimens.9-12 In vivo investigations like angiography13 and percutaneous transhepatic portography14 have had the major limitation of being invasive and hence not easily repeatable. Computed tomography has been used to delineate venous anatomy of oesophagus and upper stomach in patients with portal hypertension, but has the disadvantage of radiation exposure.7 15 16 The diagnostic value of this procedure is still unclear. Endoscopic ultrasound (EUS) has emerged as a safe, non-invasive technique providing good delineation of the cross sectional anatomy of this region.17 In patients with portal hypertension oesophagogastric varices and paraoesophageal collaterals can be visualised adequately by endosonography,18 19 and it may be repeated several times to assess changes that might occur with treatment.

Using EUS we have determined the changes in venous anatomy in the lower oesophagus and upper stomach that occur with EST in such patients. We have prospectively studied three groups of patients with severe portal hypertension: (a) controls, before initiation of elective EST, (b) responders to EST, in whom complete eradication of varices was achieved, and (c) non-responders to EST, in whom adequate reduction in variceal size was not achieved after a minimum of 10 sessions.

Methods
Fifty patients with cirrhosis of the liver and severe portal hypertension were studied. They all had a history of bleeding from gastrooesophageal varices and had been referred for elective EST. At presentation, all patients had
grade 3 or 4 oesophageal varices on endoscopic examination. Three groups of patients were studied: the control group consisted of 20 patients in whom EUS was performed before starting the first session of EST. The second group consisted of 20 patients in whom complete oesophageal variceal eradication had been achieved with repeated EST (median sessions 8, range 3 to 10). Obliteration of oesophageal varices was defined either as absence of varices or the presence of very small thrombotic veins that did not bleed after puncture with EST needle. These patients were considered as responders to EST (EST-R). The third group consisted of 10 patients who had not achieved reduction in variceal size by two grades after 11 or more sessions of EST (median sessions 13-5, range 11 to 22) and were considered non-responders to EST (EST-NR). Ten patients who were referred for EUS examination for benign pancreatobiliary diseases, served as controls for normal anatomy of oesophagus and upper stomach. These patients did not have any evidence of portal hypertension on clinical and endoscopic evaluation. Written informed consent was obtained from all patients after explaining the aims of the study.

Endoscopy was performed with an Olympus GIF-Q10 fibroscope. Oesophageal varices were graded according to Conn’s classification. Gastric varices were scored as present or absent. Intravarical injections were done randomly using the Olympus GIF-Q10 endoscope and NM-1K injector. Two to 4 ml of 1% polidocanol (Aethoxysclerol) was injected circumferentially just above the gastro-oesophageal junction and at 2-5 cm intervals as the endoscope was withdrawn.

Subsequent sessions of EST were performed at two to three weeks’ intervals until eradication of all oesophageal varices was achieved.

EUS was performed with an Olympus EU-M3 ultrasound fibroscope and display unit. The system provides 360° radial scan with frequencies of 7-5 and 12 MHz. Both frequencies were used in the examination of the lower oesophagus and upper stomach. The patient fasted overnight. After sedating the patient with intravenous diazepam (5-10 mg), the ultrasound fibroscope was inserted with the patient in the left lateral position and passed down into the stomach. EUS examination of the stomach and adjacent structures was performed with a water filled balloon over the ultrasound probe and after the instillation of 100-300 ml of deaerated water into the stomach. The distal end of the ultrasound probe was placed in the body of the stomach and examination was begun by slowly withdrawing the fibroscope. EUS evaluation was performed at three levels, that is (a) upper stomach, (b) at the gastro-oesophageal junction, and (c) 5 cm above the gastro-oesophageal junction (lower oesophagus). At each site, a complete 360° view of the stomach or oesophagus was obtained by adjusting the position of the transducer. At each of the three sites submucosal and perigastric or paraoesophageal collaterals were identified, their number counted, and the largest diameter measured. The collaterals identified at or just above the gastro-oesophageal junction were traced approximately 5 cm in the cephalad direction. The presence or absence of perforating veins connecting the submucosal with the paraoesophageal collaterals were recorded in the lower oesophagus. An independent assessment of EUS findings was also made by a second observer.

**Statistical analysis**

The results are given as median and interquartile range. Differences between the groups were analysed by non-parametric tests – that is, Mann-Whitney U test and Fisher’s exact test.

**Results**

Table 1 shows clinical details of patients in various groups. These groups were age and sex matched and no significant difference was

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**Table 1: Clinical details of the patients with portal hypertension**

<table>
<thead>
<tr>
<th>Class (Child-Pugh’s)</th>
<th>Controls (n=20)</th>
<th>EST-R (n=20)</th>
<th>EST-NR (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>10</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>B</td>
<td>7</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>C</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Alcoholic</strong></td>
<td>4</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td><strong>HBsAg+</strong></td>
<td>5</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td><strong>Non-alcoholic, non-HBsAg (+)</strong></td>
<td>11</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

*Median (interquartile range).
Endoscopic sclerotherapy for oesophageal varices

Thirteen patients had grade 4 and seven patients had grade 3 oesophageal varices in the control group. No variceal column was seen in any patient in EST-R group; however, small mucosal tags were seen in seven patients. In the EST-NR group, three patients had grade 4, six patients had grade 3, and one patient had grade 2 oesophageal varices. Gastric varices were seen in 12 patients in the control group and in seven patients each in the EST-R and EST-NR groups.

Endoscopy

Figure 2: A 180° endosonographic scan (A) and schematic drawing (B) of a normal upper stomach in a healthy subject. Note three echogenic layers alternating with two echolucent layers. These layers correspond to (1) superficial mucosa, (2) deep mucosa, (3) submucosa (4) muscularis propria, and (5) serosa and fat tissue.

Figure 3: A 360° endosonographic scan of the gastro-oesophageal junction in a patient with cirrhotic portal hypertension before EST. Oesophageal varices (submucosal veins, arrowheads) are seen within the oesophageal wall and paraoesophageal collaterals (arrows) are clearly seen outside the oesophageal wall.

Figure 4: A 360° endosonographic scan of upper stomach in a patient with cirrhotic portal hypertension. Gastric varices (submucosal veins, arrowheads) are seen within the gastric wall and paraoesophageal collateral vein (arrow) is seen outside the gastric wall.

Endoscopic ultrasound

Oesophageal and gastric wall appeared as a five layer structure; three echogenic alternating with two echolucent layers (Figs 1 and 2). These layers have been shown to correspond to the anatomical layers of the oesophagus and stomach as follows: the first hyperechoic layer corresponds to superficial mucosa, the second hyperechoic layer to deep mucosa, the third hyperechoic layer to submucosa plus the acoustical interface between the submucosa and muscularis propria, the fourth hyperechoic layer to muscularis propria minus the acoustical interface between the submucosa and muscularis propria, and the fifth hyperechoic layer to paraoesophageal fat or to serosa and periserosal fat. Oesophageal or gastric varices appeared as rounded or oval echo free structures in the submucosa (Figs 3 and 4). They also appeared as longitudinal echo free structures in the submucosa depending upon the relative position of the varix and ultrasound transducer. Similarly, paraoesophageal or perigastric collaterals were also seen as rounded, oval or longitudinal echo free structures well outside the oesophageal or gastric wall (Figs 3 and 4). Both submucosal and paraoesophageal collaterals appeared tortuous all along their extent. Perforating veins were seen as anechoic communicating channels between submucosal and paraoesophageal collaterals (Fig 5).
groups. In the upper stomach while the number of these veins was significantly lower in patients in the EST-R group, no significant difference in size could be seen between these three groups. These findings suggest that there is a pronounced reduction in the number and the size of paraoesophageal collaterals and a decrease in the number of perigastric collaterals after variceal eradication with EST.

Perforating veins were seen in 14 patients in the control group, nine in the EST-NR group, and in none in the EST-R group (p<0.001, control v EST-R: p<0.001, EST-R v EST-NR and p=NS, control v EST-NR; Fisher’s exact test).

Discussion
We could adequately visualise the venous morphology of the lower oesophagus and upper stomach in all the patients. Our findings clearly show that successful eradication of oesophageal varices by EST is associated with disappearance of perforating veins in the lower oesophagus and reduction in the number and size of paraoesophageal collaterals. In contrast, there is a persistence of these vascular channels in patients whose varices do not respond to EST.

Obliteration of submucosal veins, may depend on early or simultaneous obliteration of the perforating and paraoesophageal collaterals, which might be serving as feeders of the varices. One study showed that the degree of embolisation (extending into feeding vessels) during EST inversely correlated with longterm recurrence of varices, implying that obliteration of feeders might be important for effective variceal sclerosis.  

Lin et al. have shown that patients with bleeding oesophageal varices who have large paraoesophageal collaterals need more sessions of EST, more sclerosant, and longer periods to achieve variceal obliteration and have higher recurrence and repeat bleeding rates after EST. They considered that paraoesophageal collaterals and perforating veins affect the efficacy of EST if high pressure and blood flow continue to feed intrinsic oesophageal varices (submucosal veins) during the course of EST. The authors, however, did not perform the follow up computed tomodiagram to evaluate the effect of EST on paraoesophageal collaterals – that is, whether there

![Figure 5: A 360° endosonographic scan (A) and schematic drawing (B) of the lower oesophagus in a patient with cirrhotic portal hypertension. A perforating vein (arrow) communicating the oesophageal varices (submucosal veins, small arrow) to the paraoesophageal collaterals (large arrow) is imaged. A: aorta.]

<table>
<thead>
<tr>
<th>Table II</th>
<th>Number and size (median (interquartile range)) of submucosal veins in controls, EST-responders, and in EST-non-responders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>Upper stomach</td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>2 (1–3)</td>
</tr>
<tr>
<td>Size (mm)</td>
<td>5 (3–6)</td>
</tr>
<tr>
<td>Gastro-oesophageal junction</td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>3.5 (3–4)</td>
</tr>
<tr>
<td>Size (mm)</td>
<td>4.75 (4.5–5)</td>
</tr>
<tr>
<td>Lower oesophagus</td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>3 (3–4)</td>
</tr>
<tr>
<td>Size (mm)</td>
<td>4 (3–4.5)</td>
</tr>
</tbody>
</table>

![Figure 6: A 360° endosonographic scan of the lower oesophagus in a responder to EST (EST-R). Note submucosal vein (oesophageal varix) is seen within the oesophageal wall and only two to three small paraoesophageal collaterals (arrowheads) are seen well outside the oesophageal wall. A: aorta.]

![Figure 7: A 360° endosonographic scan of the lower oesophagus in a non-responder to EST (EST-NR). Note persistence of submucosal veins (oesophageal varices, arrowheads) and large paraoesophageal collaterals (arrows). A: aorta.]

Note: EST-R: Early responders; EST-NR: No responders; NS: Not Significant.
is reduction in number and size of paraoesophageal varices and not, after the successful obliteration of oesophageal varices. Using percutaneous transhepatic portography in patients with portal hypertension undergoing EST, Soderlund et al.\textsuperscript{14} delineated two parts of collaterals, namely, periesophageal and paraoesophageal varices around the lower oesophagus. Periesophageal varices were situated in the connective tissue surrounding the oesophagus, whereas paraoesophageal varices were mediastinal veins running longitudinally distant to or overlaying the oesophagus, or both. The authors found that large mediastinal collaterals were largely unaffected after successful EST. It has been suggested, however, that periesophageal and paraoesophageal varices might have indicated the various degrees in size and extent of collaterals around the oesophagus and both correspond to the dilated adventitial veins described by Hashizume et al.\textsuperscript{12} Percutaneous transhepatic portography in cirrhotic patients is technically demanding and cannot be recommended as a standard clinical procedure; in this study important complications were seen in 23\% of patients with one death caused by bleeding from the hepatic puncture site.\textsuperscript{14}

Perhaps the greatest proportion of portosystemic shunting of blood around the gastrooesophageal region occurs through the perigastric and paraoesophageal collaterals, with the perforators playing a major part in maintaining variceal patency by connecting the two venous channels.\textsuperscript{8,22} Using Doppler ultrasonography McCormack et al.\textsuperscript{15} have shown that blood flows in opposite directions at different levels in the same varix. They noted that during inspiration blood flow was in a caudal direction at 35 cm from the incisors and in a cephalad direction at 37 cm. The direction of flow at both positions reversed at the end of expiration. These findings lent evidence to the presence of a communicating vein joining the varix between the two sites. Injection radiography showed their presence and showed that oesophageal varices were not always the main pathway for the portal to systemic shunting and that most shunting occurred at a deeper level.\textsuperscript{22} The oesophageal varices may be considered backwaters that arise from the transmission of blood from the large paraoesophageal collaterals to the submucosal varices via the perforating veins. It seems that successful treatment of oesophageal varices with EST may depend on early obliteration of the perforating veins. Failure of EST may be associated with the persistence of perforating veins as seen in our patients in the EST-NR group.

The direction of blood flow in the oesophageal varices may explain the partial obliteration of paraoesophageal collaterals (decrease in number and size of paraoesophageal collaterals). Hence, direct action of sclerosant carried caudally into the gastric varices and peripherally into the paraoesophageal collaterals through perforating veins might have been responsible for the changes seen by us. Another explanation might be in the retrograde extension of thrombosis from the oesophageal to the gastric varices and paraoesophageal collaterals.\textsuperscript{23}

A small number of patients who failed to respond to a large number of EST sessions were of special interest. They had received a median of 13-5 sessions compared with a median of 7-5 sessions required in our hospital experience of over 400 cases to sclerosate varices (unpublished data). Further other known factors that contribute to EST failure like extravascular injections,\textsuperscript{5} associated portal vein thrombosis, and hepatocellular carcinoma,\textsuperscript{24} did not seem to be the underlying causes in them. None of these patients had hepatocellular carcinoma or portal vein thrombosis and the technique of EST was the same as for patients in the EST-R group. Therefore, we believe that failure to eradicate varices in the EST-NR group may be related to the large size of paraoesophageal veins and predominant direction of blood flow in perforating veins.

Why perforating and paraoesophageal veins get obliterated in some patients and not in others, is not clear from our study. This may be related to the large size of these veins and predominant direction of blood flow in perforating veins. This is a one point study in which the size of paraoesophageal veins were not measured before starting the EST; serial assessment of oesophageal and paraoesophageal venous circulation with both EUS and Doppler ultrasound may be helpful in resolving this issue. Rapid obliteration and low recurrence rates of oesophageal varices are also expected if embolisation of feeders with sclerosant can be achieved by preventing sclerosant flow out of the varix into the systemic circulation by a balloon tamponade of the varix inserted proximally during injections.\textsuperscript{4,23} A similar approach may be useful in diverting the sclerosant flow to paraoesophageal collaterals through perforating veins in the lower oesophagus.

In conclusion, EUS seems to be a reliable procedure in delineating changes in the venous anatomy around the gastro-oesophageal junction in patients with portal hypertension. Successful EST is associated with reduction in number and size of paraoesophageal collaterals and disappearance of perforating veins. The presence of large paraoesophageal collaterals and perforating veins after an adequate number of EST sessions may necessitate the selection of an alternative therapy in the treatment of variceal haemorrhage.
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